Asymétrie et instabilité posturales après lésion cérébrale : relation avec les déficits de la cognition spatiale

Aurélien Hugues

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Asymétrie et instabilité posturales après lésion cérébrale. Relation avec les déficits de la cognition spatiale.

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RESUME

Après un accident vasculaire cérébral (AVC), les patients présentent des troubles posturaux tels qu'une asymétrie d'appui sur les membres inférieurs et une instabilité posturale, mais également des troubles de l'équilibre. Le premier objectif de la thèse a été d'évaluer les effets des rééducations sur ces troubles par méta-analyses. Si certaines rééducations semblent bénéfiques, les effets sont cependant limités par la faible qualité méthodologique des études, mais aussi par l'hétérogénéité des participants et des interventions. La nature des effets susceptibles d'être induits par les rééducations (récupération ou compensation) reste incertaine. L'analyse des effets des rééducations selon leur approche « bottom-up » (ascendante) ou « top-down » (descendante) suggèrerait un potentiel effet cumulatif (à court et plus long terme) des seules approches mixtes sur l'équilibre. La rééducation des troubles posturaux et de l'équilibre souffrirait de ne pas s'appuyer suffisamment sur des modèles théoriques robustes. Le second objectif de la thèse a été d'étudier les relations entre l'asymétrie d'appui et l'instabilité posturale, et les déficits de la cognition spatiale après AVC, par une étude transversale chez 86 patients avec lésion droite au stade subaigu. Les résultats ont montré l'influence des perturbations du cadre référentiel spatial égocentré, qu'est l'axe corporel longitudinal, modulée par la sévérité de la négligence comportementale, sur l'asymétrie d'appui selon une relation non linéaire. Le droit devant manuel n'avait pas d'influence sur l'asymétrie d'appui. Ni les perturbations des cadres référentiels spatiaux, ni la négligence spatiale unilatérale n'ont contribué à l'instabilité posturale. Ces résultats renforcent l'hypothèse d'un déficit représentationnel spatial à l'origine de l'asymétrie d'appui après AVC. Par ailleurs, une étude préliminaire expérimentale que nous avons conduite a montré, en plus d'une amélioration de l'équilibre, une réduction de l'asymétrie d'appui conjointement à un décalage du droit devant manuel après adaptation prismatique chez des patients AVC droits chroniques. Ces résultats suggérant un effet « bottom-up » de l'adaptation prismatique sur les déficits de la cognition spatiale à l'origine d'une amélioration secondaire des troubles posturaux, ont conduit à la conception d'un essai clinique contrôlé randomisé multicentrique.

ABSTRACT

The English title: Postural asymmetry and body sway after stroke. Relationship with spatial cognition deficits.

After stroke, patients frequently have postural disorders including weight bearing asymmetry on lower limbs and body sway, but also balance disorders. The first objective of the thesis was to assess effects of physical therapy on postural and balance disorders after stroke by meta-analyses. If some categories of physical therapy could be effective, the effects are limited owing to the weak methodological quality of studies and the heterogeneity of participants and interventions. The nature of effects likely to be implemented by physical therapy (recovery or compensation) remains unclear. The assessment of effects of physical therapy according to their bottom-up or top-down approach suggests a potential cumulative (short- and long-term) effect for mixed approaches on balance. The theoretical framework supporting the rehabilitation of balance and postural disorders appears too weak. The second objective of the thesis was to evaluate the relationship of weight bearing asymmetry and body sway with spatial cognition deficits after stroke, in a cross-sectional study including 86 subacute right stroke patients. The results showed the influence of the egocentric spatial reference frame that is longitudinal body axis, modulated by the severity of behavioural neglect, on weight bearing asymmetry by a non-linear relationship. The manual straight-ahead assessment had no influence on weight bearing asymmetry. Neither spatial reference frames nor unilateral spatial neglect contributed to body sway. These findings reinforce the hypothesis of a spatial representational deficit involved in weight bearing asymmetry after stroke. Furthermore, a pilot study was conducted and showed, in addition to an improvement in balance, a decrease in weight bearing asymmetry jointly with a shift of the manual straight-ahead assessment after prismatic adaptation in patients with chronic right stroke. Suggesting a bottom-up effect of prismatic adaptation on spatial cognition deficits likely to induce a secondary improvement in postural disorders, these findings led to design a multicentric randomised controlled trial.

Mots clés

Accident vasculaire cérébral, équilibre, posture, asymétrie d'appui, instabilité posturale, cadres référentiels spatiaux, droit devant, axe corporel longitudinal, cognition spatiale, héminégligence, rééducation, efficacité, méta-analyse, modèle théorique, corrélation

Keywords

Stroke, balance, posture, weight bearing asymmetry, body sway, space reference frames, straight-ahead, longitudinal body axis, spatial cognition, hemineglect, rehabilitation, effectiveness, meta-analysis, theoretical model, correlation

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INTRODUCTION GENERALE

Dans la vie de tous les jours, chacun fait en permanence l'expérience de l'équilibre (ou du déséquilibre), de façon inconsciente lors de nos activités courantes habituelles et peu déstabilisantes, ou de façon plus consciente lors d'activités difficiles ou de perturbations. La posture est une activité sensori-motrice indispensable à la réalisation d'autres actions motrices, comme la marche, mais également à la perception et à l'interaction sociale.

L'être humain est devenu bipède au cours de l'évolution, et cette posture érigée est un prérequis indispensable à la réalisation de ses activités. Le contrôle postural assure le maintien et l'adaptation de la posture au cours du mouvement, et ce, en fonction des contraintes internes et externes auquel le sujet est soumis. Nous aborderons au cours du premier chapitre de la thèse le fonctionnement physiologique du contrôle postural, reposant notamment sur des afférences sensorielles, des processus neurologiques centraux et des effecteurs périphériques.

Après un accident vasculaire cérébral (AVC), les patients présentent des troubles posturaux, comprenant notamment une asymétrie d'appui du poids du corps et une instabilité posturale, mais également des troubles de l'équilibre, qui impactent négativement leurs activités, leur participation et leur qualité de vie. En pratique, de multiples rééducations sont mises en œuvre par les cliniciens afin de réduire ces troubles posturaux et améliorer l'équilibre des patients. Dans le second chapitre de la thèse, nous examinerons ces différentes rééducations.

L'objectif initial de la rééducation après lésion cérébrale est de favoriser et d'accompagner les processus de récupération neurologique. Pour cela, il est impératif d'inscrire les rééducations dans un cadre théorique adapté et basé sur les preuves. Parce que la rééducation des troubles de la posture et de l'équilibre est un enjeu essentiel pour les patients, et dans un contexte de développement croissant des essais cliniques sur cette thématique, nous évaluerons les effets des différentes rééducations afin non seulement d'objectiver leur efficacité, mais aussi de discuter du rationnel et des mécanismes sous-

tendant leurs potentiels effets dans le cadre du modèle théorique du contrôle postural (approche « bottom-up », « top-down » ou mixte). Tel sera l'objectif des méta-analyses présentées dans le second chapitre de la thèse.

Après un AVC, les patients présentent également des déficits de la cognition spatiale tels que des perturbations des cadres référentiels spatiaux et/ou une négligence spatiale unilatérale. Plusieurs travaux suggèrent un lien entre ces déficits et les troubles posturaux. Dans cette hypothèse, nous étudierons les relations potentielles entre l'asymétrie d'appui et l'instabilité posturale après AVC d'une part, et les déviations de la perception de l'axe corporel longitudinal, du droit devant manuel et les manifestations cliniques de la négligence spatiale unilatérale, d'autre part. Pour cela, une étude transversale issue d'un essai clinique contrôlé randomisé multicentrique « AVCPOSTIM » sera présentée dans le chapitre 3, ainsi qu'une revue narrative de la littérature discutant de la relation entre les troubles posturaux et de l'équilibre avec la négligence spatiale unilatérale. L'apport de ces travaux vise à améliorer la compréhension des troubles posturaux consécutifs à un AVC. Une meilleure connaissance des mécanismes d'action sous-tendant ces déficits posturaux pourrait contribuer à implémenter des rééducations plus efficaces car susceptibles de mieux accompagner les processus de récupérations vraies.

Dans une démarche de recherche de rééducations efficaces mais aussi d'amélioration du cadre théorique, nous étudierons dans un dernier chapitre de la thèse les effets de l'adaptation prismatique sur les troubles de la posture et de l'équilibre des patients après AVC. Pour cela, nous présenterons les résultats d'une étude préliminaire ainsi qu'un protocole d'essai clinique contrôlé randomisé multicentrique contre placebo « PEQUIE ». L'intérêt de recourir à l'adaptation prismatique dans des essais cliniques réside non seulement dans le potentiel bénéfice clinique dont pourraient tirer profit les patients d'une intervention facile de mise en œuvre et sans risque, mais également dans la relative solidité du cadre théorique supportant cette intervention, contribuant ainsi à améliorer la connaissance des mécanismes physiopathologiques.

1. PHYSIOLOGIE DE LA POSTURE ET DE L'EQUILIBRE

1.1. LA POSTURE ET LE CONTROLE POSTURAL

1.1.1. Généralités

Selon la définition d'André Thomas en 1940, la posture est une attitude caractérisée par la position relative des segments les uns par rapport aux autres mais également par leur orientation respective dans l'espace en trois dimensions.[1] Le corps humain peut être modélisé comme une superposition de cinq modules articulés au niveau du cou, des hanches, des genoux et des chevilles, et liés entre eux par des groupes musculaires selon une régulation centrale et périphérique.[2] L'être humain évolue dans un environnement terrestre contraint par la gravité. La posture de référence est la posture bipède ou érigée. Cela nécessite donc un alignement constant des modules articulés par rapport à la verticale.

Théoriquement, il existe une multitude de postures que le corps peut adopter. Cependant, le corps va chercher à assurer l'équilibre en fonction des contraintes internes comme la géométrie et les propriétés dynamiques du système, et externes comme la gravité.[3] L'équilibre est défini comme le maintien de la projection du centre de masse dans le polygone de sustentation.[3–6] Il s'agit de maintenir une posture malgré ces contraintes. L'équilibre est une condition indispensable pour réaliser toute une gamme d'activités comme la locomotion, la préhension ou les interactions.

1.1.2. Le contrôle postural : orientation et stabilisation

La finalité du contrôle postural est triple :[3,4,6]

1. antigravitaire pour assurer l'équilibre debout,
2. fournir une base de stabilité pour réaliser des mouvements, et

3. servir d'interface sujet/espace en contribuant à la constitution de représentations spatiales. En effet, par l'orientation antigravitaire et la base stabilisée, la posture fournit un référentiel permettant de définir la position du corps dans l'espace.

L'orientation posturale (maintenir une position donnée, notamment par rapport à la gravité) et la stabilisation posturale (fournir une base stabilisée) sont les deux composantes constitutives du contrôle postural.[4,5,7] Elles sont fonctionnellement distinctes mais liées l'une à l'autre dans une finalité commune.[5] Le contrôle postural suppose parfois un compromis entre orientation et stabilisation posturales, notamment dans les situations dynamiques et en fonction des objectifs à atteindre.[3,8]

Chacune de ces fonctions posturales peut être appréhender de façon globale ou segmentaire. En position érigée statique, l'orientation globale consiste à aligner l'axe longitudinal du corps (Axe Z) avec la gravité.[4,9–13] La verticale gravitaire est le référentiel privilégié pour déterminer l'orientation posturale.[14–16] La stabilisation globale assure le maintien de la projection du centre de masse dans le polygone de sustentation formé par les deux pieds. De cette dernière vont dépendre les oscillations du corps autour de sa position d'équilibre. Ainsi, la posture debout statique a pu être modélisée, sur le plan biomécanique, comme un pendule inversé oscillant.[17–19] Dans cette position, la posture n'est pas exactement verticale mais légèrement vers l'avant de sorte que la projection du centre de masse se situe un peu en amont des chevilles (<5cm).[18,20] Classiquement, deux stratégies ont été décrites pour maintenir la station debout : une stratégie de cheville réalisée dans le plan sagittal par les muscles triceps suraux, et dans le plan frontal par les muscles inverseurs et éverseurs de cheville ; et une stratégie de hanche permettant une mise en charge/décharge du poids sur les membres inférieurs par les muscles abducteurs et adducteurs de hanche.[18,19,21] S'il a été suggéré un temps que la stratégie de cheville était prépondérante pour assurer la posture debout statique avec support stabilisé et que la stratégie de hanche était mise en jeu lors de déstabilisations externes notamment du support,[21] il apparaît dorénavant que cette stratégie de cheville est insuffisante pour expliquer le contrôle postural debout sur support stable, qui relève plutôt qu'une dynamique multisegmentaire impliquant les différentes articulations des membres inférieurs.[22] Le modèle du pendule inversé est ainsi remis en cause en raison de ces limites. Actuellement, une approche multisegmentaire lui est préférée. Ainsi, en station érigée

avec les pieds disposés parallèlement sur un support stable, la stabilisation médiolatérale repose essentiellement sur un mécanisme de mise en charge/décharge du poids du corps sur les membres inférieurs au niveau des hanches, avec une contribution réduite des muscles inverseurs et éverseurs de cheville ; tandis que la stabilisation antéropostérieure est assurée par les muscles fléchisseurs plantaires selon une stratégie de cheville. En situation debout avec les pieds disposés en tandem, les stratégies sont inversées.[23–26]

L'orientation et la stabilisation posturales peuvent également concerner spécifiquement un segment corporel donné afin de fournir un référentiel stabilisé nécessaire à la perception et à l'action.[9] En effet, l'orientation de la tête et du tronc par rapport à la verticale apparaissent préservées et relativement bien stabilisées, notamment dans le plan frontal, lors de différentes taches locomotrices ou d'équilibration.[10,27–29] Ainsi, le maintien d'une orientation stabilisée de la tête, siège des organes vestibulaires et visuels, pour constituer une « plateforme inertielle », et du tronc par rapport à la verticale permet d'établir des cadres de références (visuel, gravitaire, égocentré) afin d'organiser la posture, la locomotion et la perception.[10,11,27–30] Il a été proposé deux stratégies relatives à la stabilisation posturale segmentaire de la tete.[10,31] La première est appelée la « stratégie en bloc » (« strap-down ») et consiste à fixer la tête sur le tronc par une augmentation de la raideur entre les deux segments, tandis que la seconde stratégie dite « de plateforme stabilisée » (« stable-platform ») va assurer un ancrage de la tête par rapport à l'espace.[10] La première stratégie, plus simple à mettre en œuvre, pourra être utilisée lorsqu'il n'est pas nécessaire de surveiller l'environnement ou lors de taches posturales plus simples. La seconde stratégie, qui apparaît plus tard dans le développement postural, s'inscrit dans un contrôle « top-down » de la posture. Elle facilite par exemple le traitement des informations visuelles et sera utilisée lors de la marche ou de situations d'équilibration plus complexes.[10,32]

De manière générale, le choix des segments à stabiliser dépend des conditions, de la tâche à réaliser et des stratégies disponibles.[10,33] En effet, Pozzo *et al.*[28] ont suggéré que selon la tache motrice à réaliser (debout en appui unipodal sur une poutre ou bipodal sur une plateforme à bascule), le tronc pourrait servir soit de référentiel (par son orientation stabilisée par rapport à la verticale) soit de stabilisateur (par son inclinaison). Par ailleurs, l'entrainement et l'apprentissage sont des facteurs susceptibles de modifier le choix des stratégies

d'orientation et de stabilisation posturales afin d'obtenir les meilleures performances en terme d'équilibre.[30]

En situation de microgravité, l'orientation de la tête et du tronc par rapport à la verticale reste bien préservée et stabilisée dans le plan frontal, et ce quel que soit la disponibilité de l'entrée visuelle.[11,29] Par ailleurs, la projection du centre de masse continue d'être située dans le polygone de sustentation, suggérant que la stabilisation globale soit une référence indépendante des contraintes d'équilibration.[8] Ces résultats montrent que orientation et stabilisation posturales sont les éléments constitutifs fondamentaux du contrôle postural.

Le maintien de ces fonctions d'orientation et de stabilisation posturales lors de conditions d'équilibration complexes et variées, et/ou lors de privation sensorielle (microgravité, vision) plaide également en faveur d'un contrôle postural d'origine centrale, impliquant des représentations internes du corps sous forme d'un schéma postural corporel.[4,8,10–12,28,29,32]

La posture implique une action motrice réalisée activement par les muscles striés squelettiques de l'appareil locomoteur. Ils jouent un rôle essentiel dans la cohésion des segments corporels et le maintien de leur position dans l'espace. C'est notamment par le tonus musculaire des muscles antigravitaires, qui sont des muscles extenseurs, que va être maintenue la station debout. Comme vu précédemment, les muscles triceps suraux et les muscles de la hanche jouent un rôle majeur dans les stratégies posturales en position debout. Le contrôle de l'activité tonique est assuré par des boucles de régulation qui peuvent être segmentaires (courtes) au niveau médullaire, ou supra-segmentaires (longues) non seulement médullaires mais impliquant également des connexions avec le cervelet, les noyaux vestibulaires du tronc cérébral, les noyaux gris centraux et le cortex cérébral (Figure 1).[34]

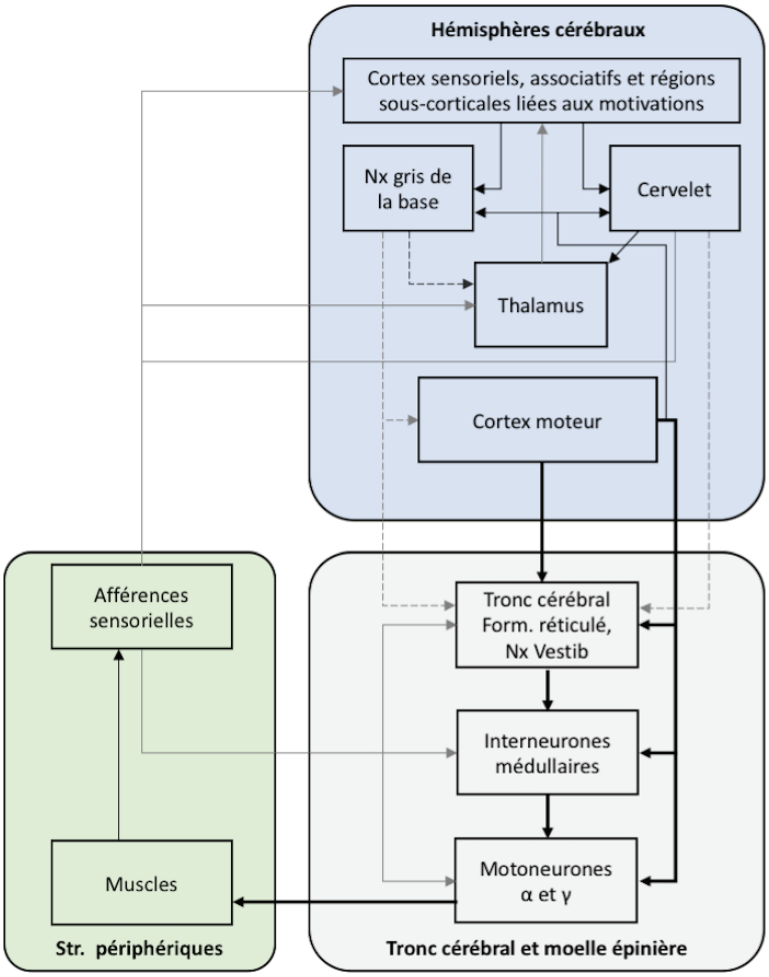

Figure 1. Schéma de synthèse des boucles sensori-motrices impliquées dans la posture (d'après Dupui, 2016)

La réalisation d'une action motrice va avoir pour conséquence de perturber la posture par un changement dans sa géométrie et par la génération de forces de réaction s'exerçant sur le système. Une coordination est donc nécessaire entre la posture et le mouvement afin d'assurer le maintien de l'orientation et de la stabilisation posturales. Lors de la réalisation d'un mouvement volontaire, les ajustements posturaux anticipateurs vont corriger par anticipation les perturbations posturales tandis que les réactions posturales vont les compenser durant ou après l'exécution du mouvement (Figure 2).[35,36] Par exemple, la réalisation d'une tache de préhension en station debout chez le sujet sain va être précédée par une diminution du tonus musculaire du muscle soléaire, puis sera accompagnée par la contraction des muscles tibiaux antérieurs, péroniers latéraux et soléaires afin de contrôler les mouvements du centre de pression.[37] Une activation des muscles érecteurs du rachis est également observée afin de stabiliser le tronc.[38]

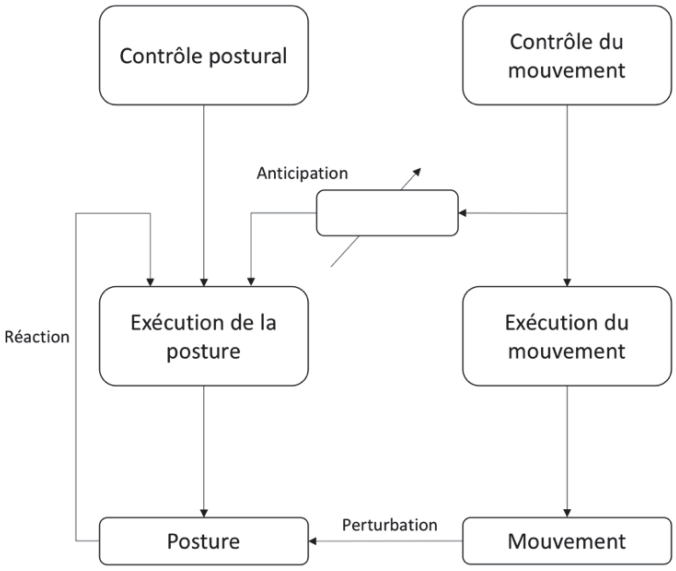

Figure 2. Représentation schématique de l'influence de la réalisation d'un mouvement dans le contrôle postural (d'après Massion, 2004)

L'orientation et la stabilisation posturales nécessitent chacune l'intégration des différentes afférences sensorielles. L'orientation posturale par rapport à la gravité est fortement liée à la perception de la verticale gravitaire construite à partir des afférences graviceptives d'origine somesthésique et vestibulaire, des afférences proprioceptives, visuelles mais également sensitives cutanées plantaires.[14,15,39–43] La stabilisation posturale nécessite, elle aussi, une intégration multisensorielle.[40–45] Aussi, l'application d'un courant électrique « TENS » (« Transcutaneous Electrical Nerve Stimulation ») sur les muscles cervicaux controlesionnels des patients négligents après AVC a montré une réduction de l'instabilité posturale par rapport à des patients non-négligents.[46]

Ainsi le contrôle postural nécessite et contribue à la perception de la position du corps et des objets dans l'espace. Ce codage spatial repose sur des cadres référentiels spatiaux définis à partir d'invariants (comme la gravité) ou de la position des différents segments du corps dans l'espace renseignés par les systèmes sensoriels.

1.2. LES INFORMATIONS SENSORIELLES

Les afférences sensorielles sont donc nécessaires au contrôle postural car elles renseignent sur l'état du système et l'espace. Chez l'être humain, trois principaux systèmes sensoriels contribuent à la posture : visuel, vestibulaire, et somatosensoriel.[4,40–45,47]

1.2.1. La vision

La vision fournit des informations visuelles sur l'environnement. L'œil est l'organe sensoriel périphérique (Figure 3). La rétine est divisée en quatre zones : la papille optique qui ne contient aucun récepteur et par laquelle les axones des neurones rétiniens quittent l'œil pour former le nerf optique ; puis de façon concentrique, on trouve, au centre, la fovéa qui est une petite dépression circulaire située dans le prolongement de l'axe visuel de l'œil et au niveau de laquelle l'acuité visuelle est maximale ; la macula lutea qui forme une région concentrique autour de la fovéa dans laquelle l'acuité visuelle est très élevée ; et enfin la rétine périphérique.[48,49]

Les photorécepteurs de la rétine, que sont les cônes et bâtonnets, sont spécialisés sur des aspects différents de la vision en fonction des propriétés de chacun. Les cônes, plus densément situés au niveau de la fovéa, permettent l'acuité visuelle en raison de leur résolution spatiale élevée et de leur faible sensibilité à la lumière, tandis que les bâtonnets, plus nombreux et présents dans toute la rétine mais avec un concentration faible au niveau de la fovéa, sont spécialisés dans la sensibilité à la lumière de part des propriétés inverses.[48] Ces photorécepteurs envoient les informations visuelles par l'intermédiaire des voies optiques jusqu'au cortex occipital.[48]

Ainsi, les cônes sont plutôt impliqués dans la vision diurne alors que les bâtonnets ont un rôle dans la vision crépusculaire ou nocturne. La fovéa permet la vision de précision (identification et discrimination fine – vision focale) alors que la rétine périphérique assure la discrimination grossière et détecte les mouvements (vision d'ambiance).[50] La vision permet d'identifier des objets et de renseigner sur le mouvement de ces objets dans l'espace.

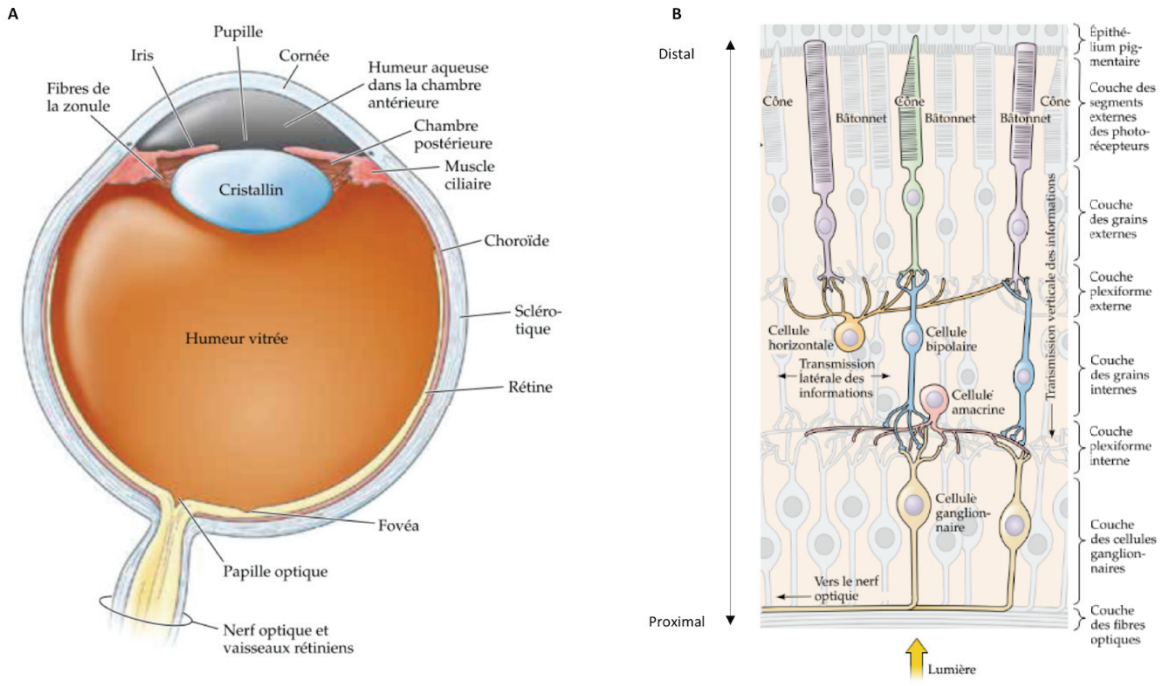

Figure 3. Anatomie de l'œil (A) et structure de la rétine (B)
(d'après Purves *et al.*, 2015)

1.2.2. Le système vestibulaire

Le système vestibulaire est composé de deux organes otolithiques (utricule et saccule) et de trois canaux semi-circulaires (supérieur, postérieur et horizontal), tous situés au niveau de l'oreille interne (Figure 4). Les otolithes sont des accéléromètres linéaires : Les saccules détectent les accélérations verticales et les utricules les accélérations horizontales. Quant aux canaux semi-circulaires, ils sont sensibles aux accélérations angulaires selon le plan dans lequel ils se trouvent. A ce titre, les otolithes et les canaux semi-circulaires renseignent sur la position de la tête par rapport à la gravité.[48]

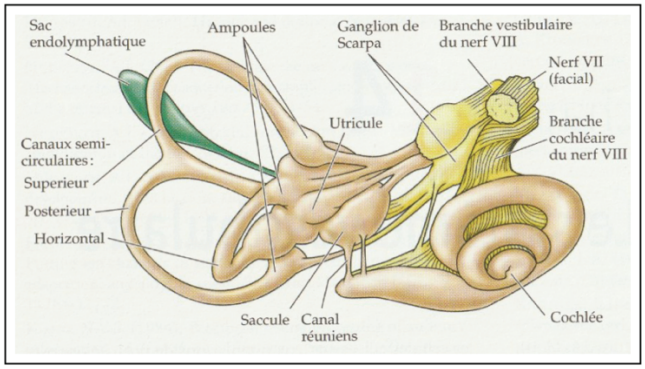

Figure 4. Anatomie de l'oreille interne (d'après Purves *et al.*, 2015)

Les afférences vestibulaires sont transmises par le nerf vestibulo-cochléraire (VIII) aux noyaux vestibulaires (latéral, médian, inférieur et supérieur). De ces noyaux, sont issues des connexions avec le système visuo-oculomoteur (voies vestibulo-oculomotrices), les muscles cervico-thoraciques et lombo-sacrés (voies vestibulo-spinales), le cervelet (voies vestibulo-cérébelleuses) et les aires corticales et sous-corticales (voies vestibulo-thalamiques et vestibulo-corticales ; Figure 5).[34,48,51] Ces connexions sont à l'origine de plusieurs réflexes :

- le réflexe vestibulo-oculaire impliquant les voies vestibulo-oculomotrices afin de stabiliser l'image sur la rétine lors des mouvements de la tête par des mouvements occulaires compensateurs (direction opposée et même amplitude)[34,48,51] ;
- les réflexes vestibulo-colliques et vestibulo-spinaux impliquant les voies vestibulo-spinales afin de stabiliser la tête et le corps en position érigée lors de mouvements.[34,48,51]

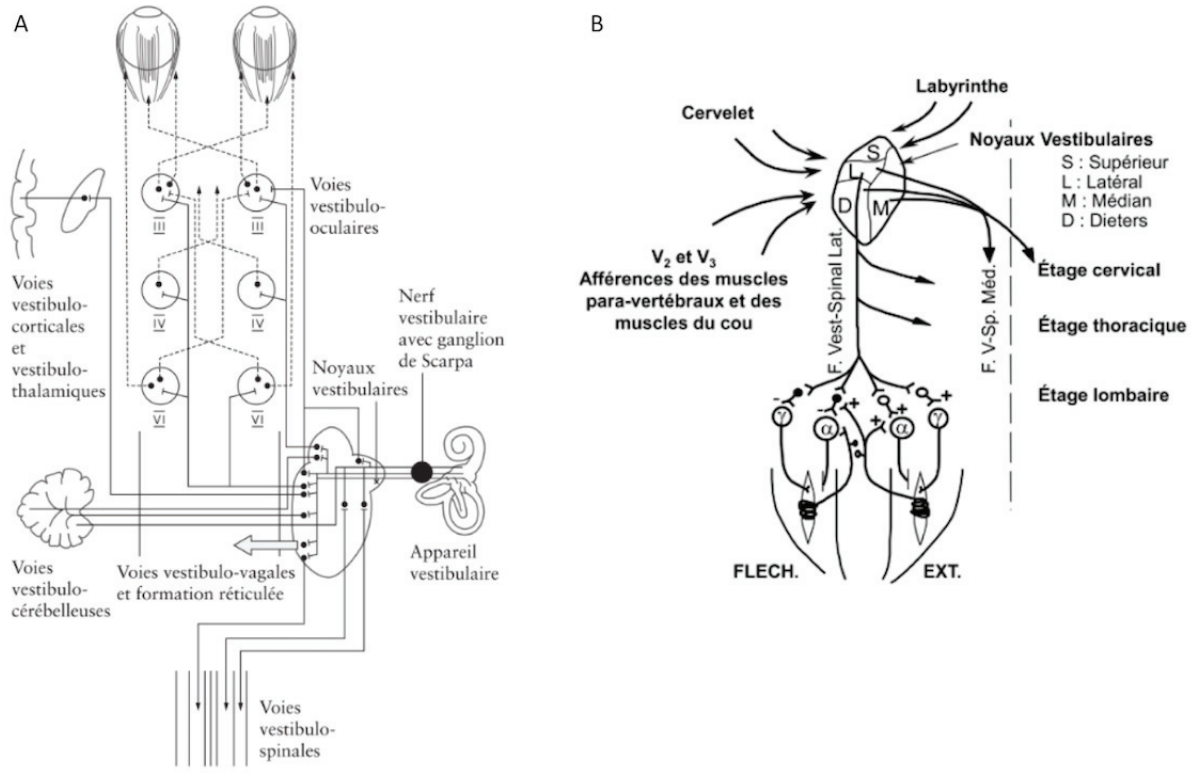

Figure 5. Les voies vestibulaires centrales (d'après Perrin *et al.*, 2016 et Dupui *et al.*, 2016)

Pour les figures A et B : Seuls les noyaux vestibulaires droits sont représentés. Sur la figure B, la ligne verticale en pointillé représente l'axe médian du corps.

Abréviation : F. V-Sp. Méd., faisceau vestibulo-spinal médial ; F. Vest-Spinal lat., faisceau vestibulo-spinal latéral.

1.2.3. La somesthésie

La somesthésie est l'ensemble des sensations provenant du corps. Elle comprend la proprioception (consciente et inconsciente) et la sensibilité tactile, impliquées toutes deux dans le contrôle postural, mais également la sensation de douleur (nociception) et de la température (sensibilité thermique).[48,52]

La proprioception consciente comprend la kinesthésie (sens du mouvement), la statesthésie (sens de la position), et la perception de la force, tandis que la proprioception inconsciente intervient dans les ajustements posturaux et le contrôle de la contraction musculaire.[53]

Il existe plusieurs mécanorécepteurs impliqués dans la proprioception (dénommés propriocepteurs). On trouve les fuseaux neuromusculaires, situés dans les fibres musculaires, en charge de renseigner sur la longueur de la fibre musculaire (sensibilité statique) et d'en détecter les variations (sensibilité dynamique). La sensibilité de ces fuseaux neuromusculaires peut être influencée depuis les centres supra-spinaux par l'intermédiaire du neurone gamma. Les fuseaux neuromusculaires seraient les propriocepteurs les plus importants dans la proprioception.[48,52,54,55]

Au niveau articulaire, les propriocepteurs sont constitués des organes tendineux de Golgi situés dans la jonction myotendineuse qui renseignent sur la tension tendino-musculaire, et des corpuscules de Ruffini situés au niveau des ligaments qui enregistrent la vitesse angulaire et les pressions intra-articulaires. On trouve également les corpuscules de Pacini et de Golgi-Mazzoni situés dans la capsule et les ligaments. Les premiers ayant un seuil de détection faible renseignent sur l'accélération dans l'articulation, alors que les seconds mesurant la tension renseignent sur les mouvements aux limites de l'amplitude articulaire en raison de leur seuil de détection élevé.[48,52,54,55]

La proprioception de la tête et du cou (par les propriocepteurs au niveau des muscles oculomoteurs informant de la position de l'œil dans l'orbite, et au niveau des articulations cervicales C0-C4) est particulièrement importante pour la posture.[48,52,54]

Une partie de l'information graviceptive proviendrait d'afférences extravestibulaires, depuis des gravicepteurs somesthésiques situés autour des gros vaisseaux au niveau du tronc. Ces récepteurs seraient sensibles à la gravité.[56,57]

La sensibilité cutanée de la plante du pied, par l'extéroception et la nociception, participe également à la posture en renseignant par exemple sur la surface du sol. Les cellules de Merkel et les corpuscules de Meissner situés dans l'épiderme, mais aussi les corpuscules de Ruffini et Pacini situés dans le derme et l'hypoderme sont les mécanorécepteurs responsables, avec les terminaisons nerveuses libres situées à la jonction dermo-épidermique, de la sensibilité fine épicritique mais aussi de la sensibilité à la pression et à la vibration (Figure 6). Quant aux nocicepteurs, ils détectent les stimuli douloureux, informations pouvant être contributive à la posture.[48,58]

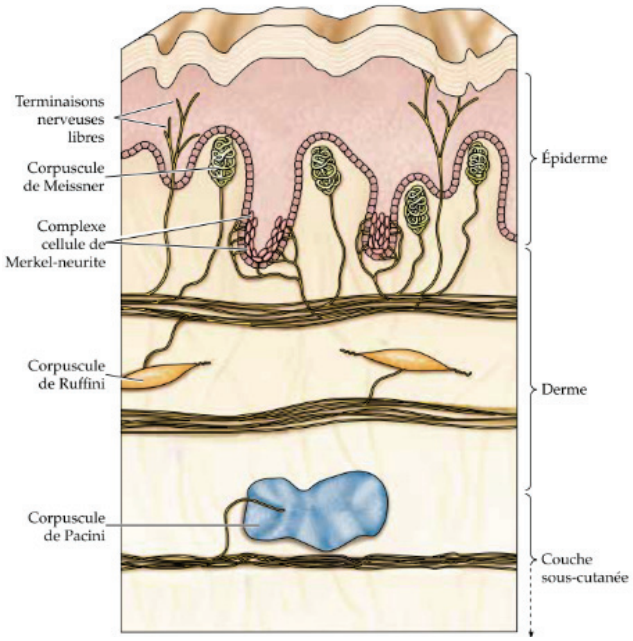

Figure 6. Les mécanorécepteurs de l'épiderme et du derme
(d'après Purves *et al.*, 2015)

Les afférences somesthésiques tactiles épicritiques et proprioceptives conscientes sont transmises par des voies ascendantes cheminant dans le cordon postérieur homolatéral de la moelle (le faisceau gracile ou de Goll pour les membres inférieurs et le faisceau cunéiforme ou de Burdach pour les membres supérieurs, le tronc et le cou) jusqu'au bulbe du tronc cérébral. Après décussation bulbaire, les voies cheminent par le lemnisque médian

jusqu'au thalamus. Un troisième neurone se projette vers le cortex pariétal somesthésique (Figure 7). Des connexions sont émises depuis le faisceau lemniscal vers le cervelet et le tronc cérébral (formation réticulée, noyaux vestibulaires).[48,54]

Quant aux afférences protopathiques, thermiques et nociceptives, elles sont véhiculées par un premier neurone jusque dans la corne postérieure de la moelle, où est réalisé un relais avec un second neurone. Après une décussation médullaire, l'axone de ce second neurone remonte par le cordon antérolatéral de la moelle controlatérale jusqu'au thalamus, constituant le faisceau spino-thalamique. Puis, un troisième neurone se projette vers le cortex pariétal somesthésique (Figure 7). Des projections sont émises par le faisceau spino-thalamique vers les formations réticulaires du tronc cérébral, l'hypothalamus, l'amygdale mais aussi depuis le thalamus vers le cortex insulaire et cingulaire antérieur.[48,54]

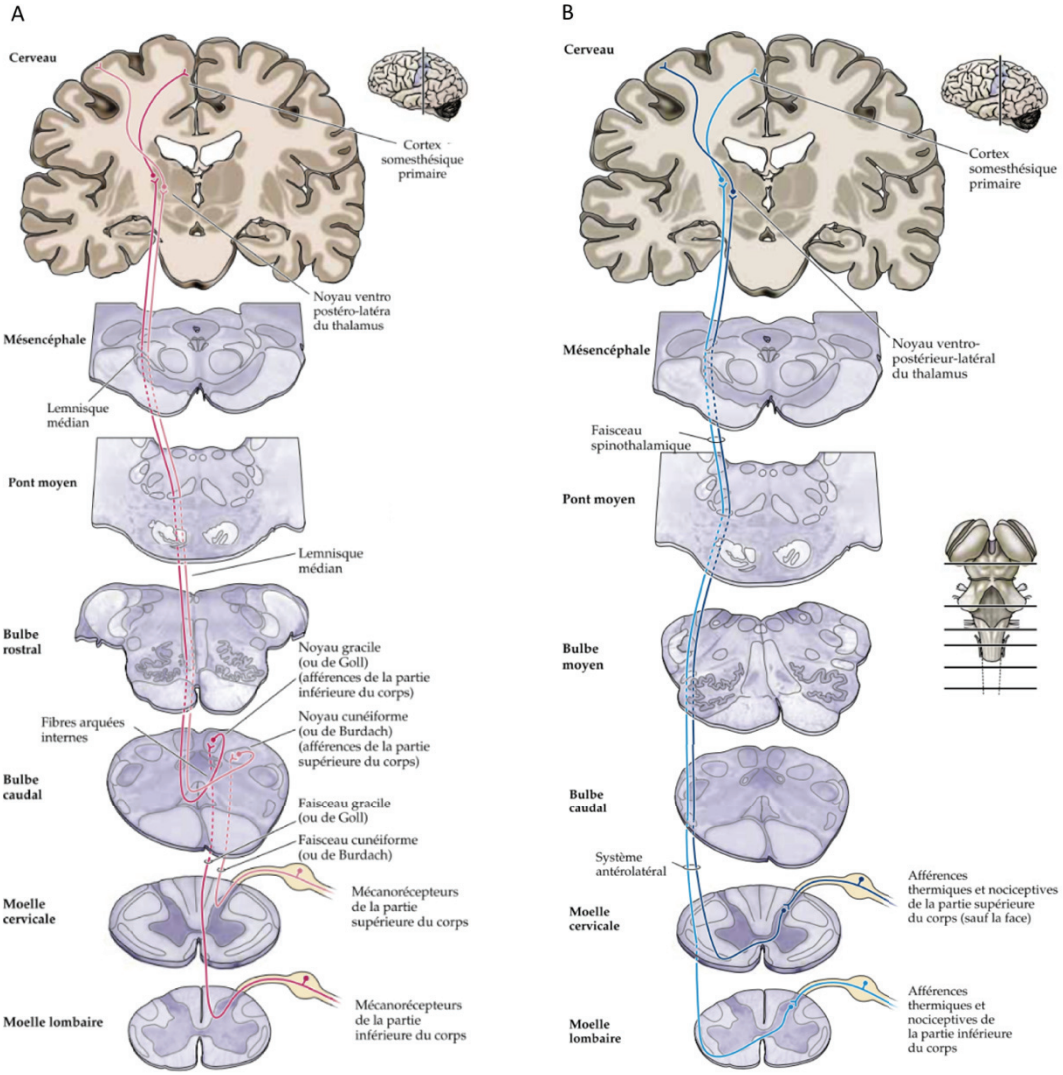

Figure 7. Les voies somesthésiques lemniscales (A) et extra-lemniscales ou spinothalamiques (B) (d'après Purves *et al.*, 2015).

La proprioception inconsciente est transmise par les voies spino-cérébelleuses (Figure 8). Les fibres afférentes provenant des membres inférieurs effectuent à la fois, une synapse au niveau de la corne dorsale de la moelle et un relais au noyau de Clarke situé dans la moelle lombaire. Puis les fibres remontent par le faisceau spino-cérébelleux dorsal (ou faisceau de Flechsig) jusqu'au cervelet. Des collatérales sont projetées en direction du noyau gracile où elles font relais pour rejoindre le faisceau lemnisque médian, accompagnant ainsi les fibres de la sensibilité tactile et proprioceptive consciente.[48,54] Pour les afférences provenant de la partie supérieure du corps, les axones du premier neurone font synapse au niveau de la corne dorsale de la moelle et remontent également vers le cervelet par le tractus cunéo-cérébelleux.[48,54]

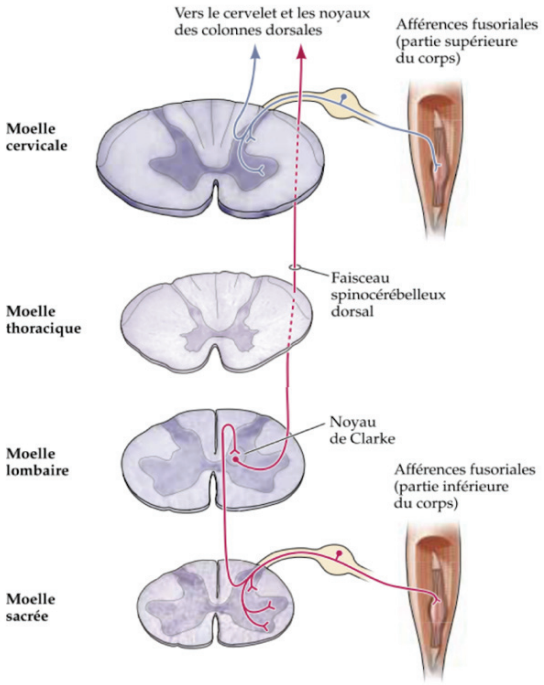

Figure 8. Les voies somesthésiques spino-cérébelleuses (d'après Purves *et al.*, 2015).

1.2.4. Synthèse des afférences sensorielles

Les afférences sensorielles provenant des systèmes sensoriels participent à des boucles de régulation sensorimotrices : segmentaires au niveau médullaire ou supra-segmentaires impliquant le tronc cérébral, le cervelet, les aires sous-corticales et corticales (Figure 1).

Chacune des afférences sensorielles apporte des informations selon des caractéristiques et des limites propres à sa modalité sensorielle (sensibilité, précision, …). De plus, chaque organe sensoriel encode l'information selon son propre système de coordonnées. La combinaison des différentes afférences sensorielles permet de lever les ambiguïtés propres à chaque système sensoriel et de repousser leurs limites respectives.[40,45,59–61]

Une pondération des informations sensorielles est réalisée en fonction de leur fiabilité respective.[44,62–66] Cette pondération dépendrait des conditions, créant ainsi un mécanisme de repondération sensorielle.[40,60,63,65,67,68] Le poids attribué à chacune des afférences sensorielles ne serait pas fixe dans le temps et selon les situations. Ainsi, le poids de la vision dans le contrôle postural augmente lorsque le sujet se tient debout sur un support instable ou réduit, source d'informations somesthésiques plus « variables ».[5,47] De plus, cette dépendance visuelle se réduit au cours de développement ontogénique de l'enfant (vers l'âge de 7 ans).[69] La pondération des afférences sensorielles dépendrait également de préférences individuelles. Ainsi, une variabilité interindividuelle dans l'utilisation des afférences visuelles pour le contrôle postural a été constatée. Certains patients semblent recourir préférentiellement aux entrées visuelles pour assurer leur orientation et leur stabilisation posturales, tandis que d'autres utiliseront préférentiellement les canaux sensoriels proprioceptifs ou vestibulaires.[33,70–73] Par ailleurs, la dépendance visuelle diminue au profit d'une dominance proprioceptive avec l'entrainement, comme cela peut être le cas chez les sportif.[74]

Plusieurs modèles computationnels ont été proposés pour expliquer l'intégration sensorielle dans le contrôle postural.[59,64,65,67,68] Le contrôle postural ne pourrait pas reposer uniquement sur des boucles de contrôles sensorimotrices directes, intégrant par sommation pondérée les différentes afférences sensorielles afin de produire directement une commande motrice.[64,66] En effet, ce modèle apparaît insuffisant pour expliquer le contrôle postural notamment lors de conditions perturbées, car il ne tiendrait pas compte des dynamiques sensorielles différentes et n'inclurait pas de capacité de prédiction nécessaire (retard lié au rétrocontrôle).[59,60,68,75,76] Des processus intégratifs adaptatifs seraient supportés par des

modèles internes au niveau central prenant en compte les informations ascendantes et descendantes.[60,68,75,76]

1.3. LES MODELES INTERNES ET LE SCHEMA CORPOREL POSTURAL

La réalisation d'une action motrice dépend du contrôle moteur. La posture s'inscrit dans ce cadre général avec le contrôle postural. Les modèles computationnels du contrôle moteur décrivent plusieurs étapes à ce contrôle moteur.[77–84]

En fonction de la tâche à accomplir, l'état désiré va être déterminé. Les caractéristiques de la tache motrice vont conditionner le choix de la trajectoire du mouvement à réaliser parmi de nombreuses possibilités, en cherchant à optimiser les couts et les récompenses. Il s'agit de la planification motrice.[79,80,85]

En fonction de la trajectoire désirée et l'état actuel du système, les modèles inverses calculent une série de séquences motrices à réaliser pour atteindre l'objectif et déterminent ainsi la commande motrice à envoyer aux effecteurs (Figure 9).[77–84]

La réalisation du mouvement implique que le système nerveux central puisse estimer l'état du système (appelé état estimé). Pour cela, il utilise les retours d'informations sensorielles, mais cela soulève deux problèmes : premièrement, ce retour se fait avec un délai par rapport à la réalisation du mouvement, et deuxièmement il existe une contamination par le bruit provenant de l'ensemble des informations sensorielles. Pour pallier ces inconvénients, l'estimation de l'état va reposer sur une combinaison des modèles prédictifs (« forward ») et des retours sensoriels. Ces modèles « forward » vont prédire l'état du système (état prédit) mais aussi les conséquences sensorielles de l'action motrice en cours de réalisation à partir d'une copie de la commande motrice efférente. Cette prédiction des conséquences sensori-motrices de l'action motrice sans attendre les retours sensoriels, permet de réduire les délais dans les boucles de contrôle.[77–84] L'état prédit comprend, cependant, un certain niveau d'incertitude et imperfection. La comparaison (erreur) entre la prédiction sensorielle, issue des modèles « forward », et les afférences sensorielles actuelles provenant des systèmes sensoriels va être combiné avec l'état prédit (réduction de l'incertitude de l'état prédit) afin de déterminer l'estimation du système (état estimé ; Figure 9).[77–81]

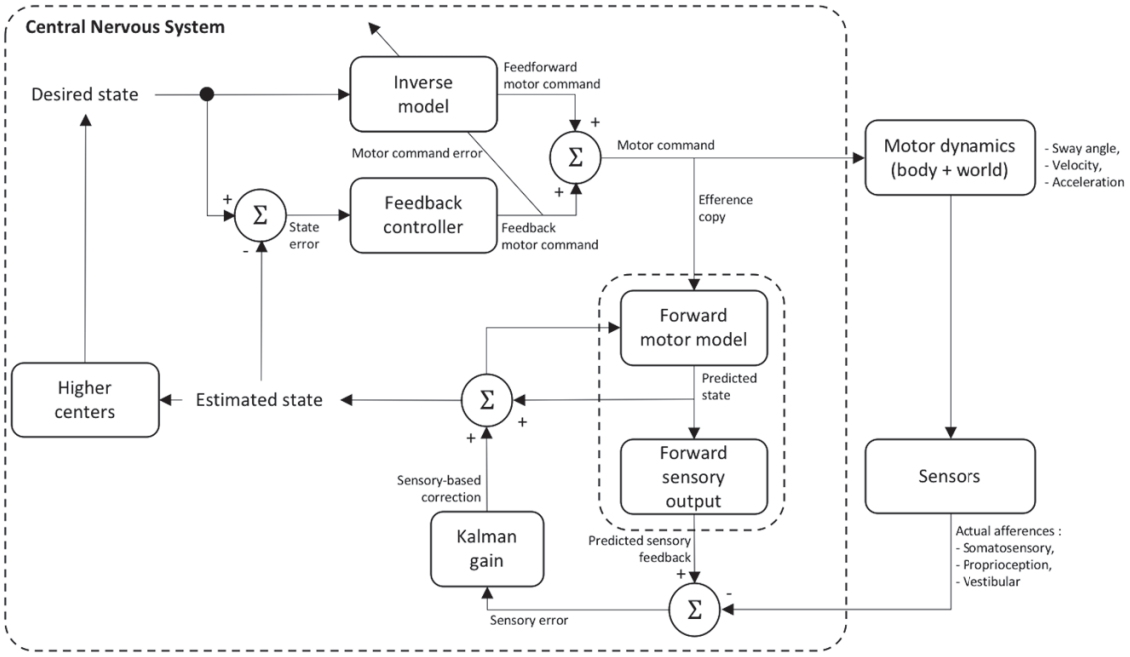

Figure 9. Représentation schématique du contrôle postural sur la base des modèles inverses, « forward » et du filtre adaptatif de Kalman (adaptée à partir de Wolpert *et al.*, 1998 ; Wolpert et Ghahramani, 2000 ; Kuo, 2005 ; Shadmehr et Krakauer, 2008 ; Horak et Macpherson, 2011 ; et Forbes *et al.*, 2018)

Plusieurs approches ont été décrites pour modéliser les processus d'estimation.[86] Plusieurs auteurs suggèrent que le contrôle sensori-moteur s'inscrit dans le cadre de la théorie Bayésienne.[77,87–90] Celle-ci se définit par l'attribution d'une probabilité à tout degré de croyance sur l'état du monde. Ainsi, l'estimation d'un paramètre (θ) qui nous intéresse se conçoit comme la détermination de la configuration la plus probable du paramètre selon les données disponibles (s) (probabilité à postériori ou « Posterior », P(θ|s)). Cette probabilité est le résultat de la combinaison entre un « à priori » sur ce paramètre θ (« prior » : P(θ)) et de la vraisemblance (« likelihood » : P(s|θ)) obtenue à partir des informations disponibles (s).[89,90] Dans le cas du contrôle sensori-moteur, le paramètre θ peut-être la position spatiale de la main lors d'une tache de préhension et les données disponibles (s) les afférences sensorielles. La vraisemblance est la probabilité d'observer les données disponibles (s) considérant la valeur du paramètre θ. Elle permet de mesurer à quel point la valeur du paramètre θ correspond aux données observées (s).[89,90] La méthode du maximum de vraisemblance cherche à déterminer les valeurs de θ qui maximisent la vraisemblance. L'approche Bayésienne ajoute à cette approche inférentielle classique du maximum de vraisemblance, un

paramètre en plus : une croyance à priori du paramètre θ (« prior », P(θ)).[89,90] Dans le contrôle sensori-moteur, la distribution finale (à postériori, P(θ|s)) d'un paramètre résulte donc de la connaissance à priori de ce dernier, issue souvent des expériences précédentes, et de l'influence des afférences sensorielles et efférences motrices, représentée par la vraisemblance (Figure 10).[77,87,88,90]

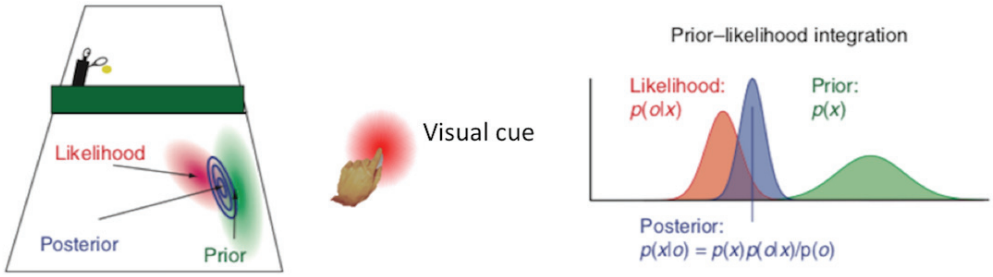

Figure 10. La théorie Bayésienne du contrôle sensori-moteur
(d'après Berniker et Kording, 2009).

La situation illustrée dans l'exemple est l'estimation du point d'impact d'une balle au tennis en fonction de l'entrée visuelle. Les ellipses représentent l'incertitude (bruit).

Le contrôle moteur est un processus dynamique. Lors d'un mouvement, l'estimation du système évolue en permanence dans le temps. Dans cette situation dynamique, l'estimation du système est classiquement modélisée au moyen du filtre adaptatif de Kalman.[77,79,87,89,90] C'est ainsi, qu'au signal d'erreur entre les conséquences sensorielles prédites et les afférences sensorielles actuelles va être ajouté un gain (dit optimal de Kalman) permettant de mettre à jour les prédictions issus des modèles « forward » et ainsi déterminer l'état estimé optimal (Figures 9 et 11).[4,59,75,77–79,86,91] Ce gain est déterminé selon une approche Bayésienne en fonction du bruit et des distributions de probabilité des signaux afférents et efférents.[86] Dans le filtre adaptatif de Kalman, les conséquences sensorielles prédites représentent la connaissance à priori (« prior ») et les afférences sensorielles actuelles la vraisemblance (« likelihood »). La distribution à postériori est l'estimation mise à jour du système (Figure 11). Le filtre adaptatif de Kalman comporte ainsi deux fonctions : la prédiction et la mise à jour. Il prédit un modèle de changement attendu dans l'état du système en fonction de la connaissance de l'état précédent (et des lois physiques), et met à jour cette prédiction selon les afférences sensorielles disponibles.[77,86,89,90,92]

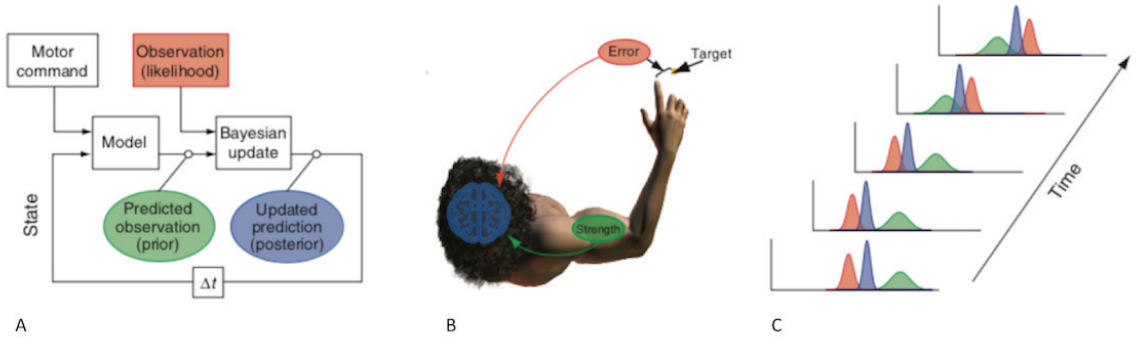

Figure 11. Le filtre adaptatif de Kalman (A) d'un système sensori-moteur (B) évoluant dans le temps (C) (d'après Berniker et Kording, 2009)

Pour réaliser un mouvement vers une cible, la croyance à priori de la force musculaire (vert) du sujet est combinée avec l'erreur motrice observée (rouge), qui renseigne sur la vraisemblance de la force musculaire du sujet, pour déterminer l'estimation mise à jour (bleu) à chaque étape du mouvement.

Le contrôle moteur doit s'adapter en permanence aux changements du système et de l'environnement, nécessitant un apprentissage des modèles internes. Le fait que l'écart entre la prédiction sensorielle et les afférences sensorielles actuelles constitue une erreur de prédiction qui permette l'estimation de l'état du système, représente d'une certaine manière, une forme d'apprentissage pour les modèles « forward ». Pour les modèles inverses, l'erreur entre l'état estimé et l'état désiré va induire par les centres de contrôle une commande motrice de correction qui va s'ajouter à la commande motrice produite par les modèles inverses. Cette commande motrice de correction peut être considérée comme un signal erreur permettant l'apprentissage (Figure 9).[78,79,84,93,94]

Ainsi, ces modèles internes assurent l'intégration des multiples afférences sensorielles et résolvent les conflits sensoriels.[59,60,63,65,68,77,91,92,95] Les processus de (re)pondération des afférences sensorielles évoqués précédemment (partie 1.2.4) seraient réalisés au niveau central selon un filtre adaptatif de Kalman.[63,65,67,68,91] Les poids des afférences sensorielles sont déterminés selon leur fiabilité respective, qui est la fonction inverse de la variabilité due au bruit (c'est à dire la variance du signal). Cette variabilité est représentée par la largeur de la distribution des probabilités (plus la largeur est grande, plus la fiabilité est petite). Ainsi la modalité avec le plus grand poids est celle contribuant avec le plus de fiabilité dans l'estimation du système. La combinaison des modalités s'avère bénéfique en cela qu'elle

réduit la variance de l'estimation comparativement à celle obtenue à partir d'une modalité sensorielle isolée (Figure 12).[77,87–89,96,97]

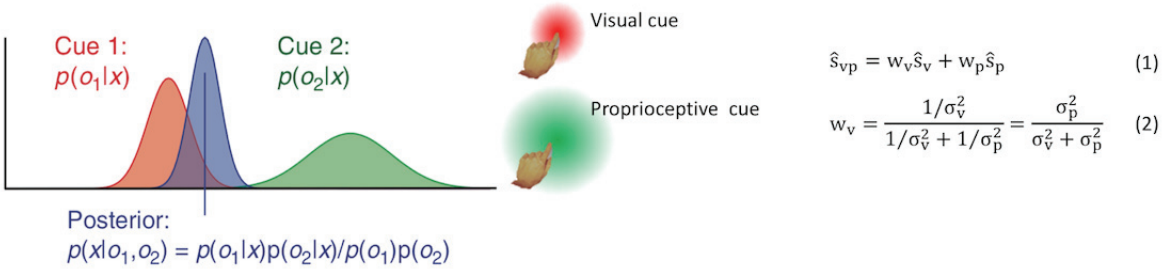

Figure 12. Combinaison des indices sensoriels selon l'approche bayesienne (d'après Berniker et Kording, 2009 ; Alais et Burr, 2019)

Chaque indice sensoriel (visuel (v) en rouge et proprioceptif (p) en vert) comporte un bruit, source d'incertitude (ellipse). La vraisemblance de l'information combinée (bleue) est la combinaison des vraisemblances de chaque indice. Avec des distributions gaussiennes, l'estimation du maximum de vraisemblance va combiner par une sommation linéaire pondérée chacune des modalités (équation 1 avec $\hat{s}$ la position spatiale et w le poids alloué à la modalité sensorielle). Le poids est calculé en fonction des variances (σ^2) de chacune des modalités (équation 2). Le maximum de vraisemblance de l'information combinée (bleue) est ainsi plus proche de celui de l'afférence visuelle (rouge) en raison de sa moindre variabilité (et donc de son poids plus élevé).

Les modèles internes assurent la construction des représentations spatiales nécessaires à la posture.[3,4,6,7,75,98,99] Apparu dans les années 1920, le schéma corporel postural est considéré comme la représentation interne de la géométrie du corps, des propriétés dynamiques du système et de la verticale gravitaire.[3,4,6,12,13,35,100–103] Le contrôle postural repose sur l'existence d'une telle représentation spatiale. Les afférences visuelles, graviceptives, vestibulaires, proprioceptives et cutanées contribuent à l'élaboration du schéma corporel postural par une intégration multisensorielle.[4,12,104,105] Comme le suggère les expériences en microgravité et sans entrée visuelle, il permet le maintien de l'orientation et la stabilisation posturales, malgré le changement majeur de contraintes.[12,13,29,32] Il assure une certaine représentation de la verticalité, même en l'absence d'information graviceptives. Le schéma corporel apparaît stable malgré les changements de conditions sensorielles.[100] De plus, il est à l'origine de l'établissement du cadre référentiel égocentré (voir sous-chapitre 1.4).[100,101]

Plus récemment, plusieurs travaux ont mis en évidence l'implication de modèles internes dans la perception de la verticalité et dans l'orientation posturale par rapport à la gravité tant chez l'animal que l'humain.[15,91,92,98]

Il est à noter que la terminologie de « modèles internes » ne semble pas recouvrir exactement les mêmes concepts selon les auteurs. Si certains auteurs restreignent ce concept aux seuls modèles inverses et modèles « forward »,[86] il semble, plus généralement, que ce terme soit utilisé pour évoquer l'ensemble des processus neurologiques qui, au niveau central, assurent des représentations neurales du corps et de l'environnement.[79,106] Ils permettent de simuler les comportements naturels en établissant des relations entre l'action et ses conséquences.[106]

1.4. LES CADRES REFERENTIELS SPATIAUX

Pour ses activités motrices ou perceptives, l'être humain a besoin d'une connaissance précise de la position et de l'orientation du corps mais aussi des objets placés dans son environnement. En physique mécanique classique, la position d'un objet est définie par rapport à un référentiel, espace stable dans lequel l'observation d'un mouvement ou la position d'un objet peut être décrite. La position d'un objet ou son mouvement ne peut être définie de manière absolue. Les organes sensorielles établissent les coordonnées spatiaux en fonction de leur caractéristique respective, définissant ainsi de multiples cadres référentiels spatiaux.[107] Classiquement, il est décrit deux grands types de référentiels spatiaux : le référentiel égocentré, dans lequel l'objet est situé par rapport au sujet ; et le référentiel allocentré, dans lequel l'objet est situé par rapport à une référence externe.[107,108]

1.4.1. Les cadres référentiels allocentrés

La gravité est une référence universelle et absolue qui définit la verticalité. Elle représente à la fois une contrainte externe et un référentiel. Dans ce référentiel gravitaire, la position spatiale des objets est indépendante de la position de l'observateur.

La perception de la verticalité est construite à partir de l'intégration des afférences vestibulaires, somesthésiques notamment proprioceptives et également visuelles par des modèles internes de verticalité. Bien que le système vestibulaire soit le système sensoriel spécifiquement en charge du codage de la gravité, il n'est pas suffisant pour déterminer la perception de la verticalité. Les afférences somesthésiques graviceptives à partir de gravicepteurs viscéraux situés autour des reins et des gros vaisseaux, proprioceptives, somesthésiques cutanées issues des capteurs de pression cutanée contribuent également à la perception de la verticalité.[15,39,56,57,98,109] En plus de cette organisation « bottom-up », les modèles internes de verticalité seraient influencés par les représentations spatiales et la perception de l'orientation corporelle, dans une approche « top-down ».[110] Chez l'être humain, la perception de la verticalité est très précise (de l'ordre de 1 degré),[15] et contribue à l'orientation posturale.[14,15,111]

Dans le référentiel visuel, les coordonnées spatiales d'un objet dans l'environnement sont définies à partir d'informations visuelles provenant de la rétine. Dans le cadre référentiel visuel, l'orientation et la position spatiales sont codées par des coordonnées rétiniennes. Le déplacement d'objet dans l'environnement est codé au moyen du défilement de la scène visuelle sur la rétine (flux visuel).[107] Le cadre référentiel visuel contribue de façon importante à l'établissement de la posture de certains individus comme en témoigne l'impact de leur dépendance visuelle sur la stabilisation posturale lors de perturbations.[33]

Alors que le référentiel gravitaire peut être considéré comme absolu, le référentiel visuel est, quant à lui, considéré comme relatif du fait qu'il définit la position spatiale d'un objet par rapport à un autre.

1.4.2. Les cadres référentiels égocentrés

Dans le référentiel égocentré, la position spatiale d'un objet est déterminée par rapport au sujet lui-même. Les principaux plans et axes du corps servent de repères. Dans un repère orthogonal, il existe 3 axes perpendiculaires entre eux et issus d'une même origine : L'axe Z qui s'étend de la tête au pied est confondu en position debout avec la direction de la

gravité ; l'axe Y allant de droite à gauche est contenu dans le plan horizontal ; et l'axe X allant d'avant en arrière est contenu dans le plan sagittal (Figure 13).

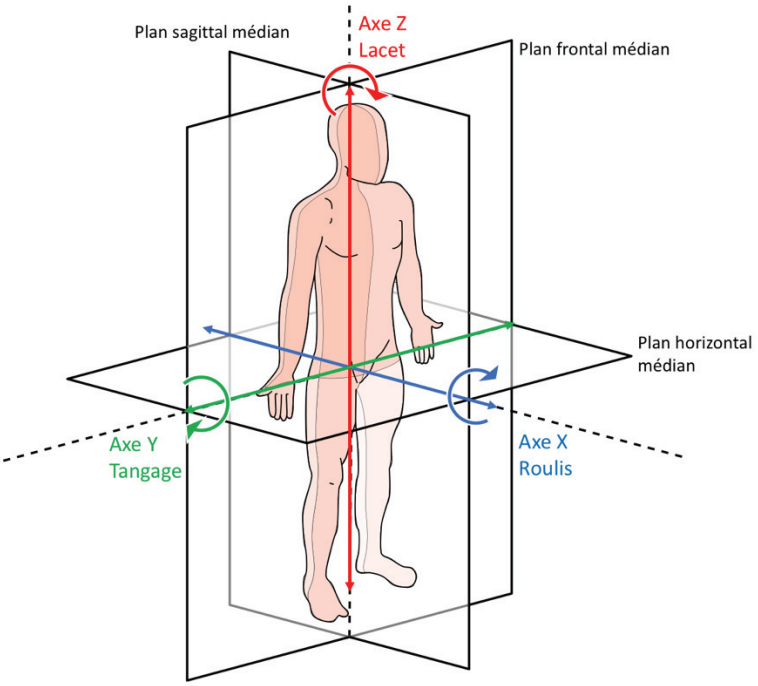

Figure 13. Les principaux plans et axes du corps en position debout
(d'après https://commons.wikimedia.org/wiki/File:Anatomical_Planes.svg)

Le référentiel égocentré est défini par la représentation interne d'un plan virtuel médian, qui est superposé au plan sagittal corporel, séparant le corps humain en deux moitiés identiques.[112] Ce plan médian permet ainsi de déterminer l'orientation (inclinaison par rapport au plan) et la localisation horizontale (position droite/gauche par rapport au plan) d'un objet par rapport à l'individu (estimation subjective). Le référentiel égocentré sert de base à l'organisation du comportement moteur orienté vers l'espace extra-personnel.[113,114] Il serait le résultat d'une construction cérébrale basée sur une intégration multi-sensorielle (visuelle, vestibulaire, somesthésique et proprioceptive) et pondérée par des facteurs individuels, comme la préférence individuelle en faveur d'une modalité sensorielle.[9,33,40,70,115–118]

Le référentiel égocentré peut être considéré comme le cadre de référence des cadres référentiels spatiaux. En effet, les cadres référentiels gravitaire et visuel contribuent à sa construction par les entrées vestibulaires, somesthésiques et visuelles,[42,43] et la construction de ce référentiel égocentré reste possible même en l'absence de ces deux référentiels

allocentrés, comme en témoigne les expériences d'impesanteur/microgravité et de suppression de l'entrée visuelle.[119] Par ailleurs, la position d'un objet dans l'espace est encodée dans le référentiel égocentré à partir de ses coordonnées dans les différents référentiels rétino-centré, céphalo-centré et tête sur tronc.[107,120] Cette perception visuelle égocentrée (c'est à dire par rapport au plan médian) est le résultat d'une transformation successive des informations visuelles à travers plusieurs systèmes de coordonnées. Tout d'abord, les afférences visuelles exprimées dans un système de coordonnées rétino-centré sont transformées dans un système de coordonnées céphalo-centré par leur combinaison avec les informations extra-rétiennes d'origine proprioceptive provenant des muscles oculomoteurs et informant de la position l'œil dans l'orbite et par rapport à la tête. Puis l'intégration des afférences proprioceptives cervicales permet un codage spatial dans un système de coordonnées tête sur tronc. Les indices sensoriels provenant du tronc seront intégrés pour aboutir à un système de coordonnées égocentré global.[107,120]

Cet emboitement des différents référentiels spatiaux pour construire un référentiel égocentré résulte des processus d'intégration des afférences sensorielles. L'utilisation d'un cadre référentiel spatial préférentiellement aux autres serait fonction des conditions et des objectifs à atteindre, mais également des caractéristiques individuelles.[33,40,70] Ceci impliquerait des modifications des pondérations sensorielles au niveau des processus d'intégration centraux, comme évoqués précédemment.[33,70] Cette capacité à changer de cadre référentiel spatial en fonction des conditions (par exemple lors de perturbations) permettrait d'assurer un meilleur contrôle postural.[33] En effet, Isableu *et al.* (2010) ont montré que les sujets dépendants visuels se basant sur le cadre référentiel visuel présentaient de plus grandes difficultés dans le maintien de leur orientation et leur stabilisation posturales lors de taches posturales plus contraignantes et lors de perturbations du cadre référentiel visuel, par rapport aux sujets non dépendants visuels utilisant d'autres cadres référentiels spatiaux construits sur les informations somesthésiques et vestibulaires.[33]

Dans la littérature, le cadre référentiel égocentré est abordé à travers plusieurs évaluations : l'axe longitudinal subjectif et le droit devant. Le premier est la perception qu'à le sujet de l'axe imaginaire allant du sommet de la tête au milieu de la distance séparant les pieds et représente l'axe corporel longitudinal.[115,121] Cet axe s'inscrit dans le plan sagittal

corporel médian et correspond à l'axe Z en position debout. Le droit devant est la perception qu'a le sujet de la direction du « juste devant soi » ou « droit devant soi », divisant l'espace en deux parties égales (droite et gauche). Le droit devant est souvent évalué en demandant au patient d'indiquer par une tache de pointage sur un plan horizontal le droit devant soi.[112] Droit devant (projection orthogonale de l'axe sagittal corporel médian vers l'avant) et axe corporel longitudinal (simple direction du plan médian) sont des représentations particulières du plan médian.

Après une lésion cérébrale, des troubles posturaux sont fréquemment retrouvés et vont affecter l'équilibre des patients. Ceci est notamment le cas après un accident vasculaire cérébral (AVC). L'objectif de la rééducation est de viser une récupération des déficits posturaux et des troubles de l'équilibre. Dans le chapitre suivant, une évaluation de l'efficacité des rééducations sur les troubles de la posture et de l'équilibre sera présentée. A cette occasion, il sera discuté du rationnel et des mécanismes sous-tendant d'éventuels effets notamment sur la base du cadre théorique du contrôle postural évoqué précédemment.

2. ASYMETRIE ET INSTABILITE POSTURALES APRES AVC

2.1. GENERALITES ET EPIDEMIOLOGIE

L'accident vasculaire cérébral (AVC) est un enjeu de santé publique majeur pour les sociétés et les systèmes de santé publique marqué par 12.2 millions nouveaux cas et 101 millions d'individus survivants en 2019 dans le monde.[122] Il s'agit de la seconde cause de mortalité mondiale.[122,123] Mais pour les patients survivants des suites immédiates d'un AVC, les séquelles sont fréquentes et souvent péjoratives en terme de fonction, d'activité et de participation. L'AVC est, en effet, la troisième cause de handicap acquis chez l'adulte.[124] Les couts humains, financiers et organisationnels qui en découlent sont majeurs.[123]

En France, 80.5% des patients ayant vécu un AVC déclarent une limitation légère ou majeure des activités de la vie quotidienne.[125] En Nouvelle-Zélande, environ un tiers des patients présentent une dépendance partielle ou totale dans leur activité de la vie quotidienne 5 ans après l'AVC.[126] Un trouble de l'équilibre est retrouvé chez 83% des patients atteints de séquelles d'AVC.[127] Dans la dernière enquête épidémiologique « Handicap-Santé » publiée en 2012 pour la période 2008-2009 et conduite tous les 10 ans en France en population générale,[128] 1354 des 1736 personnes avec antécédent d'AVC (78%) rapportaient une séquelle. Les troubles de l'équilibre (50.3%) était la séquelle la plus fréquente, suivie par les troubles de la mémoire (42.1%), puis de la parésie d'un ou plusieurs membres (37.2%).

Selon la classification internationale du fonctionnement et du handicap, les troubles de l'équilibre relèvent des limitations d'activité tandis que les troubles posturaux relèvent des déficits de fonctions (Figure 14).

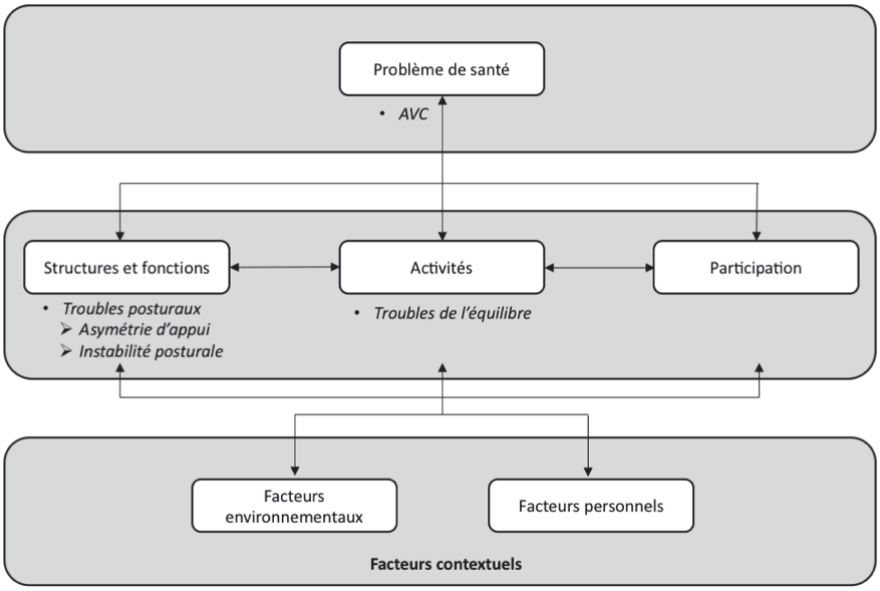

Figure 14. Les troubles posturaux et de l'équilibre dans la classification internationale du fonctionnement et du handicap

2.2. PHYSIOPATHOLOGIE DES TROUBLES POSTURAUX ET DE L'EQUILIBRE

Après un AVC, les patients peuvent présentent différents troubles posturaux comme une latéropulsion, une asymétrie d'appui du poids du corps sur les membres inférieurs et/ou une instabilité posturale. Conformément au modèle théorique de la posture présenté précédemment, ces troubles s'appréhendent différemment en termes d'orientation et de stabilisation posturales.

Alors qu'historiquement on considérait la latéropulsion comme l'inclinaison corporelle du patient dans le plan frontal et le syndrome de « pushing » comme l'addition à cette inclinaison d'une poussée active par le membre sain et d'une résistance à la correction passive, Dai *et al.* ont montré récemment que ces trois composantes posturales (inclinaison, poussée et résistance à la correction) correspondent à une seule et même entité, qui serait la latéropulsion, et dont la composante d'inclinaison corporelle serait la manifestation clinique cardinale.[14] Isolées ou associées, ces trois composantes constitueraient la latéropulsion. Également observée en cas de lésion vestibulaire ou du tronc cérébral, l'inclinaison corporelle est controlésionnelle après une lésion hémisphérique, que le sujet soit en position assise ou

debout.[15] Trois classes de patients pouvaient être distinguées selon leur score sur l'échelle « Scale for Contraversive Pushing » : « upright » pour les patients considérés sans latéropulsion, « tilters » avec une latéropulsion intermédiaire et enfin « pushers » avec une latéropulsion sévère. Les patients « tilters » et « pushers » répondaient à un gradient de sévérité sur les 3 signes cliniques que sont l'inclinaison, la poussée et la résistance à la correction.[14]

Définie comme une altération de l'orientation posturale par rapport à la gravité,[14,15,129] la latéropulsion controlésionnelle après AVC hémisphérique est la conséquence d'un modèle interne de verticalité erroné indiquant la verticale de référence inclinée vers l'espace controlésionnel.[14,15,98,130] En cherchant à s'aligner sur celle-ci, les patients s'inclineraient vers le côté opposé à la lésion cérébrale (voir chapitre 3). Retrouvée dans des proportions quasi-identiques dans les jours qui suivent une lésion droite ou gauche, une prédominance de la latéropulsion après AVC droit apparaît ensuite et augmente avec le délai post-AVC.[129,131,132]

Parmi les autres troubles posturaux consécutifs à un AVC, l'asymétrie d'appui se caractérise par une plus grande distribution du poids du corps en faveur du membre inférieur non-parétique (ipsilésionnel) que chez les sujets sains.[133,134] Il s'agit d'un déficit latéralisé fréquemment mesuré lors d'une posturographie assise ou debout. Malgré une réduction significative de 10% au cours des 4 premières semaines après l'AVC, l'asymétrie d'appui reste significative par rapport aux sujets sains 8 semaines après,[134] et persiste également à un stade chronique.[135–137] Il est à noter que les patients avec une lésion droite présente une asymétrie d'appui majorée comparativement aux patients avec une lésion gauche.[133]

Pour autant, l'ensemble des patients souffrant d'AVC ne présentent pas tous une asymétrie appui. Au stade chronique, celle-ci est retrouvée chez environ 60% des patients. Parmi ces patients considérés comme asymétriques, 80% appuient plus sur leur membre inférieur non-parétique alors que chez les 20 autres pourcents, l'asymétrie est en faveur du membre inférieur parétique.[137] Par une analyse des corrélations avec les autres paramètres cliniques, Mansfield *et al.*[137] ont mis en évidence que ces patients « asymétriques » (que ce soit en faveur du membre inférieur parétique ou non-parétique) présentaient les lésions les plus sévères et les déficits moteurs les plus importants comparativement aux patients « symétriques ». En revanche, ils n'ont pas mis en évidence de différence significative entre

les patients présentant une asymétrie en faveur du coté non-parétique et ceux avec une asymétrie en faveur du coté parétique.[137]

Les troubles posturaux relatifs à la stabilisation posturale sont également fréquemment retrouvés après un AVC. Par rapport aux sujets sains, ils se caractérisent par une oscillation corporelle plus importante lors d'une évaluation posturographique.[133,134,138–140] Bien que l'instabilité posturale régresse partiellement dans les 12 premières semaines après l'AVC, elle persiste par la suite comparativement aux sujets sains.[134] Il est à noter également que les patients avec une lésion droite présentent une oscillation corporelle majorée par rapport aux patients avec une lésion gauche.[133,141] De plus, l'instabilité posturale est dépendante des entrées sensorielles : Elle est, par exemple, majorée en cas de fermeture des yeux.[134] Après lésion cérébrale, les patients présentent pour assurer la stabilité posturale une dépendance excessive à une modalité sensorielle, le plus souvent l'entrée visuelle en fonction d'une préférence indivuelle.[142–144]

Les caractéristiques de l'instabilité posturale diffèrent selon le membre inférieur étudié. Les déplacements du centre de pression sont plus importants sous le membre inférieur non-parétique tandis que le pattern de ces déplacements sous le membre parétique est plus restreint selon l'axe longitudinal (antéro-postérieur) du pied.[139]

Alors que la stabilité posturale vise à fournir une base de stabilité pour réaliser un mouvement, il est fréquemment observé après un AVC un retard et une réduction des ajustements posturaux anticipateurs et des réactions posturales, que cela soit au niveau des membres inférieurs que du tronc.[145–150] La conséquence est une altération du pattern de déplacement du centre de pression par rapport aux sujets sains lors des mouvements volontaires ou des perturbations externes, qui se caractérise notamment par une réduction des limites de stabilité.[146]

Comme nous l'avons vu précédemment, l'asymétrie d'appui est un déficit latéralisé commun après un AVC. Mais un débat existe sur la manière de considérer ce type de déficit dans le cadre du modèle théorique de la posture. Cela pose la question des déterminants de cette asymétrie posturale. Est-elle un déficit indépendant constitutif des troubles posturaux post-AVC ou en est-elle une conséquence directe ou indirecte ?

Alors que plusieurs études ont suggéré que l'asymétrie d'appui pouvait être un trouble postural résultant de perturbations de la cognition spatiale,[46,133,151,152] d'autres ont suggéré, plus récemment, qu'il s'agissait d'une stratégie compensatrice pour réduire l'instabilité posturale.[139,153–156] Les déterminants de l'asymétrie d'appui s'avèrent complexes et sont probablement intriqués. La première hypothèse repose sur l'implication des cadres référentiels égocentrés et une possible relation avec la négligence spatiale unilatérale. Elle sera étudiée dans le chapitre 3 de la thèse.

Quant à la seconde hypothèse, elle est le résultat d'une analyse biomécanique des troubles posturaux séparant les contributions de chacun des membres inférieurs à la stabilisation posturale.[139,153–156] Avec cette méthode, il est observé une asymétrie des « patterns » de déplacement du centre de pression sous chaque pied caractérisée par une projection plus antérieure et une réduction des déplacements du centre de pression selon l'axe longitudinal du pied du membre inférieur parétique par rapport au membre non-parétique.[139] Cela signerait une diminution de la participation du membre inférieur parétique à la stabilisation posturale. Lors de mouvements de déstabilisations, Van asseldonk *et al.*[153] rapportaient également une asymétrie de contribution des membres inférieurs à la stabilisation posturale après un AVC, marquée par une plus faible contribution du membre parétique. Cette asymétrie était plus prononcée chez les patients présentant une plus grande asymétrie d'appui. Alors qu'une relation très proche était observée entre les contributions du membre inférieur parétique à la stabilisation posturale et à la distribution du poids du corps en dynamique (c'est à dire lors de déstabilisations) chez les sujets sains (ß=1.15, $p<0.001$, $R^2=0.97$), elle n'était pas retrouvée chez les patients atteints d'AVC (à noter la présence d'un « outlier » sur un effectif de 8 patients), chez qui le membre parétique contribuait moins à la stabilisation posturale qu'à la distribution du poids du corps en dynamique.[153] Cette moindre contribution du membre parétique à la stabilisation posturale comparativement à sa contribution sur la distribution du poids du corps lors d'une déstabilisation témoignerait que la contribution du membre parétique à la stabilisation posturale n'est pas le simple reflet de la distribution du poids du corps. Ainsi la mise en charge du poids sur le membre parétique après un AVC ne s'accompagnerait pas d'une plus grande contribution de celui-ci à la stabilisation posturale comme c'est le cas chez les sujets sains. Les auteurs suggéraient donc que l'asymétrie d'appui relèverait d'une stratégie de compensation pour assurer la stabilité.

Chez de Kam *et al.*,[156] les patients les plus asymétriques (0, 10 et 20% d'appui en plus sur le membre non-parétique) montraient une plus grande capacité à maintenir leur équilibre avant de devoir faire un pas (« stepping threshold ») lorsqu'ils étaient soumis à des déstabilisations externes en direction du coté parétique, en position debout statique. Roelof *et al.*[154] ont également retrouvé une asymétrie de contribution des membres inférieurs à la stabilisation posturale, qui était ici, modérément corrélée à l'asymétrie d'appui du poids, en position debout statique. De plus, ils ont montré qu'un déficit moteur sévère (Fugl-Meyer assessment [FMA] <24 points) résultait toujours en une asymétrie importante de contribution des membres inférieurs à la stabilisation posturale sans que l'inverse ne soit systématiquement vrai. En effet, 21% des patients présentaient toujours une asymétrie de contribution des membres inférieurs à la stabilisation posturale élevée malgré un bon niveau de motricité des membres inférieurs (FMA $\geq$ 24). Les auteurs ont ainsi proposé un modèle dans lequel l'asymétrie d'appui serait une compensation de la moindre contribution du membre inférieur parétique à la stabilisation posturale, notamment sur l'axe antéropostérieur. En outre, Rougier et Pérennou[155] ont montré en 2019 que la distribution du poids du corps sur les membres inférieurs serait une stratégie qui se déroulerait dans le plan frontal en mettant en jeu les muscles des hanches pour venir compenser le déficit plus important d'une autre stratégie, celle de répartition de la pression au niveau du pied dans le plan sagittal reposant sur la mise en jeu des chevilles. Ainsi ces études tendent à démontrer une origine compensatrice à l'asymétrie d'appui après AVC. En raison du caractère multifactoriel de la posture, une intrication de plusieurs déterminants est probable et justifie la poursuite des investigations.

L'évaluation de l'asymétrie d'appui et de l'instabilité posturale repose généralement sur l'utilisation de plateformes de force conçues pour mesurer l'évolution temporo-spatiale du centre de pression, qui est le point d'application de la résultante des forces de réaction du sol. Cette évaluation instrumentale repose donc sur la mesure des forces de réaction du sol et des moments de force. Les conditions de mesures d'une posturographie peuvent varier : le patient peut être assis ou debout, la plateforme peut être statique ou mobile. Il existe une diversité de paramètres de mesures en fonction notamment du matériel utilisé et des fabricants. Classiquement, les paramètres sont catégorisés selon qu'ils reflètent la position

(position moyenne du centre de pression et asymétrie d'appui) ou le déplacement et la trajectoire du centre de pression (surface d'oscillation, vitesse, variabilité, longueur de déplacement …). La plupart des paramètres peuvent se décliner sur l'axe antéropostérieur ou médiolatéral du corps.

L'asymétrie d'appui du poids du corps sur les membres inférieurs peut être convertie en position médiolatérale moyenne du centre de pression car ce sont deux paramètres d'un même déficit latéralisé.[157] Plusieurs travaux ont évalué les qualités métrologiques de la posturographie chez des patients atteints d'AVC et rapportaient une fiabilité modérée à excellente selon les paramètres.[158,159] Les résultats plaidaient pour la réalisation de 2 à 3 essais par condition afin d'atteindre la plus grande fiabilité. Le paramètre le plus fiable était la vitesse d'oscillation du centre de pression, avec une fiabilité maximale atteinte dès le premier essai.[159] L'utilisation de deux plateformes séparées (une sous chaque pied) est nécessaire pour évaluer la contribution de chacun des membres inférieurs à la stabilisation ou l'asymétrie d'appui. Chez les patients atteints d'AVC, plusieurs des paramètres de posturographie étaient bien corrélés (r>0.8) avec les échelles cliniques d'équilibre ou de marche (« Berg Balance Scale » et « Time Up and Go Test »).[160]

2.3. IMPACTS FONCTIONNELS

Dans le cadre du modèle théorique de la posture, les fonctions d'orientation posturale par rapport à la gravité et de stabilisation posturale par rapport à la base de support ont pour objectif final d'assurer l'équilibre nécessaire à la station debout, la marche ou la réalisation de mouvements. La conséquence directe des troubles posturaux est donc une perturbation de l'équilibre.

Dans une étude récente sur 220 sujets,[129] Dai *et al.* ont montré que la latéropulsion était le facteur le plus fortement associé aux troubles de l'équilibre, au stade subaigu de l'AVC. Après lésion droite, la latéropulsion expliquait l'essentiel des troubles de l'équilibre à l'entrée comme en sortie de rééducation (en moyenne 81 jours après). Dans une autre étude portant sur 293 patients au stade aigu de l'AVC, la latéropulsion mesurée très précocement (3 jours

après la lésion) était un prédicteur indépendant de la capacité de tenir assis à la sortie (23 jours après la lésion).[161] La sévérité de la lésion cérébrale et l'âge des patients étaient également des prédicteurs indépendants.

En ce qui concerne l'asymétrie d'appui en position assise, elle était retrouvée hautement corrélée avec l'équilibre, mesuré par la « Berg Balance Scale », un mois après la survenue de l'AVC.[162] L'instabilité posturale impacterait également l'équilibre. En effet, elle serait, en plus de l'âge au moment de la survenue de l'AVC, un prédicteur du risque de chute.[163]

Les troubles de l'équilibre sont une préoccupation majeure en rééducation post-AVC. Ils sont fréquemment retrouvés après une lésion cérébrale[127,164–166] et constituent d'ailleurs la séquelle la plus souvent rapportée par les patients.[128] Le stade ultime des troubles de l'équilibre est la chute, signant l'incapacité de tenir la station érigée. Plus d'un quart des patients ont chuté au moins deux fois durant la première année de leur AVC (Cohorte « FallsGOT » sur 348 participants entre octobre 2014 et juin 2016).[164] Les troubles de l'équilibre constituent des facteurs de risques de chutes importants.[164,167,168] Cette cohorte « FallsGOT » a mis en évidence que les troubles de l'équilibre d'intensité modérée et sévère, sur l'échelle « Postural Assessment Scale for Stroke patients », au 4^{ieme} jour après l'admission étaient des déterminants indépendants du nombre de chutes à un an. L'impact de ces troubles de l'équilibre est donc majeur pour les patients.

Les troubles posturaux et de l'équilibre consécutifs à un AVC impactent également la marche des patients. En effet, la latéropulsion était le facteur indépendant le plus fortement associé aux troubles de la marche au stade subaigu de l'AVC.[129] Après lésion droite, la latéropulsion expliquait même l'essentiel des déficits de marche rencontrés au stade subaigu. D'autres auteurs ont montré que la limite de stabilité (paramètre reflétant la stabilisation posturale) évaluée en position assise un mois après l'AVC était un facteur prédictif indépendant de la capacité de marche à 2 mois.[162] L'asymétrie d'appui du poids du corps debout impacterait, elle aussi, la marche. Deux publications ont, en effet, rapporté des corrélations statistiques significatives entre l'asymétrie d'appui et certains paramètres de marche lors d'une analyse quantifiée de la marche (comme le « Gillette Gait Index » reflétant

les perturbations globales, la symétrie de la phase oscillante, la symétrie de la phase d'appui, la symétrie de la longueur des pas, ou la vitesse de marche).[169,170] Par ailleurs, l'asymétrie d'appui et l'indépendance de la marche étaient significativement corrélées.[151] A un stade subaigu de l'AVC, le franchissement de façon indépendante d'un obstacle lors de la marche était le mieux prédit par la capacité de transfert de l'appui du poids du corps sur le membre inférieur parétique en position debout, avec une valeur optimale à 80.5% d'appui du poids du corps sur le dit membre.[171]

Tenir l'équilibre assis de façon indépendante à l'admission en rééducation était corrélé avec une indépendance dans la marche en sortie de rééducation (en moyenne 6 à 7 semaines après).[172,173] De plus, l'équilibre assis au stade aigu était un prédicteur indépendant de la mobilité globale (mesurée par le « Rivermead Mobility Index ») à un an de l'AVC.[174] Plus globalement, les troubles de l'équilibre sont fréquemment associés aux troubles de la marche, quel que soit le stade de l'AVC.[151,175–178] L'équilibre au stade précoce (mesuré par la « Berg Balance Scale ») était identifié comme un facteur prédictif de la récupération de la marche.[179,180] L'amélioration des troubles de l'équilibre debout semblerait plus importante pour récupérer la marche que l'amélioration de la force ou du déficit moteur du membre inférieur parétique.[181]

En terme d'activité et de participation, l'asymétrie d'appui est significativement corrélée avec l'indépendance dans les activités de la vie quotidienne au stade subaigu (r=-0.35)[182] et avec la qualité de vie au stade chronique (r=-0.55).[183] Au-delà des troubles posturaux, les troubles de l'équilibre impactent nettement le niveau d'activité et de participation des patients mais également leur qualité de vie.[183–188]

Les conséquences fonctionnelles des différents troubles posturaux et des troubles de l'équilibre sont souvent évaluées séparément. Il n'y a pas d'étude, à ma connaissance, qui a tenté de démêler leur contribution relative au moyen d'analyses multivariées. L'origine probablement multifactoriel de certains troubles posturaux comme l'asymétrie d'appui complique cette analyse. Corrélation ne signifiant pas nécessairement causalité, il est nécessaire de rester prudent quant à l'interprétation des études. Le recours à des analyses multivariées est à privilégier en prenant soin d'éliminer toute colinéarité statistique, et ce avec

l'appui de modèles théoriques étayés. Par ailleurs, il est raisonnable de penser que l'impact des troubles posturaux varie en fonction du stade de l'AVC. L'impact de l'asymétrie d'appui sur la marche, l'indépendance dans les activités de vie quotidienne et la qualité de vie serait peut-être à appréhender à travers celui des autres troubles posturaux, comme la latéropulsion ou l'instabilité posturale par exemple, et selon l'ancienneté de l'AVC.

2.4. REEDUCATION

En raison de leur fréquence et de leur retentissement fonctionnel, la rééducation des troubles de la posture et de l'équilibre est un objectif prioritaire de la prise en charge des patients après AVC. Elle occupe une partie importante de la rééducation. De multiples approches sont utilisées par les cliniciens, dans un contexte où les recommandations de bonnes pratiques sont peu nombreuses, souvent limitées et partielles.[189] Il apparaît pertinent d'évaluer les effets de ces différentes rééducations pour améliorer l'efficacité des soins mais également afin de contribuer à la compréhension des mécanismes d'action dans le cadre des modèles du contrôle postural.

L'évaluation des effets des rééducations sur les troubles posturaux et de l'équilibre après un AVC a reposé sur un programme de revues systématiques de la littérature et de méta-analyses ayant abouti à plusieurs publications dans des journaux scientifiques internationaux à comité de lecture :

1. Un « study protocol » : **Hugues A**, Di Marco J, Janiaud P, Xue Y, Pires J, Khademi H, Cucherat M, Bonan I, Gueyffier F, Rode G. Efficiency of physical therapy on postural imbalance after stroke: study protocol for a systematic review and meta-analysis. BMJ Open. 2017 Jan 30;7(1)

2. Une publication des résultats : **Hugues A**, Di Marco J, Ribault S, Ardaillon H, Janiaud P, Xue Y, Zhu J, Pires J, Khademi H, Rubio L, Hernandez Bernal P, Bahar Y, Charvat H, Szulc P, Ciumas C, Won H, Cucherat M, Bonan I, Gueyffier F, Rode G. Limited evidence of physical

therapy on balance after stroke: A systematic review and meta-analysis. PLoS One. 2019 Aug 29;14(8)

3. Une analyse secondaire portant sur l'impact de la langue de publication sur l'estimation des effets et la qualité méthodologique des études : **Hugues A**, Di Marco J, Bonan I, Rode G, Cucherat M, Gueyffier F. Publication language and the estimate of treatment effects of physical therapy on balance and postural control after stroke in meta-analyses of randomised controlled trials. PLoS One. 2020 Mar 9;15(3)

Une autre publication scientifique portant sur l'évaluation des effets « bottom-up » et « top-down » des rééducations après AVC par méta-analyse en réseau a été soumise mais refusée par la revue avec possibilité de resoumettre Sur la base des commentaires des « reviewers », l'article a été entièrement retravaillé et figure en version de pré-soumission dans la thèse. Une mise à jour de l'interrogation des bases de données, en cours, est nécessaire avant re-soumission.

Une revue narrative intitulée « Rééducation de l'équilibre du patient cérébrolésé après AVC » a été conduite en collaboration avec M. Thibaut Ferreux et le Pr Alain Yelnik (respectivement MKDE et PU-PH, Médecine Physique et de Réadaptation, Assistance Publique des Hôpitaux de Paris) pour figurer comme chapitre d'un ouvrage (intitulé « Troubles de l'équilibre : aspects sensoriels ») dirigé par le Pr Alain Yelnik. Cette revue a été soumise et acceptée. L'ouvrage est actuellement sous presse (éditeur : Masson). Ce chapitre a pour objectif d'intégrer les éléments de preuves scientifiques avec la pratique clinique à des fins pédagogiques pour des cliniciens.

Les tables, les figures et les références bibliographiques mentionnées dans le manuscrit en format de « pré-soumission » et le chapitre d'ouvrage sont répertoriées à la fin de chacun (à la manière des articles soumis). Le matériel supplémentaire des articles publiés, du manuscrit en format de « pré-soumission » et du chapitre d'ouvrage est reporté en annexe de la thèse.

2.4.1. Article 1

Open Access Protocol

BMJ Open

Efficiency of physical therapy on postural imbalance after stroke: study protocol for a systematic review and meta-analysis

A Hugues,[1,2,3] J Di Marco,[4] P Janiaud,[5] Y Xue,[6] J Pires,[7,8] H Khademi,[9] M Cucherat,[5] I Bonan,[10] F Gueyffier,[5,11] G Rode[1,2,3]

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This protocol study has been presented at the 9th World Congress for NeuroRehabilitation in Philadelphia (USA) from 10 to 13 May 2016 (http://wcnr2016.org/).

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ABSTRACT

Introduction: Stroke frequently results in balance disorders, leading to lower levels of activity and a diminution in autonomy. Current physical therapies (PT) aiming to reduce postural imbalance have shown a large variety of effects with low levels of evidence. The objectives are to determine the efficiency of PT in recovering from postural imbalance in patients after a stroke and to assess which PT is more effective.

Methods and analysis: We will search several databases from inception to October 2015. Only randomised controlled trials assessing PT to recover from poststroke postural imbalance in adults will be considered.

Outcome measures will be the Berg Balance Scale (BBS), the Postural Assessment Scale for Stroke (PASS), the 'weight-bearing asymmetry' (WBA), the 'centre of pressure' (COP) and the 'limit of stability' (LOS). WBA, COP and LOS are measured by a (sitting or standing) static evaluation on force plate or another device.

Two independent reviewers will screen titles, abstracts and full-text articles, evaluate the risk of bias and will perform data extraction. In addition to the outcomes, measures of independence will be analysed. This study will aim at determining the effects of PT on the function (WBA, COP, LOS), the activity (BBS, PASS) and the independence of patients. Subgroup analyses will be planned according to the location of brain lesion (hemispheric, brainstem or cerebellum), the time since stroke (early, late, chronic), the PT (type, main aim (direct effect or generalisation), overall duration), the type of approaches (top-down or bottom-up) and the methodological quality of studies.

Ethics and dissemination: No ethical statement will be required. The results will be published in a peer-reviewed journal. This meta-analysis aims at managing the rehabilitation after postural imbalance by PT after a stroke.

Trial registration number: Prospero CRD42016037966; Pre-results.

Strengths and limitations of this study

- To the best of our knowledge, there are few systematic reviews and meta-analyses in the literature that assess the evidence of physical therapies (PT) for rehabilitation of postural imbalance after a stroke.
- This study will compare the efficiency of all PT used after a stroke to one another.
- A series of subgroup analyses will address relevant clinical issues.
- There are several outcomes to assess postural imbalance (function and activity) that may limit comparison across studies.
- The results of this meta-analysis will be helpful for clinicians to define rehabilitation strategies for improving postural imbalance after stroke.

INTRODUCTION

Background

A stroke is defined as 'rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin'.[1] Stroke is the third cause of death and the first cause of acquired adult disability in the world (WHO). In the USA, 795 000 people suffer from a stroke every year.[2] Stroke leads to a long-term limitation of activity and disability. In France, 80.5% of the people with self-reported stroke declare a limitation (light or severe) in activities of daily living (ADL) and one in three stroke survivors are dependent.[3] In New Zealand, 71% of 5 years poststroke patients present a neurological impairment, assessed by the National Institutes of Health Stroke Scale. A restriction of activity was present in 31.4% of the patients assessed by the Modified Rankin Scale and in 35.4% assessed by the Barthel Index (BI).[4] Among limitations of activity, the postural imbalance is frequently found. Eighty-three per cent of patients with acute stroke present a postural imbalance.[5] The risk of fall is increased by 73% in the 6 months following a stroke.[6] At a chronic

stage, the quality of life is associated with the postural imbalance.[7] Postural rehabilitation seems to be crucial to achieve independence in ADL after stroke.

Human posture refers to the relative disposition of body parts.[8] Postural control aims to maintain body stabilisation based on a sensorimotor complex skill and body orientation, based on internal representation of body scheme.[9 10] Postural imbalance following stroke is defined by: (1) a larger weight-bearing asymmetry (WBA) toward the unaffected limb, in a quiet standing posture;[11–18] (2) an increased body sway of the centre of the pressure (COP);[12 13 15 19] (3) a decrease in the limits of stability (LOS);[12 20] (4) an excessive reliance on visual input[21–24] and (5) an impairment of anticipatory postural adjustments and postural reactions after external perturbations.[25 26]

State of the art

Different physical therapies (PT) aim at reducing postural imbalance. Current recommendations are limited for daily clinical practice: the level of evidence is too low and it is based on few systematic reviews and meta-analyses. The recommendations in the French evidence-based clinical practice guidelines for PT in patients after stroke were based on only 16 clinical studies.[27] Furthermore, these guidelines are not specific to postural disability and propose a rather global rehabilitation.[28 29] It is therefore necessary to assess the efficiency of PT in the recovery of postural control after stroke.

Regarding the literature, some meta-analyses have evaluated the effects of a single technique on postural imbalance like balance training using a platform with biofeedback,[30] functional electrical stimulation,[31] repetitive task training,[32] water-based exercises,[33] virtual reality,[34–36] ankle-foot orthosis,[37] aerobic exercises,[38] physical fitness training[39] or whole body vibration.[40 41] In view of the tremendous growth in the number of randomised controlled trials, it seems to be essential to evaluate one PT compared with another or the association of PT compared with control or usual care. Veerbeek *et al*[42] have evaluated the effects of PT after stroke on all outcomes based on the International Classification of Functioning, Disability and Health (ICF) and not only the balance. Pollock *et al*[43] have investigated the function and mobility recovery by PT after stroke. Compared with previous studies, the aim of this systematic review and meta-analysis is to perform a review only focused on the effects of PT on postural imbalance after stroke with identification of different parameters.

Finally, in this review and meta-analysis, we also propose to categorise the different PT according to the involved 'top-down' and 'bottom-up' processing. This processing refers to two types of interaction between sensorimotor (implicit) and cognitive (explicit) representations involved in rehabilitation. Top-down approach aims at training the patient to voluntarily compensate for his deficit and requires awareness of the disorder although bottom-up approach does not require awareness of the disorder. This categorisation has already been used in a previous Cochrane meta-analysis about cognitive rehabilitation for another spatial cognition deficit (spatial neglect).[44–46]

OBJECTIVES

The aims are: (1) to determine the efficiency of PT on the recovery of postural imbalance in adult patients after stroke and (2) to assess which PT is more effective when compared with one another.

METHODS

We will use the guide from The Cochrane Collaboration entitled 'Cochrane Handbook for Systematic Reviews of Interventions' (V.5.1.0)[47] and the software (RevMan 5.3) to construct this meta-analysis. The recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement will also be followed.([48]) No ethical statement will be required for this review and meta-analysis. Results of this research will be published. These results will contribute to improve the therapeutic strategy of patients with stroke.

Criteria for considering studies for this review

Type of studies

We will include all randomised controlled trials. The allocation between two or several groups will have to be correctly randomised. Trials without control group or those with quasi-random allocation will be excluded.

Types of participants

We will include all trials which have included human adult patients (over 18 years old) after a first or recurrent stroke. Stroke is defined, according to the WHO, as 'rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin'.[1] Therefore, the positive diagnosis is based on clinical examination. It is not compulsory to include the imaging diagnosis. Transient ischaemic accidents (TIAs) will be excluded because all neurological symptoms disappear ('TIAs are brief episodes of neurological dysfunction resulting from focal cerebral ischaemia not associated with permanent cerebral infarction.').[49]

Types of interventions

The selection process will not be based on the type or the nature of the PT in trials. We will select all trials assessing a PT whatever it may be and whatever its aim (upper limb, lower limb, posture, gait, spasticity and so on). This meta-analysis will not be limited to PT, the direct and immediate objective of which is to reduce postural imbalance. This possible expansion or generalisation of effects may be observed after intervention in rehabilitation.

The PT is defined by the World Confederation for Physical Therapy (WCPT) as 'services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan' and 'physical therapy is concerned with identifying and maximising quality of life and movement potential within the spheres of promotion, prevention, treatment/intervention, habilitation and rehabilitation' (http://www.wcpt.org/policy/ps-descriptionPT).

Types of outcome measures

Outcomes will be selected following the recommendations of the ICF. Immediate outcomes after the end of PT and delayed outcomes after a follow-up time will be included.

Primary outcomes

The Berg Balance Scale (BBS) assesses the functional postural abilities of patients in several conditions (lying on the back, sitting, standing, leaning forward, change of position and so on). This scale is composed of 14 items. The maximal score, reflecting the best functional postural abilities, is 56 points. The choice of the scale is based on its validation in patients with stroke and on its good metrological qualities, making it a reference scale.[50–54]

The Postural Assessment Scale for Stroke (PASS) also evaluates the functional postural abilities of patients with stroke in several conditions (lying on the back, sitting, standing and while changing (these) positions). This scale is composed of 12 items. The maximal score, reflecting the best functional postural abilities, is 36 points. Its metrological qualities are good, particularly during the first 3 months.[55 56]

The two scales exhibit a clinical relevance in assessment of postural imbalance in patients with stroke. They express the level of activity. Therefore, measured changes reflect modifications of postural abilities of patients in daily living.

The outcomes pertaining to balance and postural control will be the WBA, the COP and the LOS. These parameters will be measured by a (sitting or standing) static evaluation on force plate or another device.[17 51 52]

Secondary outcomes

The outcomes will be the BI, the Functional Independence Measure (FIM), the scale for instrumental activities of daily living (IADL) and the scale for ADL, reflecting the level of autonomy.

Only the primary outcomes will be considered for selection of trials.

Search methods for identification of studies

We will search the following electronic bases from their inception to October 2015: Medline, Embase, PEDro, Cochrane Central Register of Controlled Trials, Pascal and Francis. The search strategy will involve three kinds of terms: 'stroke', 'posture' and 'physical therapy'. This search strategy is described in table 1.

All published and unpublished studies, conferences or presentations will be searched without restriction in languages. The library services of three universities (Université Claude Bernard Lyon1, Université Paris 5 Descartes and Université Paris 6 Pierre et Marie Curie) and two hospital centres (Hospices Civils de Lyon, Assistance Publique-Hôpitaux de Paris) will be requested to access the unpublished and published documents.

Data collection and analysis

Selection of studies

The process of selecting the search results will be carried out on the basis of the selection criteria in three successive steps: (1) by reading the titles, (2) by reading the abstracts and then (3) by reading the full texts. Each one of these steps will be separately performed by two

Table 1 Search strategy in PubMed

1	exercise movement techniques OR physical therapy modalities OR learning OR pract* OR train* OR rehabilitation* OR therapeutic* OR therapy OR therapies OR exercise* OR physiotherap* OR neurorehabilitation OR neurophysiological OR orthopaed* OR treatment OR approach* OR concept OR home rehabilitation OR self-guided program* OR fitness OR stretching OR sport OR program* OR movement OR protocol* OR intervention OR activit* OR regim* OR recovery
2	(occupational OR physical OR manual) AND (therapy OR therapies OR therapist OR therapeutic OR therapeutics)
3	#1 OR #2
4	posture OR equilibrium OR balance OR postural balance OR weight bearing OR weight shift OR lateropulsion OR pusher OR pushing OR postural imbalance OR postural asymmetry OR postural control OR postural stability OR postural instability OR postural perturbation OR postural disorders OR postural deficit OR postural trouble OR postural sway OR postural tilt OR postural shift OR body sway OR upright stance OR (weight AND (distribut* OR transfer*))
5	(cerebrovascular OR cerebro-vascular OR cerebral OR intracran* OR hemispheric) AND (accident OR hemorrhag* OR haemorrhag* OR infarct* OR ischemi* OR thrombotic OR thrombosis OR emboli* OR hematoma OR haematoma OR bleed OR damage OR lesion OR occlus*)
6	stroke OR poststroke OR post-stroke OR hemipleg* OR hemipar* OR paretic OR paresis OR CVA
7	(right OR left) AND brain AND (lesion OR damage)
8	#5 OR #6 OR #7
9	meta-analysis OR review* OR animal* OR child* OR cerebral pals* OR case-report OR traumatic brain injury
10	#3 AND #4 AND #8 NOT #9

independent authors (AH and JDM). For the selection on the basis of titles, all studies, selected by one of these two authors, will be accepted for the next step of the selection process. For the two subsequent steps of selection, an agreement between the two authors will have to be found. In case of disagreement, three more authors (IB, FG, GR) will have to decide by consensus. The authors of the trials will be contacted if information needed for the selection process is unclear or missing.

The studies published in journals judged as stand-alone according to the analysis of Jeffrey Beall (https://scholarlyoa.com/individual-journals/), which is based on objective and clearly identified criteria (https://scholarlyoa.files.wordpress.com/2015/01/criteria-2015.pdf), will be excluded.

Cross-over trials will be included if: (1) the order of interventions has been randomised and if (2) the potential effects of the first intervention have not impacted the potential effects of the second one. They will be considered as randomised controlled trials. Moreover, some cross-over trials can present a special design: a single assessment during the intervention instead of an assessment before and one after, as is usually the case. These types of design are specifically used for some types of intervention (orthosis and so on). These cross-over trials will be included if: (1) the conditions set above regarding cross-over trials are validated (the randomised order and the absence of impact of the first intervention on the second one) and if (2) a spontaneous recovery is not possible during the time between the two interventions.

No study will be excluded because of the language of the report. Those written in languages other than French or English will be translated by the authors: YX for those written in Chinese, HK for those written in Persian, JP for those written in Portuguese.

Data extraction and management

Data extraction will be carried out independently by two authors (AH and JDM). Agreement between these two authors will have to be found. In case of disagreement, three more authors (IB, FG, GR) will have to decide by consensus. The authors of included trials will be contacted if some data are unclear or missing. Data extraction will include:

1. the design of study;
2. the details of the population: size of the population, age, gender, time since stroke, side of the paresis, unilateral or bilateral stroke, first ever or the recurrent stroke, the imaging diagnostic with the aetiologic and the localisation of stroke lesions;
3. the methodological quality of trials: details of random process, blinding, dropout, reporting and others;
4. the PT: overall duration of PT, the aims and the most important characteristics of each PT;
5. the outcomes: all outcomes measured and specifically the BBS, the PASS, the WBA, the COP, the LOS, the BI, the FIM, the IADL and the ADL will also be extracted;
6. the prior submission to an ethics committee or the respect of the declaration of Helsinki on human clinical trials.

Assessment of the risk of bias in included studies

The methodological quality of all included trials will be separately assessed by two independent authors (AH and JDM). Agreement between these two authors will have to be found. In case of disagreement, three more authors (IB, FG, GR) will have to decide by consensus. This evaluation will be based on the seven relevant domains in the 'risk of bias' tool of Cochrane Handbook for Systematic Review of Interventions: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting and (7) other biases.

The level of risk of bias will be determined for each domain: (1) high level, (2) unclear level or (3) low level.

Measures of treatment effect

The statistical analysis will be performed according to the recommendations of the Cochrane Handbook and using the software of Cochrane Collaboration, RevMan 5.3, available from the Cochrane website (http://tech.cochrane.org/revman). All outcomes will be continuous variables. The measurement of effects will be determined based on the change scores from baseline. Initially, a fixed-effect model will be used to compare the outcomes expressed in the same scale. The heterogeneity of the effects of trials will be evaluated by the χ^2 test and the I^2 test. Heterogeneity will be considered as substantial if the I^2 statistic $\geq 50\%$ and $p<0.10$. If heterogeneity is considered as substantial, reasons for this heterogeneity will be searched for and a random-effect model could be used for comparison. So, the mean difference, which is the absolute difference between the mean value in two groups in a trial, and its 95% CIs will be calculated. To express the PT effects on the function and the activity, it will be necessary to combine the outcomes measured in a variety of scales (measures of WBA, COP and LOS for the function, PASS and BBS for the activity). Thus, the standardised mean difference (SMD) and its 95% CIs will be calculated. The SMD expresses the size of the intervention effect in each trial relative to the variability observed in that trial. In Revman, the SMD is calculated based on the Hedges' g.

For the trials with more than two PT groups and to prevent a group being counted twice, we will determine which PT groups are relevant for pair-wise comparisons. Or, if all are relevant, a further possibility will be to include each pair-wise comparison separately and to divide evenly the shared group among the comparisons. For the trials for which results for a rehabilitation group are stratified, the absence of substantial heterogeneity will be verified before mixing the two subgroups of the same PT.

Data synthesis

The comparisons will focus on the effects of active PT versus: (1) no PT, (2) usual care, placebo or control PT and (3) another active PT. First, immediate outcomes will be analysed, then delayed outcomes (follow-up tests), if they have been evaluated.

Subgroup analysis and investigation of heterogeneity

Several subgroup analyses will investigate the effects of PT according to:

1. the type/nature of PT (eg, electromechanical devices including biofeedback, robotics and functional electrical stimulation, virtual reality, task-oriented training, gait training, vibration, non-invasive cerebral stimulation and so on);
2. the main therapeutic goal of PT; two groups will be established: (1) PT aiming mainly at the recovery of postural imbalance and (2) PT not specifically focused on the recovery of postural imbalance;
3. the localisation of brain lesion; to this purpose, three subgroups will be identified: (1) hemispheric stroke, (2) brainstem stroke and (3) cerebellum stroke; a subgroup analysis will also investigate the effects of PT according to the side of the hemispheric lesion (right/left);
4. the type of processing 'bottom-up' or 'top-down';
5. the methodological quality of trials; two subgroups will be identified: (1) the trials in which all criteria of methodological quality, detailed in the part entitled 'assessment of risk of bias in included studies', will present a low risk and (2) the trials in which at least one of these criteria will present an unclear or high risk;
6. the trials assessing or not the level of autonomy (BI, FIM, IADL, ADL);
7. the time since stroke; to this purpose, three subgroups will be identified: (1) early (≤30 days), (2) late (<180 days) and (3) chronic stroke (≥180 days).[57]

We will plan a metaregression of the effects according to the overall duration of PT.

Considering the high risk of heterogeneity for the different PT investigated, a network meta-analysis is, at the present, not envisaged.

DISCUSSION

Postural imbalance is frequent in patients with stroke at early, late or chronic stage. It affects walking abilities, independence and quality of life.[7] Therefore, reduction of postural imbalance in patients with stroke is a relevant objective of PT, in order to increase the level of autonomy. This meta-analysis aims (1) at determining the efficiency of PT on the recovery of postural imbalance in adult patients after stroke and (2) at assessing which PT is more effective when compared with one another. To this purpose, this systematic review and meta-analysis aims at upgrading and improving the rehabilitation of postural imbalance by a complete analysis of all PT. But our objective is to compare the effects of PT and to improve the understanding of these PT effects, using subgroup analyses.

Stroke leads to a large range of clinical subtypes of postural imbalance and related underlying disorders. One of the major issues regarding the rehabilitation of postural imbalance after stroke is the heterogeneity of stroke and the patients' deficits. For example, postural imbalance differs depending on the location and the size of the brain damage.[58] The patients with right hemispheric lesions show a greater WBA and weaker balance abilities.[13 18 58] Moreover, a second major issue is the variety of PT: human practice and/or electromechanical devices, several different (re)learning methods (biofeedback, repetitive tasks, tasks oriented and so on), 'top-down' and 'bottom-up' approaches and so on.

Therefore, many relevant issues regarding the rehabilitation of postural imbalance after stroke are asked: Which PT is the best? What is the most relevant between specific PT focused on postural imbalance and generalisation effects of non-specific PT? Does the postural imbalance rehabilitation only involve a sensorimotor approach? What is the advantage of technology? What is the efficiency of PT according to the time since stroke? Which intensity of PT is the most efficient? What are the effects on the autonomy and the quality of life? The previously detailed subgroup analyses could describe the effects of each PT and, thus, contribute to propose a guideline for rehabilitation of postural imbalance in patients with stroke. One relevant issue may be to better identify the appropriate PT for one patient at one time after stroke.

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Data sharing statement Unpublished data from this study will be available by contacting corresponding author. Unpublished data will be shared.

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2.4.2. Article 2

PLOS ONE

RESEARCH ARTICLE

Limited evidence of physical therapy on balance after stroke: A systematic review and meta-analysis

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Abstract

Background

Stroke results in balance disorders and these directly affect autonomy and quality of life. The purpose of this systematic review and meta-analysis was to determine the efficacy of physical therapy (PT) on balance and postural control after stroke.

Methods

We included all randomized controlled trials assessing the efficacy of PT on balance and postural control in adult patients after stroke without language restriction. Medline, Embase/Scopus, Cochrane Central Register of Controlled Trials, PEDro, Pascal, and Francis databases were searched until January 2019. Primary outcomes were balance (Berg Balance scale and Postural Assessment Scale for Stroke) and postural control with postural deviation or stability measurement in sitting or standing static evaluation. A pair of independent

reviewers selected studies, extracted data, and assessed risk of bias. Meta-analyses with subgroups (categories of PT, time post-stroke, and lesion location) and meta-regression (duration of PT) were conducted.

Results

A total of 145 studies (n = 5912) were selected from the 13,123 records identified. For balance, evidence was found in favor of the efficacy of functional task-training alone (standardized mean difference 0.39, 95% confidence interval [0.09; 0.68], heterogeneity I^2 = 63%) or associated with musculoskeletal intervention and/or cardiopulmonary intervention (0.37, [0.19; 0.55], I^2 = 48%), electrostimulation (0.91, [0.49; 1.34], I^2 = 52%) immediately after intervention, compared to sham treatment or usual care (ST/UC). For postural deviation eyes open, assistive devices were more effective than no treatment (-0.21, [-0.37; -0.05], I^2 = 0%) immediately after intervention; for postural stability eyes open, functional task-training and sensory interventions were more effective than ST/UC (0.97, [0.35; 1.59], I^2 = 65% and 0.80, [0.46; 1.13], I^2 = 37% respectively) immediately after intervention.

Conclusions

Functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention and sensory interventions seem to be immediately effective in improving balance and postural stability, respectively. The heterogeneity of PT and the weak methodological quality of studies limited the interpretation and the confidence in findings.

Introduction

World-wide, approximately 25.7 million people suffered from stroke in 2013 [1], and this was the third most common cause of disability in 2015 [2]. Stroke frequently results in postural disorders characterized by a mediolateral deviation towards the unaffected lower limb and a greater instability of the center of pressure [3–11]. These dysfunctions lead to balance disorders [12] that are responsible for an increased risk of falls [13] and a lower level of activity and participation in stroke patients [14,15]. Balance is associated with ambulation abilities [16–18] and quality of life [19]. Moreover, balance is a predictor for achieving the ability to walk [16,20,21] and is also found among the factors potentially modifiable by physical activity [22]. Therefore, developing physical therapy (PT) interventions for the improvement of balance is relevant for patients with stroke.

PT includes interventions aiming to develop, maintain, and restore movement and functional ability [23]. Current recommendations regarding PT for the improvement of balance after stroke are based on a poor level of evidence [24–26]. Furthermore, most meta-analyses selected only studies published in English language despite it having been established that significant results are more often published in English-language journals [27,28], introducing language bias into article selection. In addition, among the meta-analyses that have investigated the effects of PT in patients with stroke these considered multiple outcomes or some specific approaches of PT [29–42]. Although these did include balance, to the best of our knowledge no meta-analysis has investigated the effects of all PTs specifically on balance and postural control after stroke without language restriction. Therefore, the objective of this

systematic review and meta-analysis was to determine the efficacy of PT (overall and by category of PT) on these parameters in adult patients with stroke.

Methods

The protocol was developed using the PRISMA guidelines [43] and Cochrane recommendations [27], registered in PROSPERO (CRD42016037966), and published in BMJOpen [44] (S1 Checklist and S1 Protocol). Therefore, methods are described only briefly.

Definitions

According to the World Health Organization, stroke is defined as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin" [45]. PT is defined by the World Confederation for Physical Therapy as "services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the life-span" and "physical therapy is concerned with identifying and maximizing quality of life and movement potential within the spheres of promotion, prevention, treatment/intervention, habilitation and rehabilitation" (http://www.wcpt.org/policy/ps-descriptionPT) [23]. Human posture is the position of body parts relative to each other [46]. We defined postural control as the function of body stabilization based on a sensorimotor complex skill, and of body orientation based on internal representation of body scheme [47]. We further defined balance as a posture in which an ideal body mass distribution is achieved and which provides the body carriage stability and conditions for normal functions in stationary position or in movement (Medline Subject Heading; MeSH).

Eligibility criteria

All types of randomized controlled trials assessing the efficacy of PT on balance or postural control in adult patients (18 years or above) with stroke were included without language restriction. Inspired by the meta-analysis conducted by Pollock *et al.* [40], we included all PTs that may be used by physiotherapists during rehabilitation without restriction to only PTs that had a stated objective of promoting recovery of balance or postural control. We included PTs using electric devices (such as functional electric stimulation), treadmills, and assistive devices (such as a cane or orthosis). The classification of PT categories, based on that used by Pollock *et al.* [40], included assistive devices, constraint-induced therapy, cardiopulmonary intervention, functional task-training, musculoskeletal intervention, sensory interventions, and other intervention (Table 1). Only the outcomes defined as primary in the following paragraph were considered for selection of trials.

Outcomes

For this meta-analysis, we studied both balance and postural control. Based on the International Classification of Functioning, Disability and Health (ICF), we considered balance as a level of activity reflecting functional abilities, and postural control as a body structure function reflecting both orientation and stabilization body [47]. Therefore, the primary outcomes were: balance measured by the Berg Balance Scale (BBS) or the Postural Assessment Scale for Stroke (PASS); postural deviation measured by the weight bearing asymmetry (WBA) on lower limbs or the mediolateral and anteroposterior position of the center of pressure (COP); and postural stability measured by all COP sway or limit of stability (LOS) parameters. BBS and PASS are two clinical scales measuring the functional abilities of patients for various balance skills [44] (**S1 Protocol**). BBS is very widely used in studies and has metrological properties that make it

Table 1. Categories of physical therapy.

Categories	Component of categories		Definition
Assistive devices	Cane and aid to stand or walk		Described in additional Table 2 in Pollock *et al*., 2014, p. 361 [40]: "Devices to assist walking, including sticks and frames"
	Orthosis		Described in additional Table 2 in Pollock *et al*., 2014, p. 361 [40]: "Externally applied orthoses to assist walking, including AFO, knee braces"
Constraint-induced therapy	Weight, resistance		Passive and external constraint imposed on movements or mobility of patients
	Body or limb positioning		
	Wedge, lift		
Cardiopulmonary intervention	Fitness, endurance, aerobic training		Described in additional Table 2 in Pollock *et al*., 2014, p. 361 [40]: "Activities to improve cardiopulmonary fitness"
Functional task-training	Balance training		Task-oriented training specifically focus on balance in various modalities.
	Gait training		Task-oriented training of specifically focus on gait in various modalities.
	Sit-to-stand training		Task-oriented training of specifically focus on sit-to-stand in various modalities.
	Transfer training		Task-oriented training of specifically focus on transfers in various modalities.
	Reach or upper limb training		Task-oriented training of specifically focus on reach or function of upper limb in various modalities.
	Daily activity training		Task-oriented training of specifically focus on activities of daily living in various modalities.
	Other task-oriented training		Other task-oriented training in various modalities such as coordination tasks
Musculoskeletal intervention	Active	Strengthening	Described in additional Table 2 in Pollock *et al*., 2014, p. 362 [40]: "Practice of activities to progressively increase the ability to generate muscle force, including using body weight and external resistance"
		Mobilization	Described in additional Table 2 in Pollock *et al*., 2014, p. 362 [40]: "Moving a limb through its range of movement, under the patient's active control without assistance"
	Active assisted	Mobilization	Described in additional Table 2 in Pollock *et al*., 2014, p. 362 [40]: "Moving a limb through its range of movement, under the patient's active control with assistance"
		Electrostimulation	Electrical current used to produce a muscle contraction
	Passive	Mobilization	Described in additional Table 2 in Pollock *et al*., 2014, p. 362 [40]: "Moving a limb through its range of movement, whilst the patient is passive"
		Stretching	Lengthening of muscle to improve elasticity and control muscle tone.
		Immobilization	Described in additional Table 2 in Pollock *et al*., 2014, p. 362 [40]: "placing a limb or body part in a supported position, to maintain optimal alignment "
		Verticalization	Described in additional Table 2 in Pollock *et al*., 2014, p. 362 [40]: "To promote early lower limb loading"
		Massage	Described in additional Table 2 in Pollock *et al*., 2014, p. 362 [40]: "Manipulation of soft tissue, using the hands or a tool designed for the purpose
Neurophysiological intervention	Bobath, Proprioceptive neuromuscular facilitation and other neurodevelopmental interventions		Described in additional Table 1 in Pollock *et al*., 2014, p. 356–362 [40]: "Intervention which is described as facilitation of movement"
Sensory interventions	Tactile, vibration, thermal, proprioception		Practice of stimulation, perturbation or modification of sensorial input (*e.g.* tactile, thermal, proprioception, visual, vestibular) by different methods.
	Visual		
	Vestibular		

(*Continued*)

Table 1. (Continued)

Categories	Component of categories		Definition
Other intervention	Acupuncture		Described in additional Table 2 in Pollock *et al*., 2014, p. 362 [40]: "Devices to assist walking, including sticks and frames"
	Aquatic therapy		Use of aquatic environment to assist or stimulate function or mobility of body
	Body awareness therapy		Practice aimed at being aware of one owns body and reflect upon how the body feels when performing the movements
	Other		

This classification was based on the classification reported in Pollock *et al*., 2014, a Cochrane meta-analysis (additional Table 1 p. 356–361 and additional Table 2 p. 361–363).

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a gold standard to assess balance in patients with stroke. We included studies that assessed postural control with postural deviation or stability measurement in sitting or standing static evaluation on a force plate with eyes open (EO) or closed (EC). Postural deviation included mediolateral postural deviation (measured by WBA and mediolateral position of COP) and anteroposterior postural deviation (measured by anteroposterior position of COP). Additionally, we included studies that measured WBA by means of another device than force plate, such as weight scale, if the measure was done in static position. The secondary outcome was autonomy measured by the Barthel Index, the Functional Independence Measure, the Activities of Daily Living or the Instrumental Activities of Daily Living scales.

Data sources

Medline, Elsevier databases (*i.e*. EMBASE until October 2015, SCOPUS thereafter), Cochrane Central Register of Controlled Trials, PEDro, Pascal, and Francis databases were searched from inception until January 14, 2019 (S1 Table and **S1 Protocol** for search strategy [44]). Scopus was replaced by Embase because we had no longer access to it. These two databases are both produced by Elsevier and the recall by Scopus of references found by Embase was optimal or suboptimal that is considered as acceptable [48]. Unpublished studies, conferences, and presentations were searched without language restriction.

Study selection

Based on eligibility criteria, two authors (AH, JDM) independently selected the studies. The judgment of three other authors (IB, FG, GR) was used to resolve potential conflicts [44] (**S1 Protocol**). No language restriction was applied.

Data extraction

Two authors (AH and JDM) independently extracted data; potential conflicts were resolved with the help of three other authors (IB, FG, GR). In case of unclear or missing data, we contacted the authors of the respective studies. Extracted data included: study design, participant characteristics, risk of bias, PT characteristics, and outcomes (**S1 Protocol** [44]). All outcomes were statistically treated as continuous measures. We extracted the mean value, the standard deviation (SD), and the number of participants to the outcome measurements in each intervention group. The change-from-baseline was used to determine the outcome. Due to poor, variable or incomplete reporting of change score, different methods were used to obtain the mean and SD of changes when necessary. The most parsimonious statistical treatment was preferred. Finally, when only mean and SD values for before and after intervention

assessments were given, SD was imputed by using a correlation coefficient with respect to the most conservative approach.

Risk of bias assessment

Two authors (AH and JDM) independently assessed the seven items of the risk of bias tool from the Cochrane Collaboration [27] for each study, and used the Grades of Recommendation, Assessment, Development, and Evaluations (GRADE) as reported in Cochrane Handbook [27] to assess the overall quality of evidence of this meta-analysis. The judgment of two other authors (MC, FG) was used to resolve potential conflicts.

Data synthesis and analysis

Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria; available in http://www.R-project.org/; version 3.5.2). Concordance between authors for the selection of studies was estimated using the Cohen's Kappa coefficient and the recommendations of Landis and Kock [49]. Post-intervention effects were investigated by calculating the change from baseline to the immediate post-intervention assessment, and persisting effects by computing the change from baseline to the last follow-up assessment. These changes were compared between groups. The inverse-variance method was applied to summarize effects across studies. The summary effect estimate for all scales was calculated as the mean difference and its 95% confidence interval (95%CI). The estimate for outcomes was calculated as the standardized mean difference (SMD) and its 95%CI [44] because each outcome pooled several scales. We used Hedges'g to calculate SMD. The fixed-effect model was applied by default and the random-effect model was used in case of substantial heterogeneity ($I^2 \geq 50\%$) [44] (**S1 Protocol**). We summarize effects of crossover trials by following the recommendations of Cochrane Handbook (chapter 16.4) [27]. When several scales were available for the same outcome and to prevent any overweight of a study in a same SMD analysis, we ranked the scales based on the frequency of use in all trials. We selected the most frequent scales.

We performed subgroup analyses according to categories of PT, time post-stroke, and location of stroke lesion. We also performed sensitivity analyses to explore the effects of methodological quality according to appraisal of risk of bias. We investigated publication bias by funnel plots, contour-enhanced funnel plot, and Egger tests [27,50,51]. If publication bias was suspected, we performed the trim and fill method as a form of sensitivity analysis of the pooled estimate [50,52,53]. To determine the impact of the dose of PT, effect estimates were correlated with parameters of duration of PT using meta-regression. We compared PT versus no treatment (NT) and PT versus sham treatment (ST) or usual care (UC), irrespective of the design of study used (direct design, *e.g.* A versus B; or "add-on" design, *e.g.* A+C versus B+C). ST was a placebo treatment or a control treatment different from a PT, such as music or relaxation, delivered using the same protocol as that used in the experimental group. UC was various and non-protocoled standard care freely defined by therapists according to practices at that time.

Results

Study selection

Among the 13,123 records identified, 10,663 single records were screened. For title screening, 8345 studies were excluded because they clearly did not address the topic of stroke or that did not include human subjects, or that the design mentioned in the title was explicitly different from a randomized controlled trial. The reasons for exclusion of records during the abstract screening then the full-text assessment are reported in the flow chart (Fig 1). For assessment of

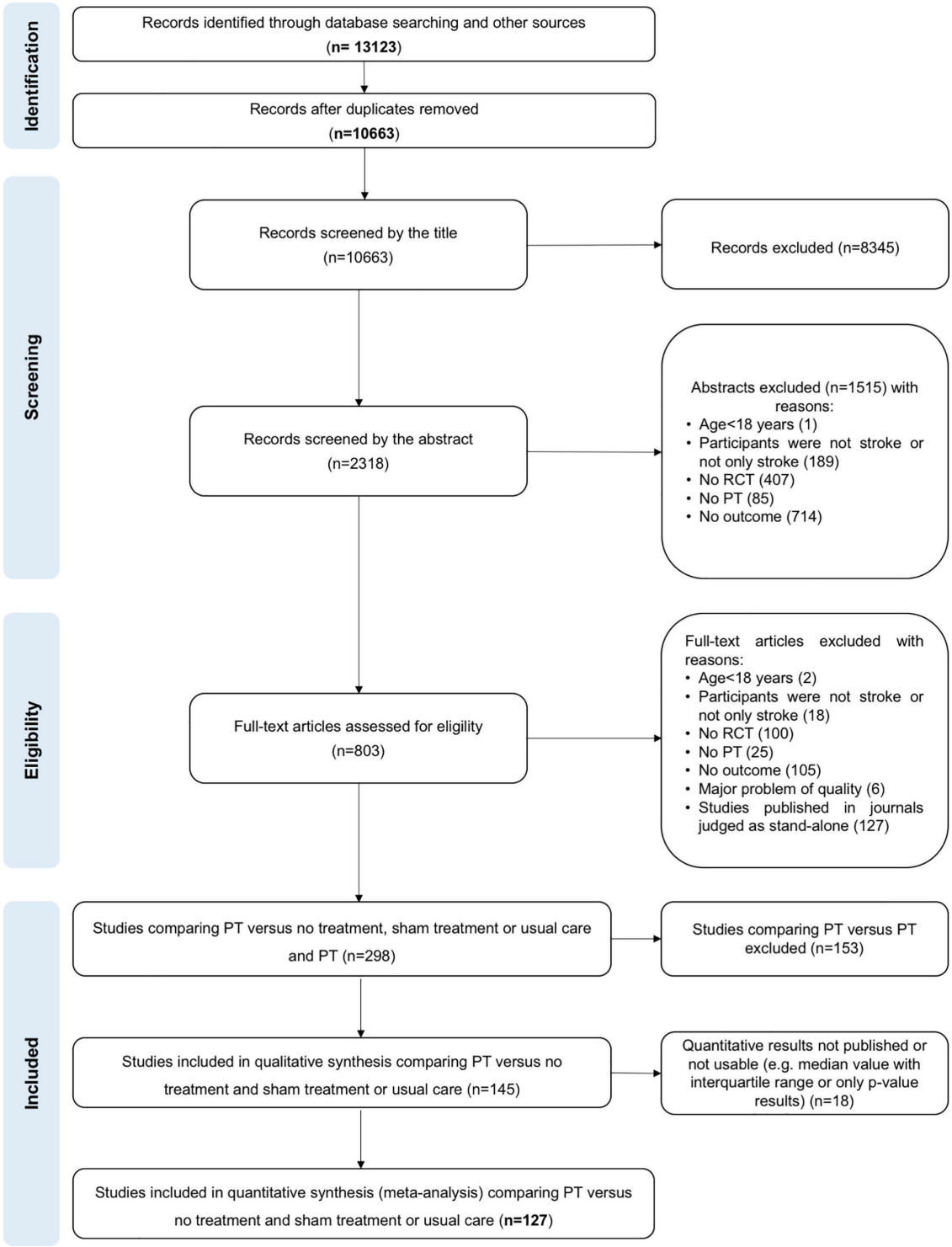
Identification
Records identified through database searching and other sources (n= 13123)
Records after duplicates removed (n=10663)
Screening
Records screened by the title (n=10663)
Records excluded (n=8345)
Records screened by the abstract (n=2318)
Abstracts excluded (n=1515) with reasons:
• Age<18 years (1)
• Participants were not stroke or not only stroke (189)
• No RCT (407)
• No PT (85)
• No outcome (714)
Eligibility
Full-text articles assessed for eligility (n=803)
Full-text articles excluded with reasons:
• Age<18 years (2)
• Participants were not stroke or not only stroke (18)
• No RCT (100)
• No PT (25)
• No outcome (105)
• Major problem of quality (6)
• Studies published in journals judged as stand-alone (127)
Included
Studies comparing PT versus no treatment, sham treatment or usual care and PT (n=298)
Studies comparing PT versus PT excluded (n=153)
Studies included in qualitative synthesis comparing PT versus no treatment and sham treatment or usual care (n=145)
Quantitative results not published or not usable (e.g. median value with interquartile range or only p-value results) (n=18)
Studies included in quantitative synthesis (meta-analysis) comparing PT versus no treatment and sham treatment or usual care (n=127)

Fig 1. Flow-chart.

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full-text eligibility, 56 studies were translated by co-authors (Chinese: n = 27, German: n = 6, Korean: n = 5, Spanish: n = 4, Russian: n = 3, Italian: n = 2, Persian: n = 2, Portuguese: n = 2, Turkish: n = 2, Japanese: n = 1, Norwegian: n = 1, Polish: n = 1). A total of 145 studies were selected (Fig 1 and S2 Table). The mean concordance between the two independent authors for the three steps of selection process, was substantial (kappa = 0.64). The authors of 130 of the 145 studies regarding unclear or missing data were contacted; answers were received for 20 studies.

Study and participant characteristics

A total of 91 comparisons of PT versus NT in 76 studies and 81 comparisons of PT versus ST/UC in 70 studies were analyzed; 1 study was included in both comparisons. Among these 145 studies, 18 were of crossover design and 127 parallel group design; they included a total of 5912 participants (mean: 40.8, SD: 42.9, range: 7–408). Weighted participant age was 60.8 years (SD: 44.3, range: 46.9–78.5; S3 Table).

Risk of bias

Risk of bias was low for random sequence generation in 55% of studies, for allocation concealment in 13% of studies, for blinding outcome assessment in 44% of studies, for incomplete outcome data in 17% of studies, and for selective reporting in 16% of studies. Most studies had a high or unclear risk of bias for blinding of patients and therapists (99%) but a low risk for other bias (92%; S1 Fig and S4 Table). Funnel plots and Egger tests found no evidence of publication bias for PT versus NT on balance, mediolateral postural deviation EO, postural stability EO, or autonomy; whereas for comparison PT versus ST/UC, there was a potential publication bias on balance (post-intervention effects and persisting effects), postural stability EO (post-intervention effects), and autonomy (post-intervention effects and persisting effects). The number of unpublished studies estimated by the trim and fill method was 0 for post-intervention effects on postural stability EO and post-intervention effects on autonomy, 1 for post-intervention effects on balance, 4 for persisting effects on autonomy, and 9 for persisting effects on balance (S2 Fig and S5 Table).

Physical therapy

Functional task-training (including balance training) and assistive devices were the most common categories of PT that were compared to NT. Functional task-training, musculoskeletal interventions, and sensory interventions were the most common categories of PT that were compared to ST/UC (S6 Table).

Expressed as median values, participants received an additional 300 minutes dispensed in 12 sessions of 20 minutes for 3 weeks (PT versus NT). When PT was compared to ST/UC, treatment was delivered over 570 minutes, and dispensed in 16 sessions of 30 minutes for 5 weeks (S7 Table).

Outcomes/Measures

BBS was the most common scale of balance used in studies for both post-intervention and persisting effects. For autonomy, the Barthel Index was the most frequent scale used. Sixty-four different parameters for WBA, LOS, and COP were identified. Fifty-one of these were assessed in $\leq$5 studies and the most common parameter was assessed in 23 studies (S8 Table).

Effects

Balance. PT had a significantly beneficial post-intervention effect compared to NT (37 studies, 1721 participants, SMD 0.46, 95%CI [0.37; 0.56]) with low heterogeneity (I^2 = 19%). Significant positive SMDs were found for constraint-induced therapy, functional task-training, functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention, musculoskeletal intervention with body awareness therapy, and musculoskeletal intervention by active strengthening; and non-significant SMDs for acupuncture, musculoskeletal intervention by electrostimulation, sensory interventions and other intervention (no significant between-subgroup difference, p = 0.29; Fig 2). There were significant positive SMDs for acute-subacute stroke patient and chronic stroke patient subgroups without significant between-subgroup difference (p = 0.50; S9 Table). A significant positive SMD was found for a subgroup of studies that included only supratentorial stroke patients (S10 Table). There

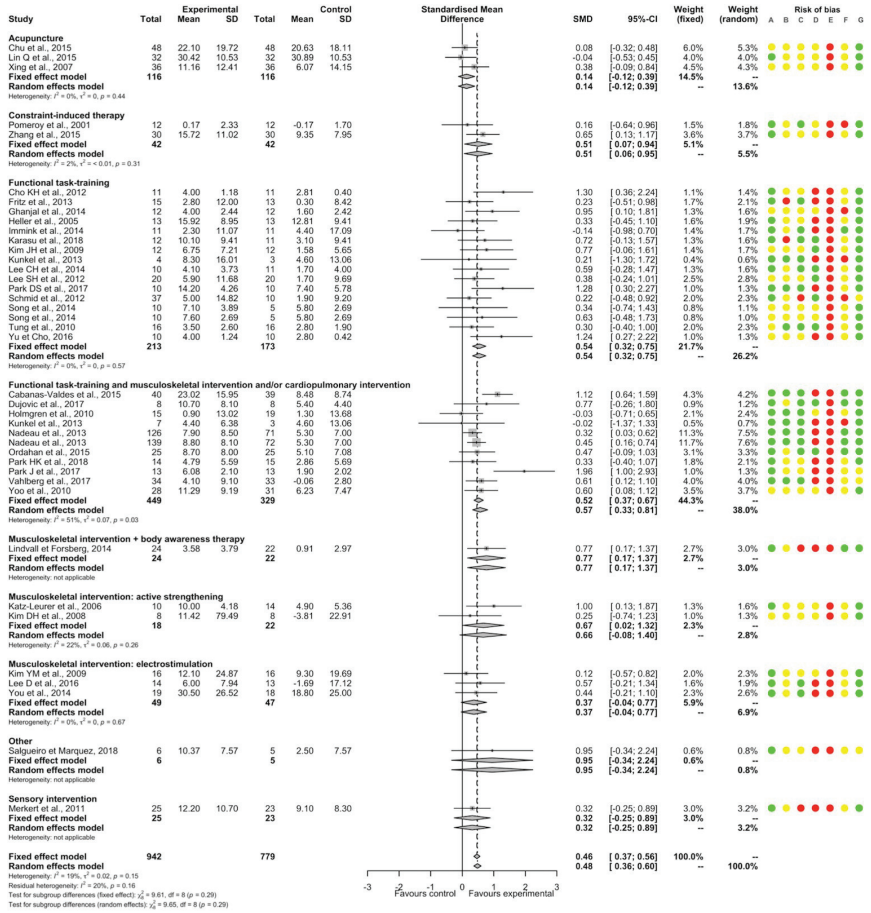

Fig 2. Forest plot of PT versus NT. Outcome: Balance, post-intervention effects. Risk of bias: A, Random sequence generation; B, Allocation concealment; C, Blinding of outcome assessment; D, Incomplete outcome data; E, Blinding of participants and therapists; F, Selective reporting; G, Other bias. Risk of bias: green color corresponds to low risk, yellow color unclear risk, and red color high risk. Abbreviations: CI, Confidence interval; SD, Standard deviation; SMD, Standardized mean difference.

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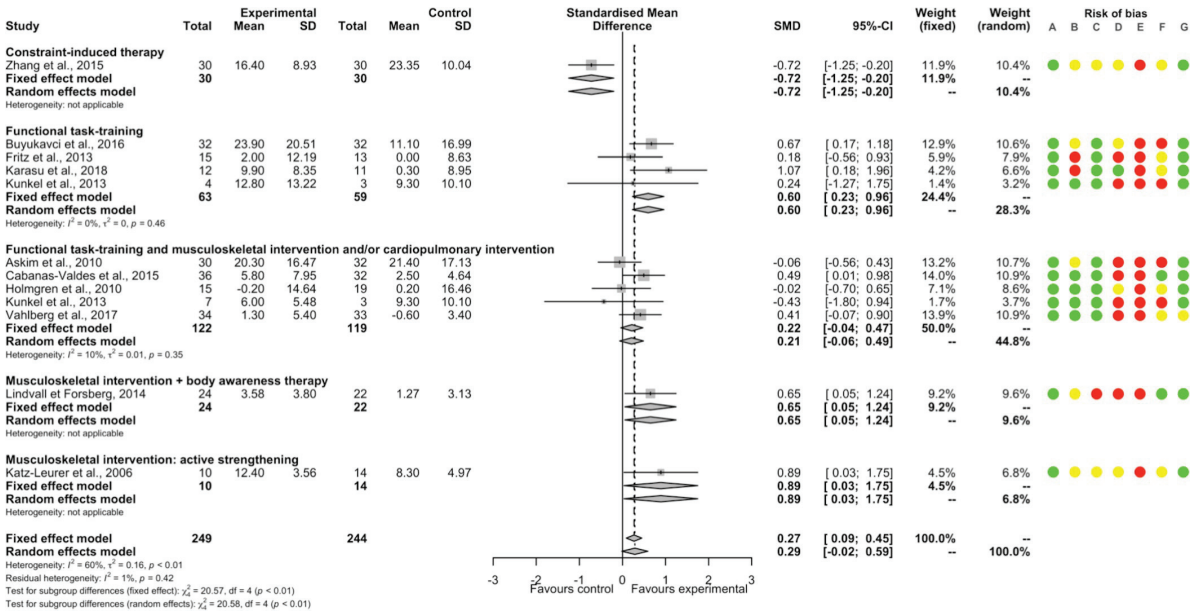

Fig 3. Forest plot of PT versus NT. Outcome: Balance, persisting effects. Risk of bias: A, Random sequence generation; B, Allocation concealment; C, Blinding of outcome assessment; D, Incomplete outcome data; E, Blinding of participants and therapists; F, Selective reporting; G, Other bias. Risk of bias: green color corresponds to low risk, yellow color unclear risk, and red color high risk. Abbreviations: CI, Confidence interval; SD, Standard deviation; SMD, Standardized mean difference.

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was no significant meta-regression with duration of PT. For each item of bias, removing the studies judged as having high or unclear risk found a similar direction of SMDs favoring PT (except for blinding of patients and therapists because all studies showed a high or unclear risk; S3 Fig).

There was a non-significant SMD between PT and NT for persisting effects (11 studies, 493 participants, SMD 0.29, 95%CI [-0.02; 0.59]) with substantial heterogeneity (I^2 = 60%). A significant between-subgroup difference was found (p<0.01); there were significant positive SMDs for subgroups of functional task-training, of musculoskeletal intervention with body awareness therapy and of musculoskeletal intervention by active strengthening; a significant negative SMD for the subgroup of constraint-induced therapy; and non-significant SMDs for the subgroup of functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention (Fig 3). There was a significant positive SMD for the subgroup of chronic stroke patients and a non-significant SMD for the subgroup of acute-subacute stroke patients, without significant difference between subgroups (p = 0.64; S9 Table).

PT had a significantly beneficial post-intervention effect compared to ST/UC (46 studies, 2051 participants, SMD 0.43, 95%CI [0.28; 0.59]) with substantial heterogeneity (I^2 = 61%). There was a significant between-subgroup difference (p<0.01). There were significant positive SMDs for functional task-training alone or associated with musculoskeletal intervention and/or cardiopulmonary intervention, musculoskeletal intervention by electrostimulation, and respiratory training; and non-significant SMDs for musculoskeletal intervention by active strengthening or by immobilization and sensory interventions (Fig 4). There were significant positive SMDs for acute-subacute stroke patient and chronic stroke patient subgroups, without between significant between-subgroup difference (p = 0.16; S9 Table). A non-significant SMD was found for a subgroup of studies that included only supratentorial stroke patients (S10 Table).

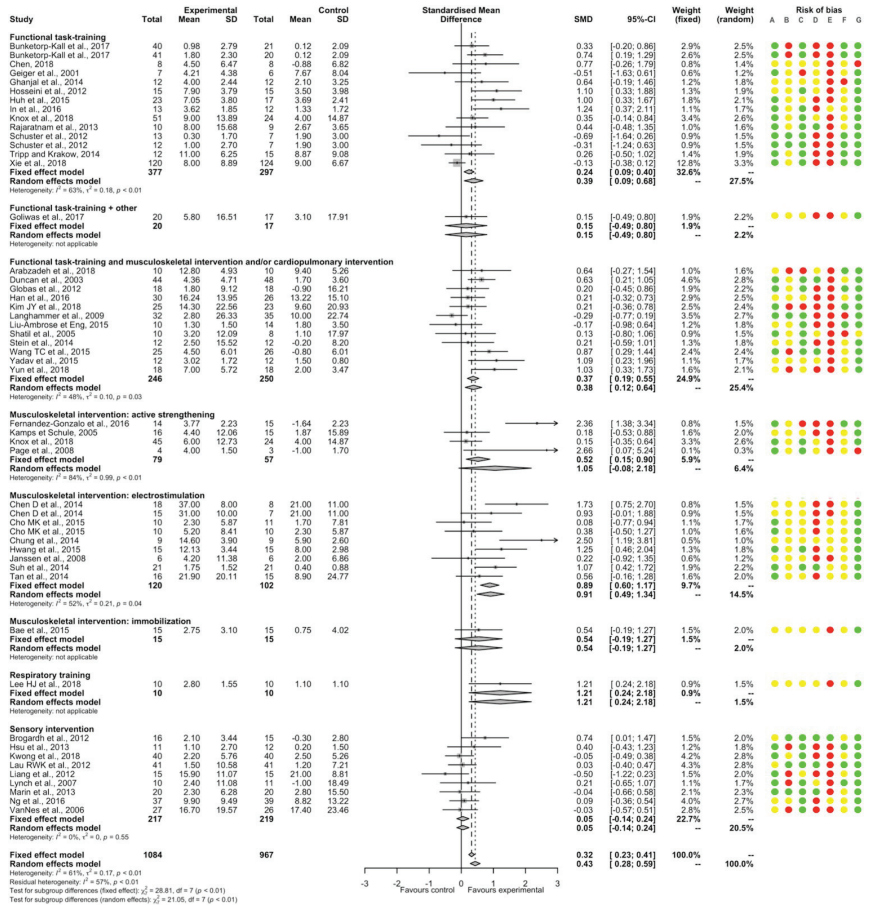

Fig 4. Forest plot of PT versus ST/UC. Outcome: Balance, post-intervention effects. Risk of bias: A, Random sequence generation; B, Allocation concealment; C, Blinding of outcome assessment; D, Incomplete outcome data; E, Blinding of participants and therapists; F, Selective reporting; G, Other bias. Risk of bias: green color corresponds to low risk, yellow color unclear risk, and red color high risk. Abbreviations: CI, Confidence interval; SD, Standard deviation; SMD, Standardized mean difference.

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There was a significant negative meta-regression between SMD and the number of weeks of PT (p = 0.04; S4 Fig). Removing all studies judged as having high or unclear risk for random sequence generation, blinding of participants and therapists, blinding of outcome assessment, incomplete outcome data, and other bias found a similar direction of SMDs favoring PT, whereas for allocation concealment and selective reporting SMDs became non-significant (S5 Fig). The summary post-intervention effect estimate adjusted for the potential publication bias concerning balance for the comparison PT versus ST/UC was similar and still in favor of PT (1 missing point, SMD 0.43, 95%CI [0.27; 0.58], I^2 = 61% according to the trim and fill method).

PT had a significantly beneficial persisting effect compared to ST/UC (18 studies, 1150 participants, SMD 0.18, 95%CI [0.06; 0.30]) with moderate heterogeneity (I^2 = 49%). A significant positive SMD was only found for the subgroup of musculoskeletal intervention by electrostimulation (Fig 5). There were significant positive SMDs for acute-subacute stroke patient and chronic stroke patient subgroups (S9 Table); and a non-significant SMD for a subgroup of

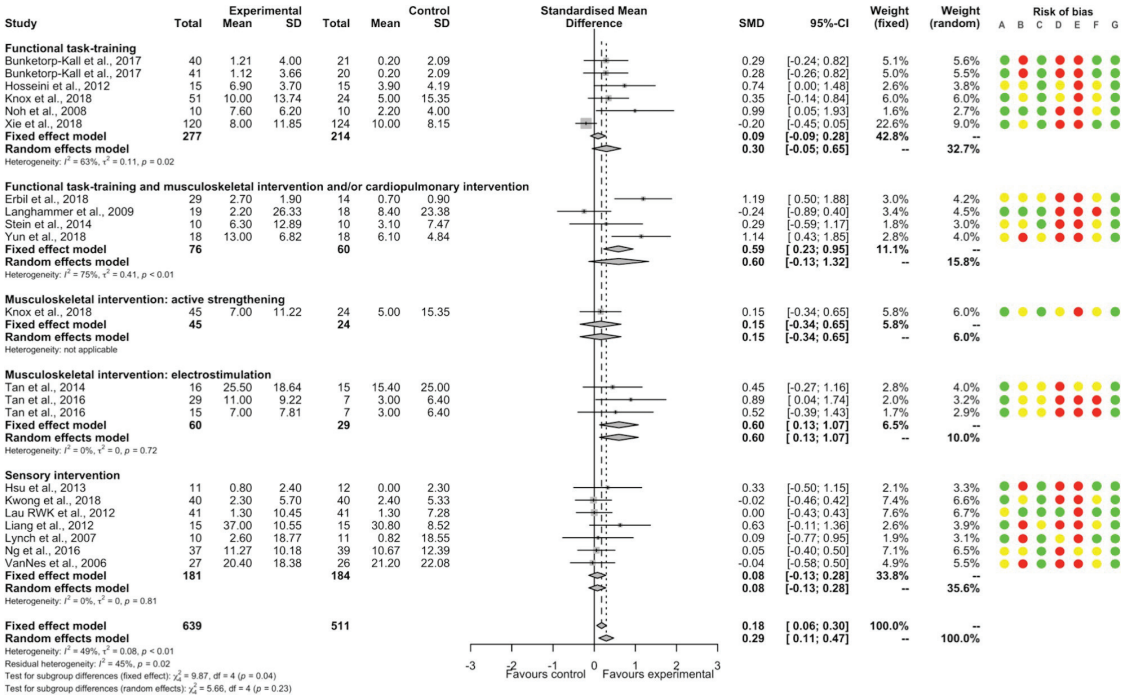

Fig 5. Forest plot of PT versus ST/UC. Outcome: Balance, persisting effects. Risk of bias: A, Random sequence generation; B, Allocation concealment; C, Blinding of outcome assessment; D, Incomplete outcome data; E, Blinding of participants and therapists; F, Selective reporting; G, Other bias. Risk of bias: green color corresponds to low risk, yellow color unclear risk, and red color high risk. Abbreviations: CI, Confidence interval; SD, Standard deviation; SMD, Standardized mean difference.

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studies that included only supratentorial stroke patients (S10 Table). The summary persisting effect estimate adjusted for the potential publication bias on balance for the comparison PT versus ST/UC became non-significant (9 missing points, SMD 0.03, 95%CI [-0.17; 0.23], I^2 = 67%, according to the trim and fill method).

Mediolateral postural deviation. PT had a significantly beneficial post-intervention effect EO compared to NT (11 studies, 329 participants, SMD -0.23, 95%CI [-0.36; -0.09]) without heterogeneity (I^2 = 0%). There were significant negative SMDs for assistive device and functional task-training; and a non-significant SMD for constraint-induced therapy and musculoskeletal intervention by immobilization; with a significant between-subgroup difference (p = 0.06; Fig 6). There was a significant negative SMD for the subgroup of acute-subacute stroke patients and a non-significant SMD for the subgroup of chronic stroke patients (1 study), without between significant between-subgroup difference (p = 0.34). There was a non-significant SMD for a subgroup of studies that included only supratentorial stroke patients (S9 and S10 Tables). We found no significant meta-regression with duration of PT. Removing all studies judged as having high or unclear risk for incomplete outcome data and other bias showed a similar direction of SMDs favoring PT, whereas for random sequence generation and selective reporting, SMDs became non-significant (S6 Fig).

A non-significant SMD was found between PT and NT for persisting effects EO (3 studies, 50 participants, SMD -0.44, 95%CI [-1.05; 0.16]), without heterogeneity (I^2 = 0%) and significant difference between categories of PT (p = 0.96; Fig 6).

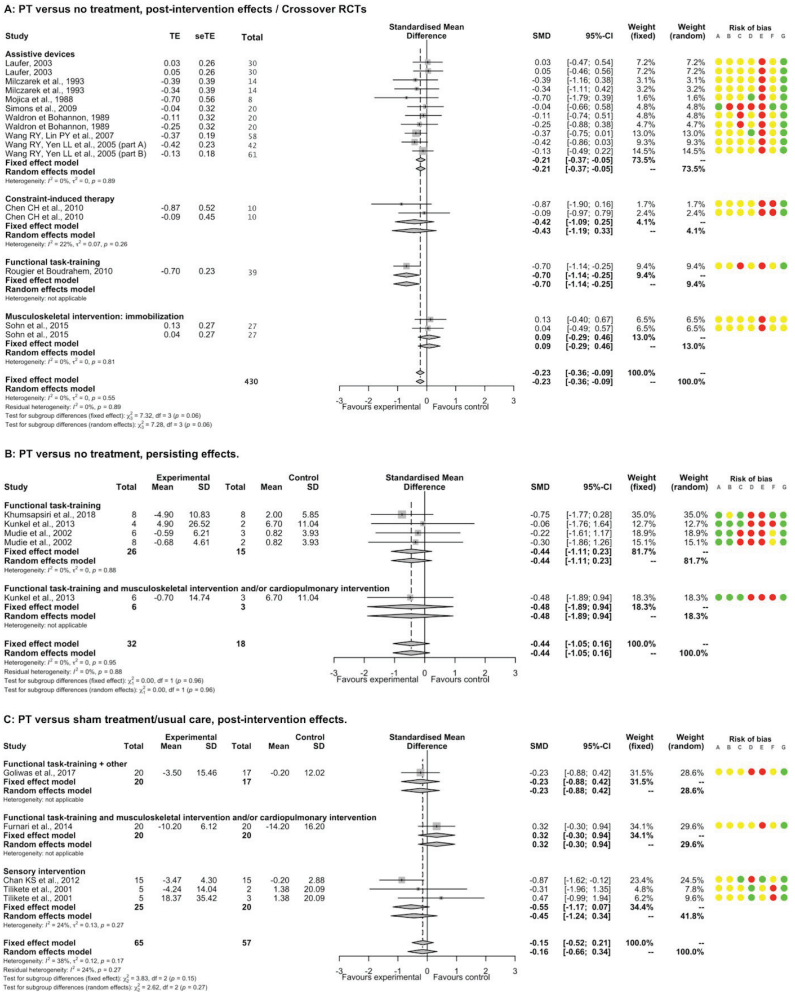

Fig 6. Forest plot of PT versus NT and versus ST/UC. Outcome: Mediolateral postural deviation EO. Risk of bias: A, Random sequence generation; B, Allocation concealment; C, Blinding of outcome assessment; D, Incomplete outcome data; E, Blinding of participants and therapists; F, Selective reporting; G, Other bias. Risk of bias: green color corresponds to low risk, yellow color unclear risk, and red color high risk. Abbreviations: CI, Confidence interval; SD, Standard deviation; SMD, Standardized mean difference.

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A non-significant SMD was found between PT and ST/UC for post-intervention effects EO (4 studies, 122 participants, SMD -0.15, 95%CI [-0.52; 0.21]) with moderate heterogeneity (I^2 = 38%). All category of PTs such as functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention, or with another intervention and sensory interventions had non-significant SMDs (Fig 6). There was a significant negative SMD for chronic stroke patients subgroup and a non-significant SMD for acute-subacute stroke patients subgroup (1 study), without significant between-subgroup difference (p = 0.11; S9 Table). A non-significant SMD was found for a subgroup of study that included only supratentorial stroke patients (1 study; S10 Table). There was a positive meta-regression between SMD and the overall duration of PT (5 studies, p = 0.052). Removing all studies judged as having

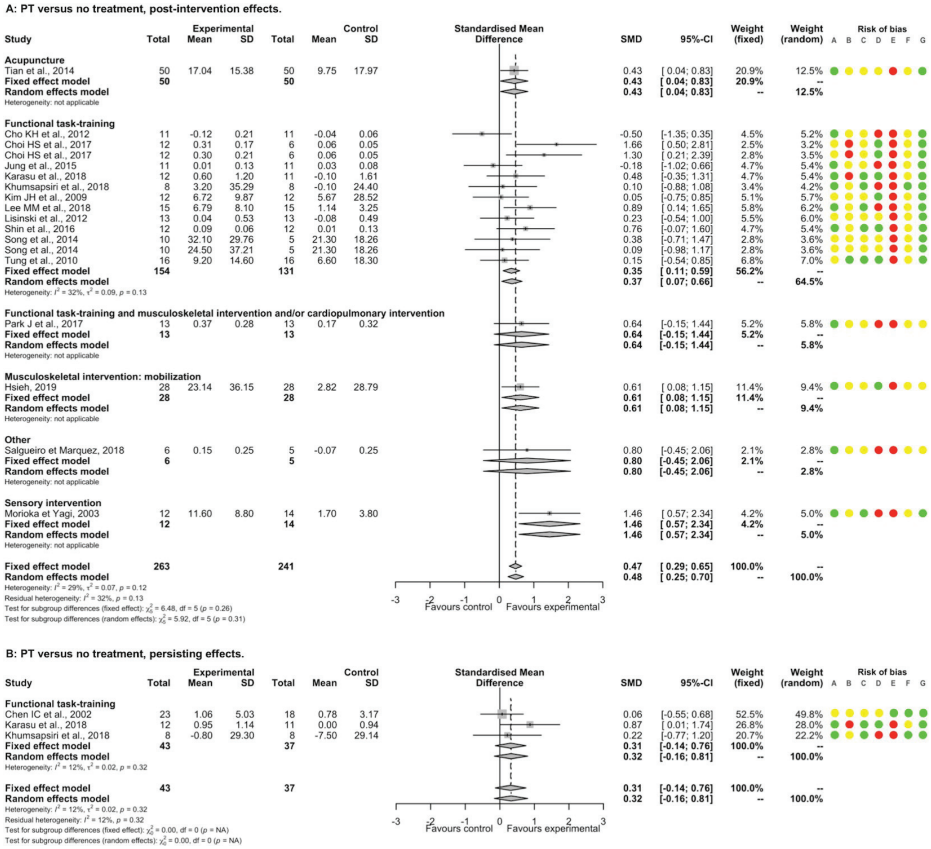

Fig 7. Forest plot of PT versus NT. Outcome: Postural stability EO. Risk of bias: A, Random sequence generation; B, Allocation concealment; C, Blinding of outcome assessment; D, Incomplete outcome data; E, Blinding of participants and therapists; F, Selective reporting; G, Other bias. Risk of bias: green color corresponds to low risk, yellow color unclear risk, and red color high risk. Abbreviations: CI, Confidence interval; SD, Standard deviation; SMD, Standardized mean difference.

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high or unclear risk for blinding of outcome assessment and blinding of patients and therapists changed the direction of SMDs favoring PT, whereas for incomplete outcome data and other bias, SMDs still were non-significant (S7 Fig). No study investigated persisting effects of PT compared to ST/UC.

Postural stability. PT had a significantly beneficial post-intervention effect EO compared to NT (16 studies, 504 participants, SMD 0.47, 95%CI [0.29; 0.65]) with low heterogeneity (I^2 = 29%). There was a significant positive SMDs for acupuncture, functional task-training, musculoskeletal intervention by mobilization, and sensory interventions; and non-significant SMDs for functional task-training associated with musculoskeletal intervention and/or cardio-pulmonary intervention and for other interventions; without significant between-subgroup difference (p = 0.26; Fig 7). There was a significant positive SMD for acute-subacute stroke patients subgroup, and a non-significant SMD for chronic stroke patients subgroup, without significant between-subgroup difference (p = 1.00; S9 Table). A non-significant SMD was found for a subgroup of study that included only supratentorial stroke patients (S10 Table). There was no significant meta-regression with duration of PT. Removing all studies judged as

having high or unclear risk for random sequence generation, blinding of outcome assessment, incomplete outcome data and other bias showed a similar direction of SMD favoring PT, whereas for concealment allocation and selective reporting, SMDs became non-significant (S8 Fig). For EC, PT had a significantly beneficial post-intervention effect compared to NT (9 studies, 229 participants, SMD 0.34, 95%CI [0.08; 0.61]) without heterogeneity (I^2 = 0%; S9 Fig).

PT had a significantly beneficial post-intervention effect EO compared to ST/UC (15 studies, 574 participants, SMD 0.96, 95%CI [0.55; 1.37]) with substantial heterogeneity (I^2 = 78%). There were significant positive SMDs for functional task-training, musculoskeletal intervention by mobilization, and sensory interventions; and non-significant SMDs for assistive devices, functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention or with another intervention, musculoskeletal intervention by active strengthening and musculoskeletal intervention by immobilization; without significant between-subgroup difference (p = 0.29; Fig 8). There was a significant positive SMD for chronic stroke patients subgroup and a non-significant SMD for acute-subacute stroke patients subgroup, with a significant between-subgroup difference (p = 0.09; S9 Table). We found a non-significant SMD for a subgroup of study that included only supratentorial stroke patients (1 study; S10 Table). There was a significant positive meta-regression between post-intervention effects and the overall duration of PT for the subgroup of sensory interventions (S4 Fig). Removing all studies judged as having high or unclear risk for random sequence generation, blinding of outcome assessment, and other bias showed a similar direction of SMD favoring PT, whereas for incomplete outcome data, SMD became non-significant. All studies showed a high or unclear risk of bias for concealment allocation and for blinding of patients and therapists (S10 Fig). The summary post-intervention effect estimate adjusted on the potential publication bias concerning postural stability EO for the comparison PT versus ST/UC was not changed (0 missing point according to the trim and fill method). Considering the atypical treatment effect of a study, Furnari *et al.* (2014) [54] compared to other studies, we performed a sensitivity analysis that found a summary SMD still in favor of PT (14 studies, 534 participants, SMD 0.72, 95%CI [0.45; 0.98], I^2 = 46%). For EC, there was a significantly beneficial post-intervention effect of PT (10 studies, 352 participants, SMD 1.02, 95%CI [0.38; 1.67]) with substantial heterogeneity (I^2 = 86%; S9 Fig). A sensitivity analysis removing one study, Furnari *et al.* (2014) [54], found a summary SMD still in favor of PT (SMD 0.62, 95%CI [0.25; 0.98], I^2 = 57%). For either EO or EC, the persisting effects of PT compared to NT and these of PT compared to ST/UC are reported in Figs 7 and 8 and in S9 Fig.

Other outcomes and quality of evidence. The results of analyses on data extracted for autonomy are presented in S11–S13 Figs and in S9 and S10 Tables. Moreover, the quality of evidence according to GRADE for all outcomes is presented in S11 Table.

Discussion

The present study found that the overall post-intervention effects were in favor of PT compared to NT for balance, mediolateral postural deviation EO, and postural stability (EO or EC), and compared to ST/UC for balance and postural stability (EO or EC) after stroke. Few categories of PT were more effective than NT in improving balance after stroke immediately after intervention. However, caution should be taken when interpreting these results owing to a small number of studies, participants, or substantial heterogeneity within subgroups. The findings therefore only support that functional task-training alone had a beneficial effect in improving balance compared to NT, owing to the absence of heterogeneity and a sufficient number of trials and participants. For instance, a beneficial effect for functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention could be concluded if there

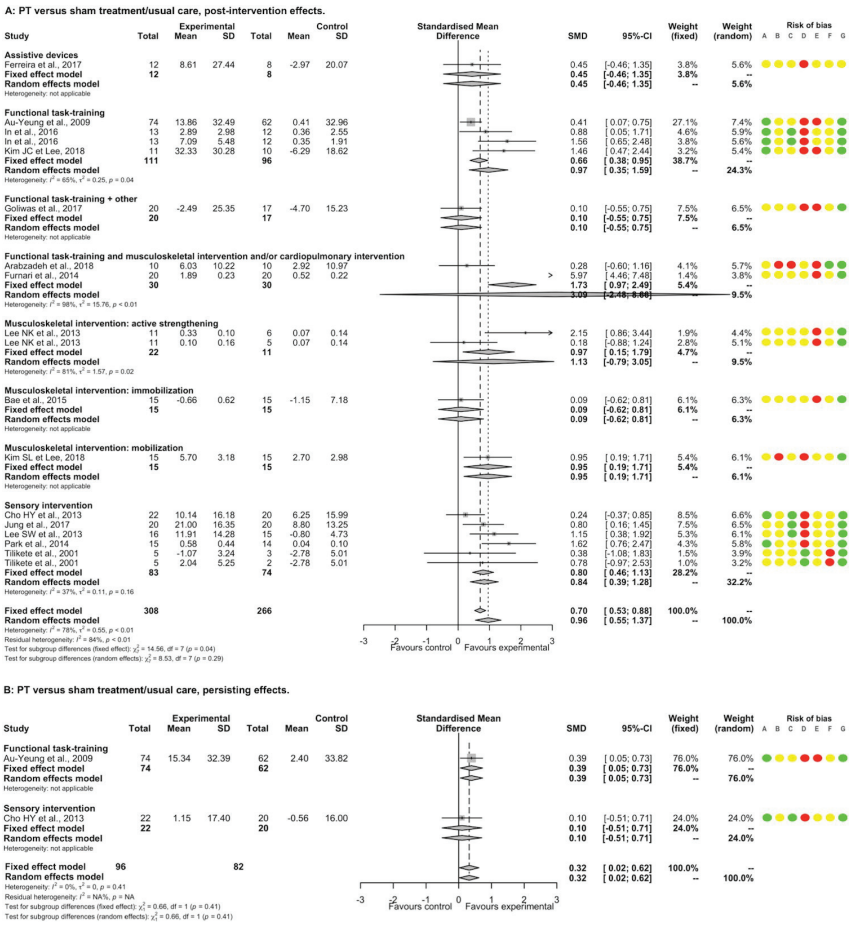

Fig 8. Forest plot of PT versus ST/UC. Outcome: Postural stability EO. Risk of bias: A, Random sequence generation; B, Allocation concealment; C, Blinding of outcome assessment; D, Incomplete outcome data; E, Blinding of participants and therapists; F, Selective reporting; G, Other bias. Risk of bias: green color corresponds to low risk, yellow color unclear risk, and red color high risk. Abbreviations: CI, Confidence interval; SD, Standard deviation; SMD, Standardized mean difference.

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was less heterogeneity. The present study also found limited evidence for the effect on balance compared to ST/UC in patients with stroke. The results allow only to conclude a beneficial effect immediately after intervention of functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention but also the lack of efficacy of sensory interventions (such as vibration or tactile stimulation); substantial heterogeneity precludes conclusions as to the efficacy of functional task-training alone, or of musculoskeletal intervention by electrostimulation. Similarly, for persisting effects of PT, only the lack of efficacy for sensory interventions compared to ST/UC could be concluded. Another point of interest of the present study is the investigation of effects on postural control. We could conclude for post-intervention effects that assistive devices were more effective than NT in reducing mediolateral postural deviation EO, and that functional task-training alone and sensory interventions were, respectively, more effective than NT and ST/UC in increasing postural stability (either EO or EC).

Another point is that the beneficial effect of functional task-training alone on both balance, which is considered as activity according to the ICF, and postural stability (EO or EC), which is considered as body structure function according to the ICF, could suggest a transfer of learning from body structure function to activity level. Van Duijnhoven *et al.* (2016) [42] found ambiguous results for outcomes addressing body structure function and beneficial effects for balance (considered as activity) and suggested an optimization of compensatory balance strategies. Fewer studies (n = 36) were included in their meta-analysis than herein, which may go some way to explain this difference. Another important finding of the present meta-analysis is that with respect to comparisons made between PT and NT, those made between PT and ST/UC had smaller effect sizes and/or greater heterogeneity, which leads us to question whether or not there are specific effects of PT. It should be also noted that the reduction or the non-significance of SMD, in most cases, between post-intervention and persisting effects supports a short-term effect of PT.

Treatment modalities, such as the dose or the way to apply the PT, were very different between studies within a category of PT. This could explain part of the heterogeneity, and a better understanding of the mechanisms of action of the various categories of PT could improve the interpretation of any potential effect. More generally, the weak methodological quality of studies and the absence of significant effect when only studies at a low risk of bias were considered indicates that caution should be taken when interpreting the results. Therefore, implications of the present findings for clinical practice are limited. To address this issue, priority should be given to conduct trials of better methodological quality, especially regarding random sequence generation, allocation concealment [55], blinding outcome [56], and incomplete outcome data. It is also of note that data regarding the included population, therapies, and the size and precision of effects were often unclear or missing in the studies identified herein, and could be a source of the heterogeneity observed. This underlines the importance of the quality of reporting, as also identified by the Stroke Recovery and Rehabilitation Roundtable [57]. The sample size of studies was often too small, increasing the risk of overestimate the effect size [58], and the outcome measures used to assess effects were too wide. Larger, multicenter trials with standardization and consensus of outcome measures, as well as a rigorous control of potential bias, should therefore be conducted to provide more robust data.

Conclusion

PT had beneficial overall post-intervention effects on balance and postural stability after stroke. Only functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention and sensory interventions seemed to be immediately effective in improving balance or postural stability respectively. The heterogeneity of PT studied and the weak methodological quality of studies strongly limited the meaning and the confidence in findings.

Supporting information

S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Fig. Risk of bias.
(DOCX)

S2 Fig. Funnel plots.
(DOCX)

S3 Fig. Forest plot of physical therapy versus no treatment. Outcome: Balance, post-intervention effects. Subgroup: risk of bias.
(DOCX)

S4 Fig. Meta-regression of effects of PT according to duration of PT.
(DOCX)

S5 Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Balance, post-intervention effects. Subgroup: risk of bias.
(DOCX)

S6 Fig. Forest plot of physical therapy versus no treatment. Outcome: Mediolateral postural deviation EO, post-intervention effects. Subgroup: risk of bias.
(DOCX)

S7 Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Mediolateral postural deviation EO, post-intervention effects. Subgroup: risk of bias.
(DOCX)

S8 Fig. Forest plot of physical therapy versus no treatment. Outcome: Postural stability EO, post-intervention effects. Subgroup: risk of bias.
(DOCX)

S9 Fig. Forest plot of physical therapy. Outcome: Postural stability EC, post-intervention effects.
(DOCX)

S10 Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Postural stability EO, post-intervention effects. Subgroup: risk of bias.
(DOCX)

S11 Fig. Forest plot of physical therapy. Outcome: Autonomy. Subgroup: Categories of PT.
(DOCX)

S12 Fig. Forest plot of physical therapy versus no treatment. Outcome: Autonomy, post-intervention effects. Subgroup: risk of bias.
(DOCX)

S13 Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Autonomy, post-intervention effects. Subgroup: risk of bias.
(DOCX)

S1 Table. Search strategy in databases.
(DOCX)

S2 Table. Identification of studies included in the systematic review and meta-analysis.
(DOCX)

S3 Table. Characteristics of studies and participants.
(DOCX)

S4 Table. Overall score of risk of bias and ethic statement for each study included.
(DOCX)

S5 Table. Results of Egger tests detecting bias of publication.
(DOCX)

S6 Table. Description of PT.
(DOCX)

S7 Table. Duration of PT.
(DOCX)

S8 Table. Outcome measures.
(DOCX)

S9 Table. Results of subgroup analyses according to the time since post-stroke.
(DOCX)

S10 Table. Results of subgroup analyses according to the location of stroke lesion.
(DOCX)

S11 Table. Summary of findings and quality of the evidence.
(DOCX)

S1 Protocol. Study protocol published.
(PDF)

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Writing – review & editing: Aurélien Hugues, Julie Di Marco, Shams Ribault, Hugo Ardaillon, Yufeng Xue, Michel Cucherat, Isabelle Bonan, François Gueyffier, Gilles Rode.

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2.4.3. Article 3

PLOS ONE

RESEARCH ARTICLE

Publication language and the estimate of treatment effects of physical therapy on balance and postural control after stroke in meta-analyses of randomised controlled trials

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Abstract

Background

Findings regarding the impact of language bias on treatment effect estimates (TEE) are conflicting, and very few studies have assessed these impacts in rehabilitation. The purpose was to compare TEE between studies published in non-English language (SPNEL) and those published in English language (SPEL) included in a previously published meta-analysis assessing the effects of physical therapy on balance and postural control after stroke.

Methods

Six databases were searched until January 2019. Two independent reviewers selected randomised trials, extracted data, and assessed risk of bias. We conducted subgroup meta-analyses according to the language of study publication, then compared TEE between SPEL and SPNEL subgroups by using a random-effects meta-regression model.

Results

From 13,123 records, 132 SPEL (n = 5219) and 13 SPNEL (n = 693) were included. SPNEL had a weight in the pooled estimate (8.2%) significantly lower than SPEL (91.8%; p<0.001). Compared to SPEL, SPNEL had both significantly worse methodological quality (p = 0.002) and quality of reporting for blinding of outcome assessment (p<0.001); and a significantly worse quality of reporting for incomplete outcome data (p<0.001). SPNEL had a significantly worse precision (*i.e.* inverse of variance) of TEE than SPEL (p = 0.005). Overall, the TEE was not significantly different between SPNEL and SPEL (standardised mean difference

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-0.16, 95% confidence interval [-0.53; 0.22], heterogeneity I^2 = 78%). However, when PT was compared to sham treatment or usual care, SPNEL significantly over-estimated treatment effects (SMD -0.68, 95%CI [-1.03; -0.33], I^2 = 39%) compared to SPEL. Restriction of the search to SPEL only did not change the direction of TEE for 8 out of 9 comparisons.

Conclusions

SPNEL had a worse methodological quality than SPEL and were likely to over-estimate treatment effect. If inclusion of SPNEL in a systematic review is considered to be relevant, the impact of such studies on TEE should be explored by sensitivity analyses to ensure the findings validity.

Introduction

After stroke, patients suffer frequently postural and balance disorders [1–5] leading to an increased risk of falls [6] as well as a reduced level of activity and participation [7,8]. Balance disorders have a negative impact on gait abilities [9–12] and quality of life [13]. Addressing the issue of rehabilitation of stroke patients is therefore relevant. Owing to the large of number of studies investigating rehabilitation after stroke, and particularly that of balance disorders, meta-analyses evaluating the effects of physical therapy (PT) on balance after stroke are important tools to help health professionals make decisions in clinical practice [14]. To ensure the highest possible validity, the Cochrane Collaboration recommends to prevent publication bias by performing a large and extensive literature search including grey literature and unpublished studies [15]. This is supported by evidence of an association between direction of results and publication; studies with positive or significant results are more likely to be published than those with negative or non-significant results [16–24]. For example, Dechartres *et al.* (2018) showed a treatment effect overestimation of 10% in favour of published trials compared to unpublished trials [16]. The Cochrane Collaboration also recommends to prevent language bias by not restricting the search to studies published in English language (SPEL) only [15]. However, studies investigating language bias report divergent results [18,25]. For instance, Egger *et al.* (1997) found that non-statistically significant trials were more likely to be published in a language other than English [26] whereas other studies found a treatment effect overestimation (14 to 16%) in favour of studies published in non-English language (SPNEL) compared to SPEL [16,27,28]. The impact of language could vary according to different specialties of medicine and health. The over-estimation of treatment effects by SPNEL was found in complementary and alternative medicine but not in conventional medicine [27,28]. To the best of our knowledge, the influence of publication language has not yet been described in the field of rehabilitation, and more specifically in the evaluation of the effects of PT on postural control and balance after stroke. The purpose of the present study was therefore to determine the contribution and impact of SPNEL and SPEL on estimates of treatment effects and conclusions of such analyses.

Methods

The study presented herein is a secondary analysis of a previously published meta-analysis, Hugues *et al.*, 2019 [29]. For the latter, we established a protocol following the recommendations of the PRISMA statement [30] and the Cochrane Collaboration [15], which was

registered in PROSPERO (CRD42016037966), and published [31]. We therefore only briefly report herein the method used.

Selection criteria

We included all randomised controlled trials (RCTs) assessing the efficacy of PT on postural control and balance in adult stroke patients (≤18 years) without language restriction. Only the primary outcomes were considered for the selection of trials. One of the outcomes was balance measured by the Berg Balance Scale (BBS) or the Postural Assessment Scale for Stroke (PASS) that reflected functional ability of patients. The other outcomes assessed postural control and were postural deviation and postural stability. Autonomy was the secondary outcome, measured by the Barthel Index, the Functional Independence Measure, the Activities of Daily Living, or the Instrumental Activities of Daily Living scales.

Sources

We searched MEDLINE, Elsevier databases (*i.e.* EMBASE until October 2015, SCOPUS thereafter), Cochrane Central Register of Controlled Trials, PEDro, Pascal, and Francis databases from inception until 14 January 2019. The search strategy and keywords are described in the published protocol and the meta-analysis [29,31]. Unpublished trials and grey literature were searched by contacting experts, reading conference proceedings, and with the help of a librarian. Unpublished studies, conference abstracts, and presentations were searched without language restriction.

Study selection, data extraction, and risk of bias assessment

Two independent authors (AH, JDM) selected all records according to the selection criteria, then conducted data extraction and assessed risk of bias for each study included. In case of disagreement for the selection and the extraction, we requested the judgement of three other authors (GR, IB, FG) to resolve conflicts [31]. In case of disagreement for the assessment of the risk of bias, we also asked the judgement of two other authors (MC, FG) to resolve conflicts [31]. We extracted data related to study design, participant characteristics, risk of bias, PT characteristics, and outcomes [29,31]. We assessed risk of bias for each study following the risk of bias scale of the Cochrane Collaboration [15]. The risk of bias for each item (*i.e.* random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, blinding of patients and personnel, selective reporting, and other bias) was judged as low, high, or unclear. All outcomes were continuous measures. We determined treatment effect estimates of each study for each outcome by extracting the number of participants, the mean value and the standard deviation (SD) in each group.

Data synthesis and analysis

In Hugues *et al.* [29], we compared PT to no treatment and PT to sham treatment or usual care. For each outcome, we determined the post-intervention effect by the change from baseline to the immediate post-intervention assessment, and the persisting effect by the change from baseline to the last follow-up assessment. To estimate the mean and SD values of the change score when they were not reported by authors in the published article, we used the most parsimonious statistical treatment. When we needed to perform an imputation of the change SD, we used the most conservative correlation coefficient [15]. The treatment effect estimate was based on the difference between groups of changes from baseline in each group. The pooled estimate of treatment effects was based on the inverse variance method and was

expressed for each outcome by the standardised mean difference (SMD) and its 95% confidence interval (95%CI).

To evaluate the impact of language, we performed subgroup meta-analyses according to language of publication (SPEL and SPNEL) and using a random-effects model. We then compared the weight, the variance, the precision (*i.e.* inverse of variance), the SMD (expressed in absolute value indicating the magnitude of effect, and in real number with the sign indicating in addition the direction of effect), the number of studies, and the number of participants of pooled estimates between SPEL and SPNEL subgroups. We subsequently calculated the difference of treatment effect between study subgroups for each outcome by means of the standardised difference between pooled treatment effect estimates of each subgroup meta-analysis, using a random-effects meta-regression model to incorporate heterogeneity between studies. We then performed a meta-analysis of theses treatment effect differences by using a random-effects model to estimate the overall effect of language.

We investigated differences of methodological quality between SPEL and SPNEL by comparing the number of studies judged as having a low risk of bias to that having an unclear or high risk. To better understand effects of language, we investigated whether the difference between the treatment effect estimate from all studies without restriction of publication language and that from SPEL only depended on the weight of SPNEL subgroup. To estimate the difference of quality of reporting between SPEL and SPNEL, we compared the number of studies judged as having an unclear risk of bias in each group. After having assigned a discrete value to three levels of judgement for all items of risk of bias (high: 0, unclear: 1, low: 2), the overall score for the risk of bias was compared between SPEL and SPNEL. We assessed the risk of publication bias by funnel plots, contour-enhanced funnel plot, and Egger tests [15,32,33].

We compared characteristics of studies, PT, and outcomes between SPEL and SPNEL. Categorial or qualitative measures were compared using Fisher's exact test or Chi^2 test, and continuous measures were compared by non-parametric tests, if the hypothesis of normal distribution was rejected or by parametric tests, otherwise. We considered a p-value$\leq$0.05 as statistically significant. We performed all statistical analyses using R software (R Foundation for Statistical Computing, Vienna, Austria; available in http://www.R-project.org/; version 3.6.1).

Results

Study selection

The selection process is reported in Fig 1. Briefly, among the 13,123 records identified, we selected 145 studies for the qualitative synthesis. Data were available for 127 studies. For full-text eligibility, 56 of 803 studies were translated by co-authors (Chinese: n = 27, German: n = 6, Korean: n = 5, Spanish: n = 4, Russian: n = 3, Italian: n = 2, Persian: n = 2, Portuguese: n = 2, Turkish: n = 2, Japanese: n = 1, Norwegian: n = 1, Polish: n = 1). Among the 145 studies selected, 132 were SPEL and 13 were SPNEL (Chinese: n = 7, Korean: n = 3, Persian: n = 1, Portuguese: n = 1, Spanish: n = 1; S1 Fig and S1 Table).

Study and participant characteristics

The date of publication for SPEL ranged from 1988 to 2019, and that for SPNEL ranged from 2004 to 2018 (S2 Fig). All SPNEL were parallel group RCTs and 14% of SPEL were cross-over RCTs, without significant difference between groups. The number of intervention groups in the study were significantly different between SPEL and SNPEL (p = 0.03). The number, the sex, and the age of participants included were not significantly different between SPEL and SNPEL. There was also no significant difference in terms of stroke lesion characteristics (location, number of episodes, side, aetiology and time post-stroke), and the use of brain imagery to

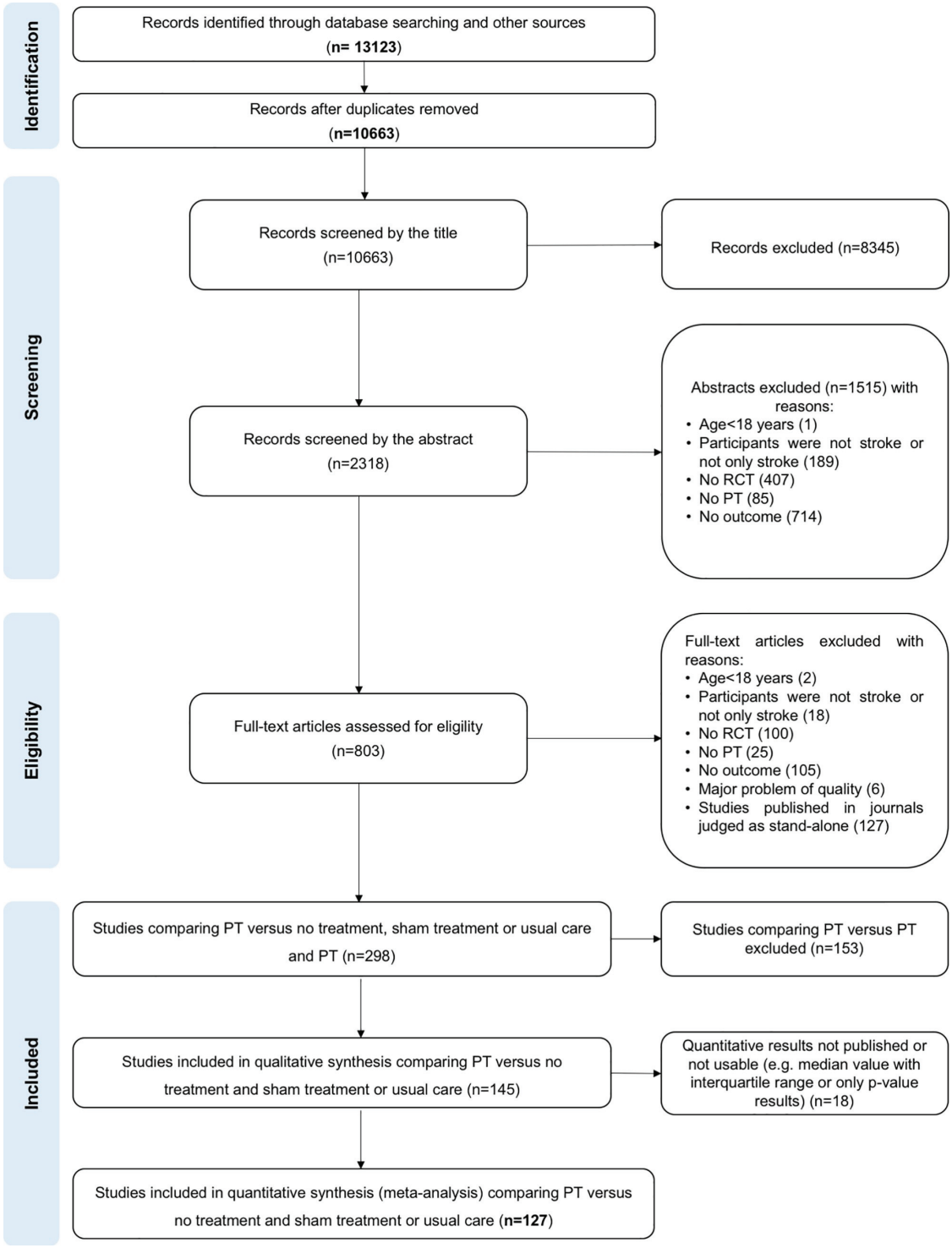

Fig 1. Study flow diagram.

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explore the stroke lesion. SPEL reported significantly more frequently the consultation of an ethics committee than SPNEL ($p<0.001$), whereas no significant difference was found for the reporting of the respect of the Helsinki declaration (Table 1).

Risk of bias

SPEL had a significantly better methodological quality than SPNEL for blinding of outcome assessment ($p = 0.002$; Fig 2). The quality of reporting was significantly better in SPEL than SPNEL for blinding of outcome assessment ($p<0.001$) and incomplete outcome data ($p<0.001$; Fig 2; S3 Fig and S2 Table). There was a trend towards a higher overall score for risk of bias in SPEL than SPNEL ($p = 0.07$; S4 Fig and S3 Table). In case of PT compared to NT, funnel plots and Egger tests showed no suspicion of publication bias for SPEL only and for all studies together (SPEL and SPNEL). When PT was compared to ST/UC, a potential publication bias was suspected for post-intervention effects on balance, postural stability eyes open (EO), and autonomy, as well as for persisting effects on balance and autonomy when assessment included all studies together (SPEL and SPNEL); when SPEL only were assessed, the same potential publication bias was found except for post-intervention effects on autonomy (S5 and S6 Figs and S4 and S5 Tables).

SPEL, studies published in English language; SPNEL, studies published in non-English language.

Physical therapy and outcomes

SPNEL used more frequently an "on-top" comparison than SPEL (S6 Table). Among the categories of PT the most frequently investigated in SPNEL, there were categories of PT also frequently investigated in SPEL (such as functional task-training) and traditional PTs of the countries where the investigations took place (such as acupuncture in China). For instance, acupuncture was a category of PT frequently assessed in SPNEL (24%), and theses SPNEL contributed to 80% of assessments of acupuncture (S7 Table). The mean duration of session, number of weeks, and total duration of PT delivered were not significantly different between SPEL and SPNEL. SPNEL provided a significantly greater number of sessions per week (mean±SD: 4.6±1.6) and a greater total number of sessions (mean±SD: 20.2±10.8) than SPEL (respectively mean±SD: 3.1±1.9, $p = 0.04$; and mean±SD: 13.6±14.7, $p = 0.04$; S8 Table). Balance was the most frequent outcome assessed in both SPEL and SPNEL, and BBS was the scale of balance the most frequently used in both subgroups (S9 Table).

Impact of language on estimation of effects

The SPEL subgroup included significantly more studies and participants (respectively, mean: 11.8, SD: 11.2, range: 0–44; and mean: 549.4, SD: 536.8, range: 0–1979) than the SPNEL subgroup (respectively, mean: 1.4, SD: 2.1, range: 0–8; $p<0.001$; and mean: 65.4, SD: 97.0, range 0–375; $p<0.001$; Fig 3). The weight of the SPEL subgroup in pooled estimates (mean: 91.8%, SD: 8.4%, range: 77–100%) was significantly greater than that of the SPNEL subgroup (mean: 8.2%, SD: 8.4%, range: 0–23%; $p<0.001$; Fig 3). The SMD of pooled estimates in the SPEL subgroup (mean: 0.35, SD: 0.21, range: 0.08–0.92) was not significantly different to that in the SPNEL subgroup (mean: 0.51, SD: 0.59, range: -0.72–1.41; $p = 0.22$; Fig 3). Using the absolute value, the SMD of pooled estimates in the SPEL subgroup (mean: 0.35, SD: 0.21, range: 0.08–0.92) was significantly lower than that in the SPNEL subgroup (mean: 0.67, SD: 0.38, range: 0.28–1.41; $p = 0.03$; Fig 3). The precision (inverse of variance) of pooled estimates in the SPEL subgroup (mean: 8.8, SD: 4.0, range 3.2–15.3) was significantly higher than that in the SPNEL subgroup (mean: 4.3, SD: 2.0, range: 2.0–8.4; $p = 0.005$; Fig 3).

Table 1. Summary of characteristics of studies and participants.

	SPEL	SPNEL	Subgroup difference (p-value)
Studies / comparisons, n	132 / 155	13 / 17	NA
Date of publication	From 1988 to 2019	From 2004 to 2018	NA
Crossover / parallel group, n (%)	18 (14%) / 114 (86%)	0 (0%) / 13 (100%)	p = 0.33[a]
Studies with 2 / 3 / 4 groups, n (%)	113 (86%) / 16 (12%) / 3 (2%)	8 (62%) / 5 (38%) / 0 (0%)	p = 0.03[a]
Participants, sum / mean±sd / range	5219 / 39.5±43.6 / 7–408	693 / 53.3±37.6 / 12–145	p = 0.08[b]
Age in years, mean±sd / range	60.8±6.3 / 46.9–78.5	58.3±4.4 / 50.9–67.0	p = 0.15[b]
Men / Women, %	61% / 39%	61% / 39%	p = 1[a]
Time post-stroke in days, mean±sd / range	528.7±570.7 / 11.0–1985.6	374.9±544.4 / 4.5–1568.7	p = 0.12[b]
Location of stroke lesion			p = 1[c]
Only supratentorial stroke, n (%)	17 (13%)	1 (8%)	
Only brainstem stroke, n (%)	0 (0%)	0 (0%)	
Only cerebellum stroke, n (%)	0 (0%)	0 (0%)	
Only other stroke, n (%)	0 (0%)	0 (0%)	
Mixed location of stroke or not determined, n (%)	115 (87%)	12 (92%)	
Episode of stroke			p = 0.90[a]
Only first episode, n (%)	63 (48%)	5 (38%)	
Only multiple episodes, n (%)	1 (1%)	0 (0%)	
First or multiple episodes, n (%)	11 (8%)	1 (8%)	
Not determined, n (%)	57 (43%)	7 (54%)	
Side of stroke lesion			p = 0.68[c]
Only unilateral stroke, n (%)	107 (81%)	10 (77%)	
Only bilateral stroke, n (%)	0 (0%)	0 (0%)	
Unilateral or bilateral stroke, n (%)	6 (5%)	0 (0%)	
Not determined, n (%)	19 (14%)	3 (23%)	
Aetiology of stroke			p = 0.53[c]
Only ischemic stroke, n (%)	10 (8%)	2 (15%)	
Only haemorrhagic stroke, n (%)	0 (0%)	0 (0%)	
Only ischemic or haemorrhagic stroke, n (%)	82 (62%)	8 (62%)	
Other stroke or not determined, n (%)	40 (30%)	3 (23%)	
Stage of stroke for eligibility or inclusion of participants in studies			p = 0.31[a]
Only acute stroke, n (%)	10 (8%)	1 (8%)	
Only subacute stroke, n (%)	7 (5%)	1 (8%)	
Only chronic stroke, n (%)	55 (42%)	2 (15%)	
Mixed stages or not determined, n (%)	60 (45%)	9 (69%)	
Description of stroke lesion using brain imagery			p = 0.12[a]
No imagery used, n (%)	84 (64%)	6 (46%)	
Use of imagery reported but without description of lesion, n (%)	37 (28%)	7 (54%)	
Imagery used with description of lesion in text, n (%)	11 (8%)	0 (0%)	
Ethics			
Consultation of ethics committee, n (%)	111 (84%)	4 (31%)	p<0.001[a*]
Respect of Helsinki declaration, n (%)	24 (18%)	0 (0%)	p = 0.20[a]

[a] Chi^2 test

[b] Wilcoxon rank sum test

[c] Fisher's exact test

* Significant difference ($p \leq 0.05$) between SPEL and SPNEL.

NA, not applicable; NT, no treatment; PT, physical therapy; SPEL, studies published in English language; SPNEL, studies published in non-English language; ST, sham treatment; sd, standard deviation; UC, usual care

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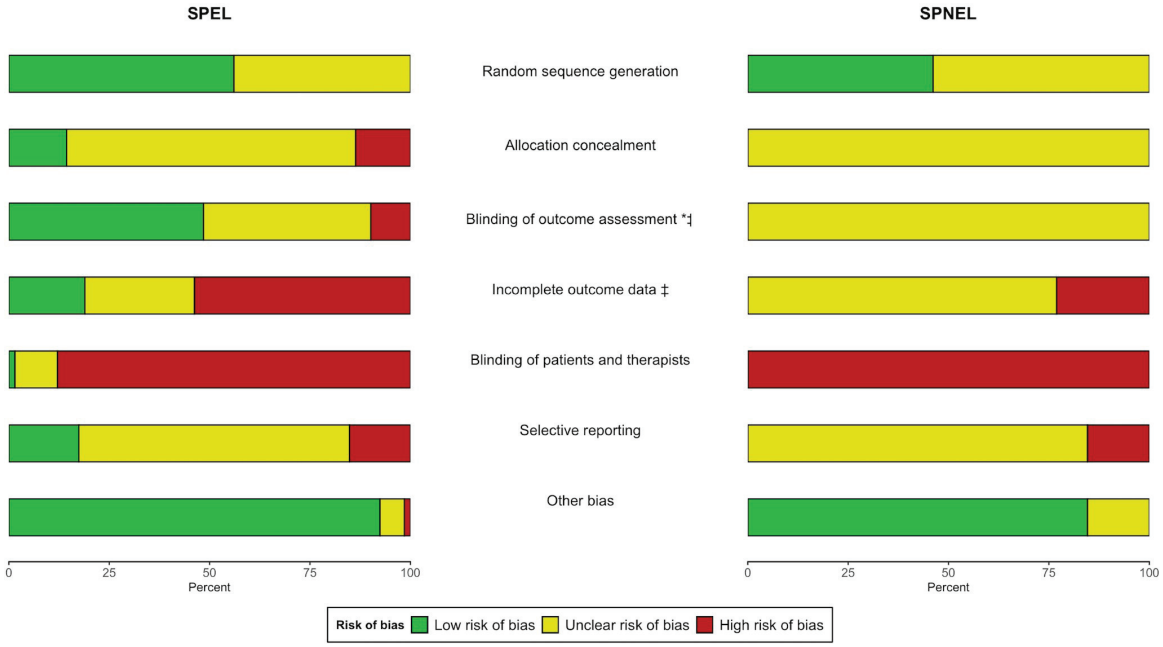

Fig 2. Comparison of risk of bias between SPEL and SPNEL. * Significant difference ($p \leq 0.05$) for the quality of studies (low risk versus both unclear and high risks); ‡ Significant difference ($p \leq 0.05$) for the quality of reporting (amount of unclear risk).

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Six of the 9 comparisons including 2 languages of publication subgroups showed a higher SMD in the SPNEL subgroup compared to the SPEL subgroup, whereas 2 others showed a higher SMD in the SPEL subgroup than in the SPNEL subgroup. In 4 comparisons, there was substantial heterogeneity ($I^2 \geq 50\%$) between SPNEL and SPEL subgroups (Fig 4). We found that the SPNEL subgroup had a significantly greater SMD than the SPEL subgroup for immediate effects on autonomy when PT was compared to ST/UC; the treatment effect was significantly in favour of PT in the SPNEL subgroup and non-significant in the SPEL subgroup. For persisting effects on balance when PT was compared to NT, we found that the SPEL subgroup had a significantly greater SMD than the SPNEL subgroup; the treatment effect was significantly in favour of PT in the SPEL subgroup and significantly in favour of the control group in the SPNEL subgroup. For all other comparisons, including both SPEL and SPNEL subgroups, the direction of treatment effects in subgroups was similar (Figs 4 and 5). Overall, the treatment effect estimate was not significantly different between the SPNEL subgroup and the SPEL subgroup (SMD -0.16, 95%CI [-0.53; 0.22], Fig 5) with substantial heterogeneity ($I^2 = 78\%$). A subgroup meta-analysis according to outcome, comparator group or type of effects assessed found that SPNEL had significantly greater effects than SPEL with moderate heterogeneity when the PT was compared to ST/UC (SMD -0.68, 95%CI [-1.03; -0.33], $I^2 = 39\%$; Fig 5). The difference between SMDs from all studies without restriction of publication language (SPEL+SPNEL) and these from SPEL only was not significantly correlated with the weight of SPNEL subgroup ($p = 0.77$). We found a significant linear regression between SMDs from all studies without restriction of publication language (SPEL+SPNEL) and these from SPEL (estimate 0.68, $R^2 = 0.71$, $p = 0.003$; S7 Fig). Among the 96 studies which contributed to the 9 comparisons including both SPEL and SPNEL subgroups, 38 contributed to two different comparisons, 2 to 3 and 11 to 4. Sensitivity analyses found that removing the SPNEL subgroup from the 9 comparisons which

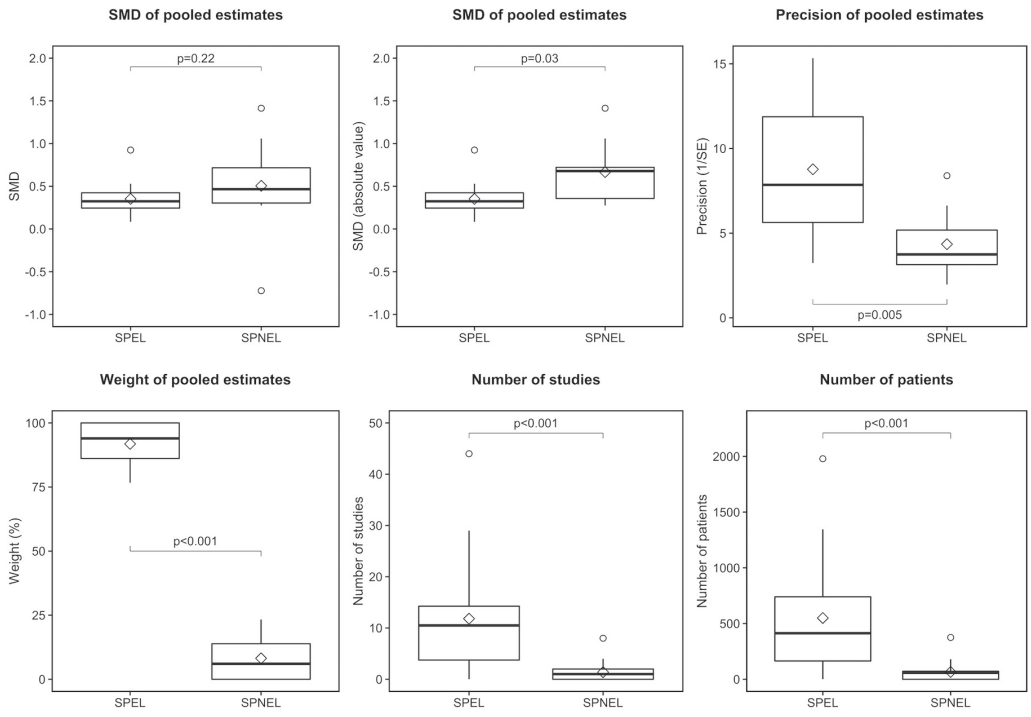

Fig 3. Comparison of treatment effect estimates between SPEL and SPNEL. SE, standard error; SMD, standardised mean difference; SPEL, studies published in English language; SPNEL, studies published in non-English language.

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included both SPNEL and SPEL subgroups did not change the direction of treatment effect for 8 of them; only the estimation of persisting effects of PT compared to NT on balance became significantly in favour of PT after exclusion of SPNEL (S8 and S9 Figs).

Discussion

The present study found that there were fewer SPNEL than SPEL in analyses reported in Hugues *et al.* (2019) [29], and that their overall weight was lower than that of SPEL. The precision of treatment effect estimates from SPNEL was worse than that from SPEL, which could be explained by the lower number of SPNEL. The effect size magnitude from SPNEL was larger than that from SPEL. However, the weighted analysis of treatment effect estimates found that, overall, there was no significant difference between SPEL and SPNEL, although the substantial heterogeneity limits interpretation of results. This led to subgroup analyses that allowed to conclude that when PT was compared to ST/UC, the treatment effect estimate was overestimated by SPNEL compared to SPEL. Jüni *et al.* (2002; a pooled analysis of 50 meta-analyses) and Dechartres et *al.* (2018; a pooled analysis of 147 meta-analyses) have reported that the treatment effect estimate from SPNEL was, respectively, a mean 16% (ratio of odds ratios 0.84, 95%CI [0.74; 0.97], $I^2 = 66\%$) and 14% (ratio of odds ratios 0.86, 95%CI [0.78; 0.95], $I^2 = 0\%$) more beneficial than that from SPEL [16,28]. In subgroup analyses across medical specialities, Jüni *et al.* found a significantly greater treatment effect from SPNEL than SPEL in the complementary medicine subgroup (4 meta-analyses) and a non-significant difference of treatment effect between SPEL and SPNEL in the conventional medicine subgroup (46 meta-analyses),

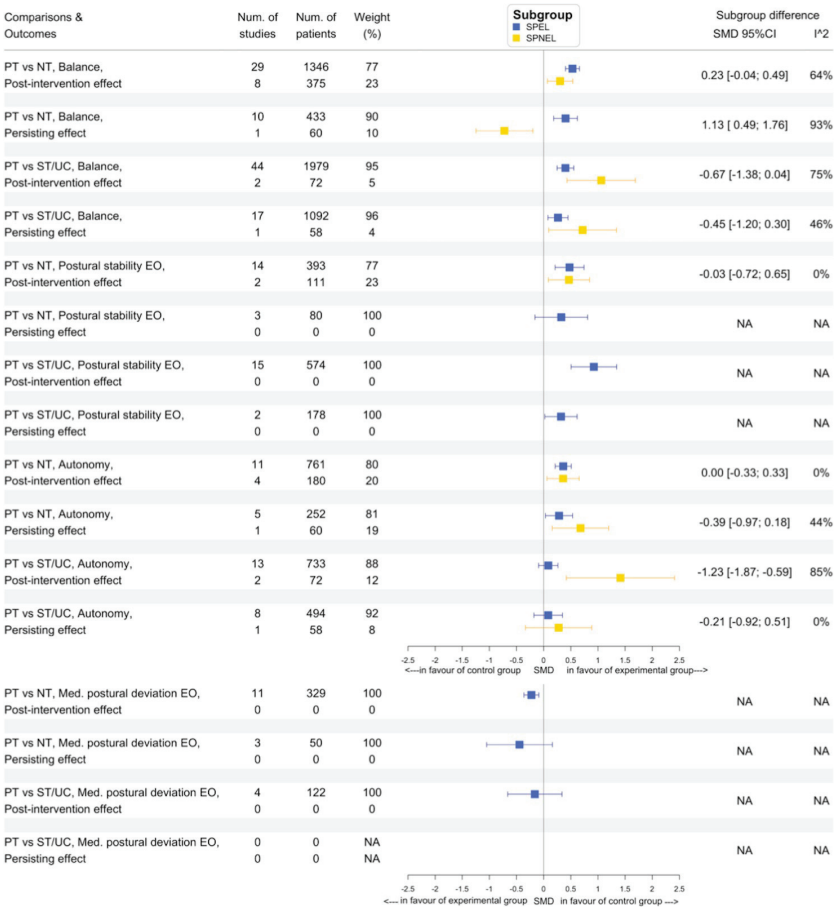

Fig 4. Summary forest plot of subgroup analyses for all outcomes according the language of study publication. Weight is expressed in percent. EO, Eyes open; Med, mediolateral; NA, not applicable; Num, number; NT, no treatment; PT, physical therapy; SPEL, studies published in English language; SPNEL, studies published in non-English language; ST/UC, sham treatment and usual care; vs, versus.

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without significant difference between subgroups [28]. After having found a non-significant difference between SPEL and SPNEL and a substantial heterogeneity in the overall analysis, Pham *et al.* (2005; pooled analysis of 42 meta-analyses) reported a treatment effect from SPNEL significantly greater than that from SPEL in the complementary medicine subgroup (8 meta-analyses), and a non-significant difference between SPNEL and SPEL in the conventional medicine subgroup (34 meta-analyses); the between-subgroup difference was not reported in the publication [27]. Although results presented in the present study do not lead to clear and unequivocal interpretations, they suggest that there was a language bias in the field of rehabilitation of balance and postural disorders after stroke. The results were, however, based on a lower number of studies than those of the analyses cited above, and therefore, a lack of statistical power could explain the non-significance of certain comparisons.

Another interesting point of the present study is that SPNEL were worse than SPEL for methodological quality and reporting quality regarding blinding of outcome assessment, and for reporting quality regarding incomplete outcome data. Other studies also reported a lower

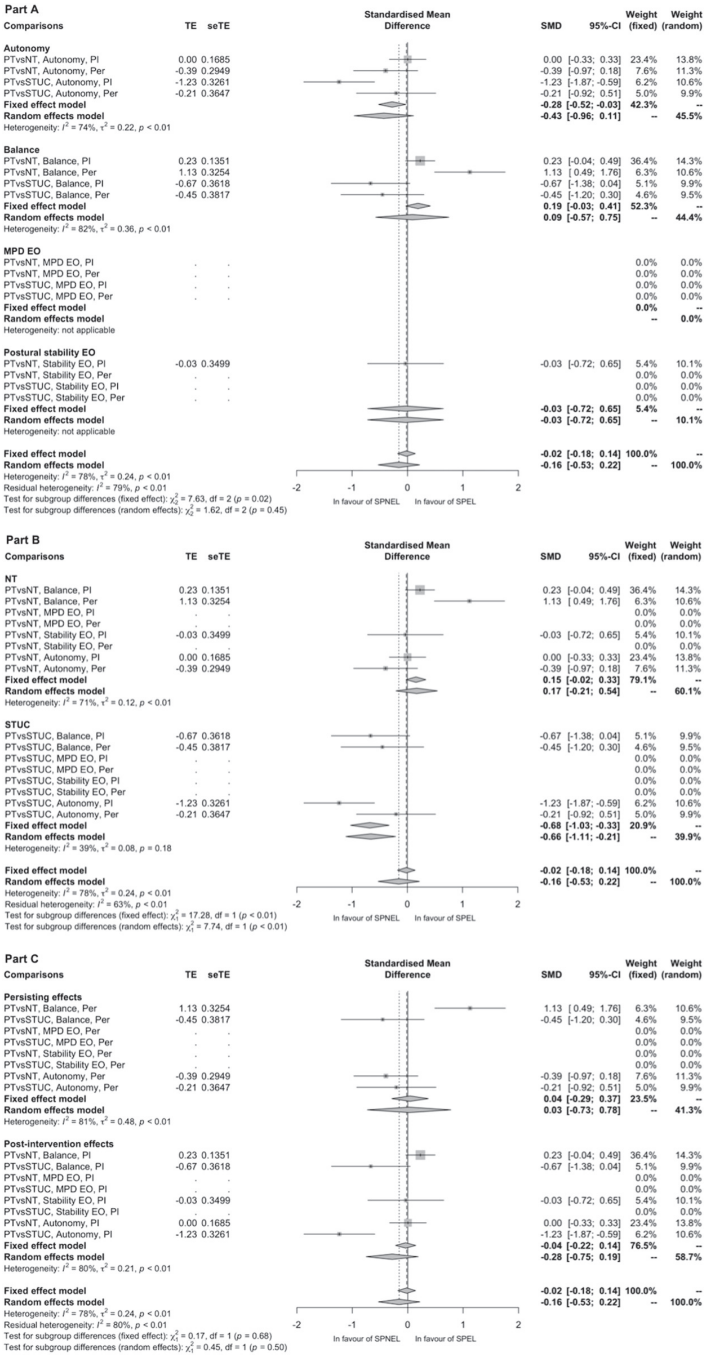

Fig 5. Forest-plot of estimates of treatment effects from studies published in non-English language compared to those published in English language for analyses of all outcomes. EO, eyes opened; Imm, immediate; MPD, mediolateral postural deviation; NT, no treatment; Per, persisting; PT, physical therapy; seTE, standard error of treatment effect; SMD, standardised mean difference; SPEL, studies published in English language; SPNEL, studies published in non-English language; STUC, sham treatment and usual care; TE, treatment effect; vs, versus.

https://doi.org/10.1371/journal.pone.0229822.g005

methodological quality of SPNEL compared to SPEL [16,28,34]. A low methodological quality of studies limits the validity of evidence reported and could explain the overestimation of effects by SPNEL. Indeed, it has been previously established that a high risk of bias for blinding outcome assessment and an inadequate or unclear allocation concealment were correlated with an overestimated treatment effect [35–37].

The current recommendations for systematic reviews promote searches without language restriction and the inclusion of SPNEL to limit language bias [15]. This approach increases the workload and costs, and therefore whether or not it is useful and relevant to search for SPNEL to estimate treatment effects of intervention may be questioned. In the study presented herein, limiting the search to the SPEL only would not have changed the direction of treatment effect for 8 out of 9 comparisons performed [29]. However, for 1 of the comparisons, the direction of treatment effect would have been changed by restricting the search to SPEL only, from a non-significant effect towards a significantly beneficial effect of PT. Therefore, the present study found that the exclusion of SPNEL from the literature search would have led to a weak, but not inexistent, risk of misinterpretation of effects. In addition, SPNEL were the main source of information concerning some particular topics of rehabilitation (*e.g.* acupuncture in studies published in Chinese language), despite the low weight of SPNEL in the summary treatment effect estimate. In particular cases, it therefore seems that to consider SPNEL in reviews on rehabilitation could be relevant in view of regional specificities of some categories of PT.

Conclusion

The present study found that the methodological quality of SPNEL was worse than that of SPEL, and were likely to over-estimate treatment effect. If inclusion of SPNEL in a systematic review is considered to be relevant, the impact of such studies on treatment effect estimates should therefore be explored by sensitivity analyses to ensure the validity of findings.

Supporting information

S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Fig. Histogram of studies according to the language of publication for studies included.
(DOCX)

S2 Fig. Date of publication for studies included.
(DOCX)

S3 Fig. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study.
(DOCX)

S4 Fig. Summary of overall score of risk of bias.
(DOCX)

S5 Fig. Funnel plot for all studies (SPEL and SPNEL).
(DOCX)

S6 Fig. Funnel plot for all studies for SPEL only.
(DOCX)

S7 Fig. Linear regression between treatment effect estimates of all studies (SPEL and SPNEL) and these of SPEL only.
(DOCX)

S8 Fig. Forest plots of physical therapy versus no treatment. Subgroup: Language of publication of studies.
(DOCX)

S9 Fig. Forest plots of physical therapy versus sham treatment or usual care. Subgroup: Language of publication of studies.
(DOCX)

S1 Table. Studies included in the systematic review and meta-analysis.
(DOCX)

S2 Table. Summary of risk of bias of studies included.
(DOCX)

S3 Table. Summary of overall score of risk of bias.
(DOCX)

S4 Table. Results of Egger tests detecting bias of publication for all studies (SPEL and SPNEL).
(DOCX)

S5 Table. Results of Egger test detecting bias of publication for SPEL only.
(DOCX)

S6 Table. Summary of comparisons of intervention.
(DOCX)

S7 Table. Summary of categories of physical therapy investigated in studies included.
(DOCX)

S8 Table. Summary of duration of physical therapy compared.
(DOCX)

S9 Table. Summary of outcome measures.
(DOCX)

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Writing – original draft: Aurélien Hugues.

Writing – review & editing: Aurélien Hugues, Julie Di Marco, Isabelle Bonan, Gilles Rode, Michel Cucherat, François Gueyffier.

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2.4.4. Manuscrit d'article en format « pré-soumission » 1

Cumulative effects of mixed bottom-up and top-down approaches in rehabilitation of balance after stroke. A network meta-analysis

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Abstract

Introduction: After stroke patients had balance disorders leading to activity limitations and participation restrictions. Effects of physical therapy (PT) on balance were usually assessed according to the nature of PTs delivered. Following the example of the rehabilitation of hemineglect, the different PTs used for the rehabilitation of balance could be considered according to the type of integration of information (explicit or implicit): top-down (TD), bottom-up (BU) and mixed.

Objective: To determine post-intervention and persisting effects of PT on balance in patients with stroke according to TD, BU and mixed approaches.

Methods: Medline, Embase/Scopus, Cochrane Central Register of Controlled Trials, PEDro, Pascal, and Francis databases were searched until January 2019 without language restriction. All randomised controlled trials (RCT) assessing effects of PT on balance in adult patients after stroke were included. Relative effects among approaches by standardised mean difference (SMD) and its 95% confidence interval (95%CI), and the rank ordering of approaches were estimated by a network meta-analysis. A subgroup meta-analysis was conducted if the

assumptions to perform a NMA were not satisfied or if the number of RCTs were insufficient (<10 RCTs).

Results: We selected 105 RCTs. BU, TD and mixed approaches had beneficial post-intervention effects compared to sham treatment or usual care (ST/UC; SMD=0.36, 95%CI [0.14; 0.58]; SMD=0.42, 95%CI [0.13; 0.71]; and SMD=0.43, 95%CI [0.25; 0.61], respectively). Only mixed approach had beneficial persisting effects compared to ST/UC (SMD=0.96, 95%CI [0.52; 1.39]).

Conclusion: While PTs based on TD, BU and mixed approaches had beneficial post-intervention effects, only PTs based on a mixed approach had cumulative beneficial post-intervention and persisting effects on balance after stroke.

Keywords

Stroke, rehabilitation, meta-analysis, top-down, bottom-up, balance

Introduction

Patients with stroke experience balance disorders, likely to result in falls,[1,2] and strongly suspected to be responsible to activity limitations and participation restrictions.[3–6] Balance is associated with gait,[7–10] and is a predicting factor for recovery of gait.[11,12] The improvement of balance was found as more important to regain gait following stroke than the improvement of paretic lower limb strength or motor performance.[13] Therefore, rehabilitation of balance is relevant.

Several meta-analyses have assessed effects of physical therapy (PT) on balance in patients with stroke according to the nature of PTs delivered.[24–27] The findings showed limited evidences in favour of PT, with beneficial effects immediately after intervention without persisting effect, besides a high number of different PTs assessed.

Concerning these different PTs assessed, 3 types of processing may be considered according the explicit or implicit integration of information: top-down (TD), bottom-up (BU) and mixed.[28] TD processing is defined as “the flow of information from ‘higher’ to ‘lower’ centres, conveying knowledge derived from previous experience rather than sensory stimulation” and BU processing as “information processing that proceeds in a single direction from sensory input, through perceptual analysis, towards motor output, without involving feedback information flowing backwards from ‘higher’ centres to ‘lower’ centres” (p. 201).[29]

These two types of processing have already been proposed for the understanding of attention,[29–37] memory,[31,38] sensory perception,[39–42] direction of gaze[43], and mental imagery.[42]

In rehabilitation, TD approach would be considered as that aiming at improving sensory-motor deficit by acting on the patient's awareness (explicit), while the BU approach would be that aiming at modifying the sensory-motor information by passive manipulations or visuo-motor adaptation which bypasses the patient's awareness (implicit).[28,44,45] BU and TD approaches may be mixed. This categorization of rehabilitation methods according to the type of approach (TD, BU and mixed) has been used in previous studies assessing effects of rehabilitation on hemineglect.[44–48] To our knowledge, this categorization has never been applied for the rehabilitation of balance after stroke. The aim of the present study was to determinate effects of PTs on balance according to BU, TD or mixed approach in patients with stroke by means of a network meta-analysis.

Methods

Registered in Prospero (CRD42021224377), the protocol has been developed according to PRISMA statements [49] and recommendations from Cochrane Collaboration.[50]

Selection criteria

We included all randomised controlled trials (RCTs) without language restriction which assessed effects of PT on balance in adults (18 years or more) after stroke compared to no treatment (NT), sham treatment (ST) or usual cares (UC). PT was defined by the World Confederation for Physical Therapy.[51] Balance was assessed by the Berg Balance Scale or the Postural Assessment Scale for Stroke which reflect functional abilities of balance of patients.[52–55]

Search

We searched Medline, Elsevier databases (*i.e.* EMBASE until October 2015, SCOPUS thereafter), Cochrane Central Register of Controlled Trials, PEDro, Pascal, and Francis databases from inception until 14 January 2019. The search strategy was reported in a study protocol and a meta-analysis previously published.[24,59] The search was not restricted

according to publication language. To get unpublished RCTs, we contacted of experts and searched in conference proceedings or in registers of clinical trials, with the help of a librarian.

Study selection, data extraction, and risk of bias assessment

A pair of independent authors (AH and JDM) screened title and abstract of records identified, then selected studies by reading of full-text publication, and finally conducted the data extraction and the risk of bias assessment for all studies selected. Data extracted were: study design, participants' characteristics, risk of bias, PT characteristics, and outcomes. In case of unclear or missing data, the authors of studies were contacted. The risk of bias assessment was conducted by using the risk of bias tool from the Cochrane Collaboration. Each PT was categorised according to the type of approach by two authors (AH and JDM). Three categories were defined: TD, BU, and mixed approaches.[44–46,60,61] TD approach included functional task-training (associated with or without mental imagery, virtual reality, cueing, mirror therapy, biofeedback, or observation and imitation of tasks),[62–64] active musculoskeletal intervention such as active strengthening or active mobilization,[65,66] body awareness therapy,[67] sensory intervention based on training or relearning of sensitive discrimination, [68,69] visual and oculomotor training,[44] constraint-induced therapy,[70,71] and active cardiopulmonary intervention.[65,66] BU approach included passive musculoskeletal intervention such as passive mobilization or immobilisation,[72,73] musculoskeletal intervention by electrostimulation,[74] sensory manipulation such as prismatic adaptation.[75] Mixed approach was defined as that combining both TD and BU approaches. If the categorisation of a PT was problematic, this PT was considered as not determined and was not included in analyses. In case of disagreement, we requested the judgement of other authors to resolve conflicts (GR, IB and FG for study selection and data extraction; MC and FG for the risk of bias assessment; GR and IB for PT categorisation).[24,59]

Data synthesis and analysis

Data regarding study design, participants' characteristics, risk of bias, PT characteristics, and outcomes were compared between type of approach. For qualitative measures, Fisher's exact test or Pearson's Chi-squared test were used while for continuous measures, parametric tests were used if the hypothesis of normal distribution was not rejected, or non-parametric tests

otherwise. A p-value ≤0.05 was considered as statistically significant. For multiple comparisons, p-values were adjusted by using the Bonferroni method. We performed all statistical analyses using R software (version 4.0.0).

Treatment effect estimate was based on the difference between intervention groups of changes from baseline for each group. The pooled estimate of treatment effects was computed using the inverse variance method and was expressed by the standardised mean difference (SMD) and its 95% confidence interval (95%CI). A fixed-effect model was applied for a low or moderate heterogeneity (I^2<50%) and a random-effects model for a substantial heterogeneity (I^2≥50%).[50] A post-intervention effect was estimated at the immediate post-intervention assessment, and a persisting effect at the last follow-up assessment.

A frequentist network meta-analysis (NMA) was performed. NMA combine direct and indirect comparisons for the same outcome in order to estimate relative effect among all approaches and rank ordering of the approaches. To limit the risk to be influenced by an outlier, NMA was conducted for networks including at least 10 RCTs. For three-arm RCTs, the mean, the standard deviation (SD) and the sample size of intervention arms assessing the same approach were combined by following the recommendations of Cochrane Handbook (Section 6-5-2-10).[50] After having performed pairwise comparisons, NMA was fitted using a random-effects model if the global network heterogeneity was substantial (I^2≥50%). The geometry of the network was examined by plotting the network graph. A matrix of treatment effect estimates and the proportion of direct and indirect contributions to each comparison were computed. Then, the relative treatment rankings were estimated using P-score, as well as treatment effects of each approach compared to ST/UC. Finally, the validity of results was assessed by using a full design-by-treatment interaction model to examine global inconsistency and a node-splitting method for each comparison to identify local inconsistency. A netheat plot was also used for detecting and locating potential inconsistency in the network. Transitivity assumption was checked by comparing descriptive statistics of study and participants' characteristics. If a global or local inconsistency was found or that the transitivity assumption was not ensured, the validity of results was judged as compromised and results of the NMA were not therefore reported. In this case or when a NMA could not be performed due to an insufficient number of RCTs (<10), a subgroup meta-analysis according to approaches was conducted.

Results

Study and participants' characteristics

Among the 105 studies included (Fig. 1; Appendix 1), the categorisation of PT was available for 100 studies. Thirteen RCTs included more than two groups. There was a total of 113 comparisons: 32 for BU approach, 15 for mixed approach, and 66 for TD approach. There were significantly more comparisons for TD approach than for BU approach (p=0.002) and than for mixed approach (p<0.001), but also significantly more comparisons for BU approach than for mixed approach (p=0.04; Table 1). There was no significant difference between approaches concerning the mean age and the sample size of participants, stroke lesion characteristics (Table 1) and risks of bias (Fig. 2).

Physical therapy

The nature of comparator group was significantly different according to approaches (p<0.001): BU approach was more frequently compared to ST whereas TD and mixed approaches were compared to NT and to UC (Appendix 2). The overall duration of PT delivered was significantly higher in TD approach (median=600.0 min) than in BU approach (median=450.0 min; p=0.02), without difference with mixed approach (median=540 min; TD vs mixed: p=1 and BU vs mixed: p=0.39).

Effects on balance

The NMA of post-intervention effects included 79 studies, 85 comparisons and 3990 participants. BU, TD, and mixed approaches had significant positive SMDs compared to NT and to ST/UC. TD approach had the highest P-score (0.80), followed very closely by mixed approach (0.78), and lastly by BU approach (0.67). SMDs were not significantly different between these 3 approaches (Fig. 3). There was a substantial total heterogeneity (I^2=51.5%; 95%CI [37.2%; 62.5%]) attributable to within-design heterogeneity (p<0.0001), without significant global inconsistency (p=0.51). No local inconsistency was detected (Appendix 3).

The NMA of persisting effects included 29 studies, 31 comparisons and 1660 participants. A substantial total heterogeneity was found (I^2=56.1%; 95%CI [32.5%; 71.5%]) with a significant within-design heterogeneity (p=0.01) and a significant global inconsistency (p=0.03). Even if the global inconsistency became non-significant using a random-effects model (p=0.11), local

inconsistencies were found (Appendix 4). The validity of results was therefore not ensured. The subgroup meta-analysis for persisting effects on balance found a significant positive SMD for mixed approach and non-significant SMDs for BU and TD approaches compared to ST/UC, without within-subgroup heterogeneity and with between-subgroup difference (Fig. 4).

Discussion

The objective of this study was to assess effects of PT on balance according to TD, BU or mixed approach, in patients with stroke by means of a network meta-analysis. Immediately after intervention, BU, TD and mixed approaches were effective. Even if none of these approaches was more effective than another, TD and mixed approaches were likely to be the best approaches. For persisting effects, only mixed approach seemed to be effective compared to ST/UC. With both short- and long-term beneficial effects, mixed approach could be an interesting approach for clinical practisers.

These findings appear consistent with these reported by meta-analyses assessing effects of PT on balance according to the nature of PTs.[24–26] The efficacy of functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention on balance was found recently.[24] This is a category of PT generally based on TD or mixed approach owing to the cognitive involvement to initiate and conduct a functional skill, such as balance or gait.

Short- and long-term effects of mixed approaches on balance could be interpreted as cumulative effects of both BU and TD approaches, causing more long-lasting improvements. Such effects were already found in rehabilitation of hemineglect by mixed approach after stroke.[48,77–79] The non-superiority of mixed approach compared TD and BU approaches on balance immediately after intervention suggests that this cumulative effect of both BU and TD approaches would be not an addition of effect sizes but might rather be the reflect of complementary effects likely to be more adaptative than compensative. Further investigations are needed to clarify this.

This present study has several potential limitations. NMA requires a transitivity assumption. In the study presented herein, there was no difference between groups for the main characteristics of studies. However, the weakness of data reporting for some studies included [24] could limit the exploration of transitivity assumption. A substantial statistical

heterogeneity was often found in NMA and subgroup meta-analyses. The heterogeneity reflects the variability of effects and limits their interpretation. However, the level of heterogeneity found in the analyses could be considered as similar to this measured usually in meta-analyses in rehabilitation, and there was no inconsistency in analyses presented herein.

Conclusion

While PTs based TD, BU and mixed approaches had beneficial post-intervention effects, only PTs based on a mixed (TD and BU) approach had cumulative beneficial post-intervention and persisting effects on balance. Using complementary approaches in rehabilitation could be an advantage, but further investigations are needed to confirm these findings.

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Table 1. Summary of characteristics of studies and participants

	BU approach	TD approach	Mixed approach	p-value
Studies, n / comparisons, n	27 / 32	59 / 66	14 / 15	p<0.001#
Pairwise comparisons†	a	c	b	
Date of publication	From 2005 to 2018	From 1998 to 2018	From 2010 to 2018	
Participants, sum / mean±sd / range	1115 / 34.8±18.1 / 12-82	2772 / 42.0±44.1 / 7-269	771 / 51.4±65.6 / 14-282	p=0.7¶
Age in years, mean±sd / range	58.9±4.2 /49.7-70.1	61.6±6.8 / 48.1-78.5	59.9±7.1 / 49.6-74.5	p=0.1¶
Time post-stroke in days, mean±sd / range	556.6±647.1 / 11.0-1899.3	508.2±561.0 / 4.5-1985.5	487.8±653.0 / 20-1907.5	p=1¶
Location of stroke lesion				p=0.5§
Only supratentorial stroke, n (%)	3 (9%)	7 (11%)	3 (20%)	
Only brainstem stroke, n (%)	0 (0%)	0 (0%)	0 (0%)	
Only cerebellum stroke, n (%)	0 (0%)	0 (0%)	0 (0%)	
Only other stroke, n (%)	0 (0%)	0 (0%)	0 (0%)	
Mixed location of stroke or not determined, n (%)	29 (91%)	59 (89%)	12 (80%)	
Episode of stroke				p=0.7#
Only first episode, n (%)	16 (50%)	33 (50%)	8 (53%)	
Only multiple episodes, n (%)	0 (0%)	1 (1%)	0 (0%)	
First or multiple episodes, n (%)	1 (3%)	9 (14%)	1 (7%)	
Not determined, n (%)	15 (47%)	23 (35%)	6 (40%)	
Laterality of stroke lesion				p=0.2#
Only unilateral stroke, n (%)	29 (91%)	48 (73%)	11 (73%)	
Only bilateral stroke, n (%)	0 (0%)	0 (0%)	0 (0%)	
Unilateral or bilateral stroke, n (%)	0 (0%)	6 (9%)	2 (13%)	
Not determined, n (%)	3 (9%)	12 (18%)	2 (13%)	
Aetiology of stroke				p=0.2§
Only ischemic stroke, n (%)	1 (3%)	6 (9%)	2 (13%)	
Only haemorrhagic stroke, n (%)	0 (0%)	0 (0%)	0 (0%)	
Only ischemic or haemorrhagic stroke, n (%)	25 (78%)	37 (56%)	10 (67%)	
Other stroke or not determined, n (%)	6 (19%)	23 (35%)	3 (20%)	

Stage of stroke for eligibility or inclusion of participants in studies				p=0.4[#]
Only acute stroke, n (%)	2 (6%)	10 (15%)	1 (7%)	
Only subacute stroke, n (%)	0 (0%)	6 (9%)	2 (13%)	
Only chronic stroke, n (%)	14 (44%)	26 (39%)	5 (33%)	
Mixed stages or not determined, n (%)	16 (50%)	24 (36%)	7 (47%)	

† In case of significant difference between approaches, results of multiple pairwise comparisons were reported by using letters. Two approaches were significantly different if no letter was shared between them. Otherwise, these were not significantly different; [#] Pearson's Chi-squared test; [‡] Wilcoxon rank sum test; [§] Fisher's exact test, [¶] Kruskal-Wallis rank sum test; NA, not applicable; sd, standard deviation

Figure 1. Flow-chart

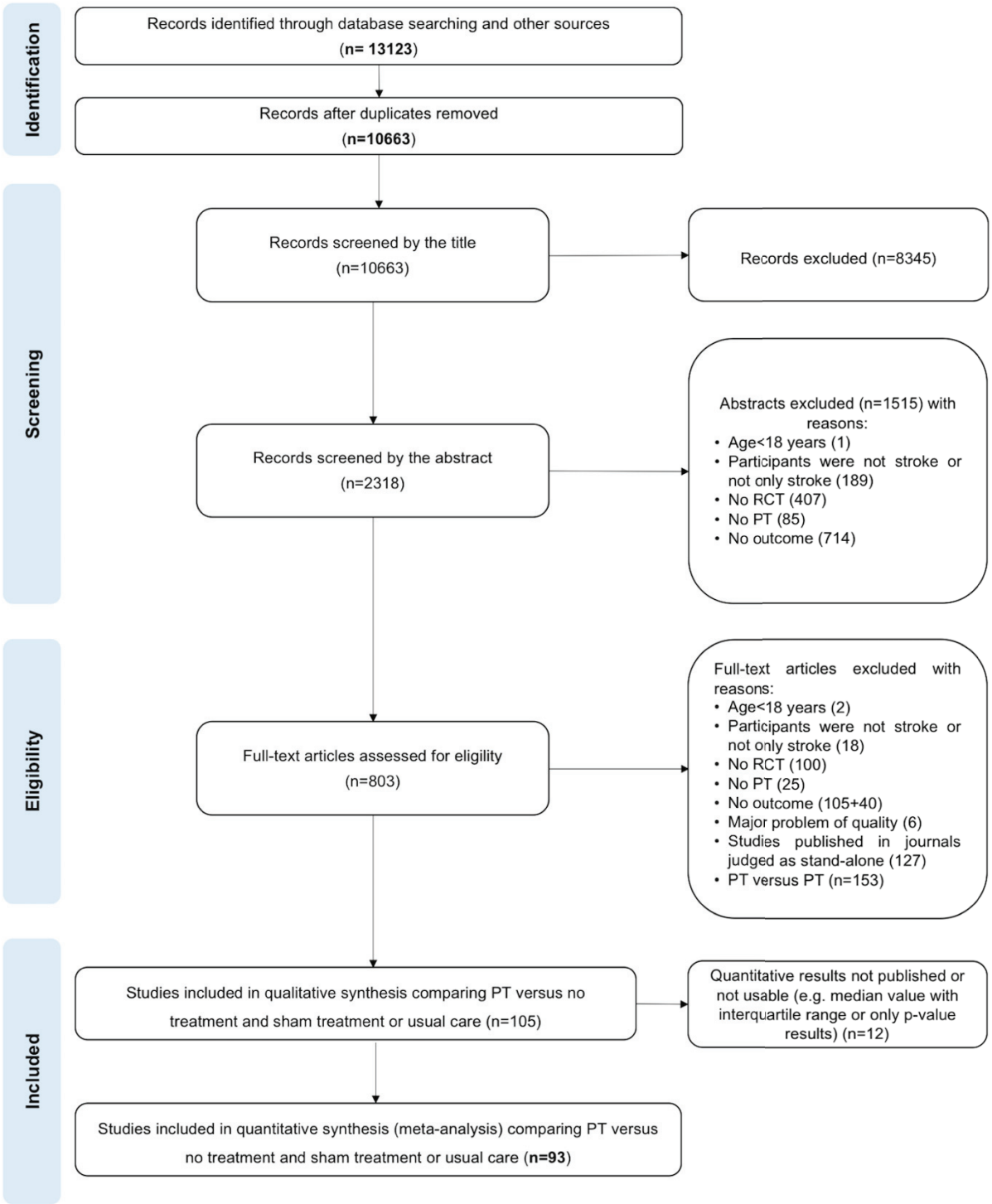


Figure 2. Risk of bias for each item of Cochrane Collaboration tool according to type of approach

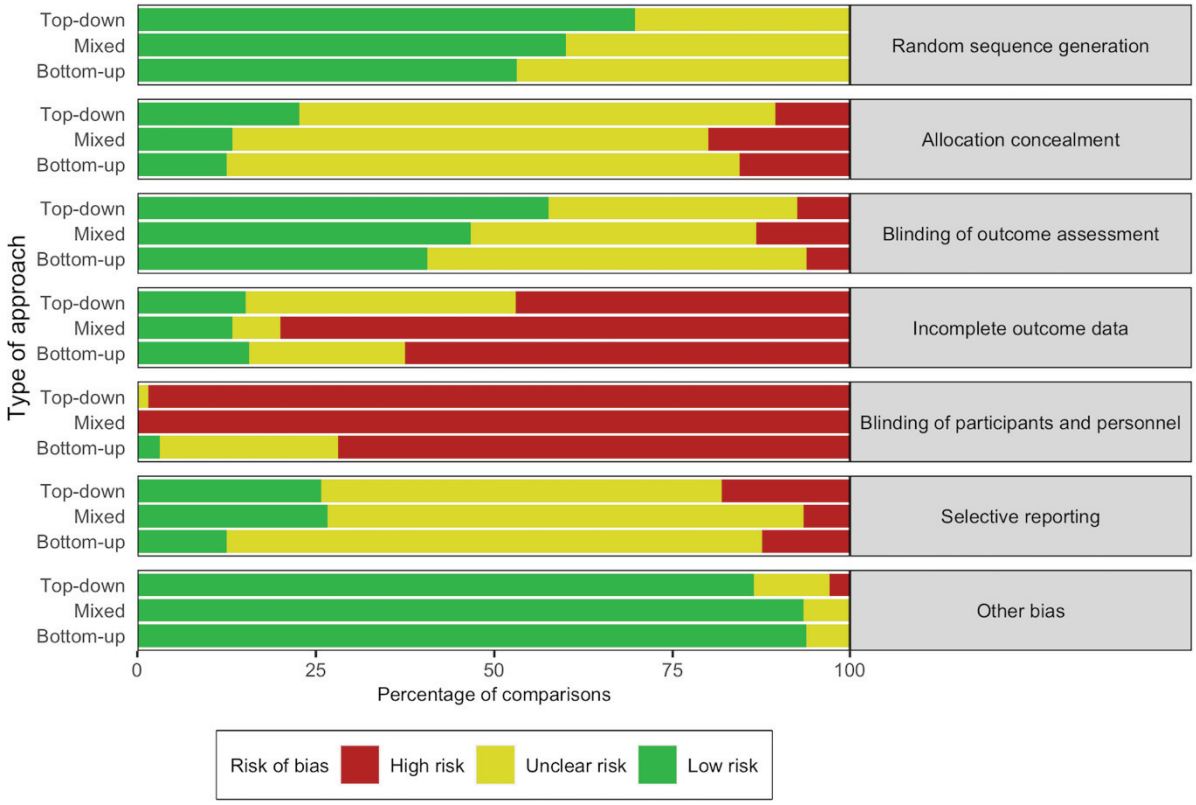
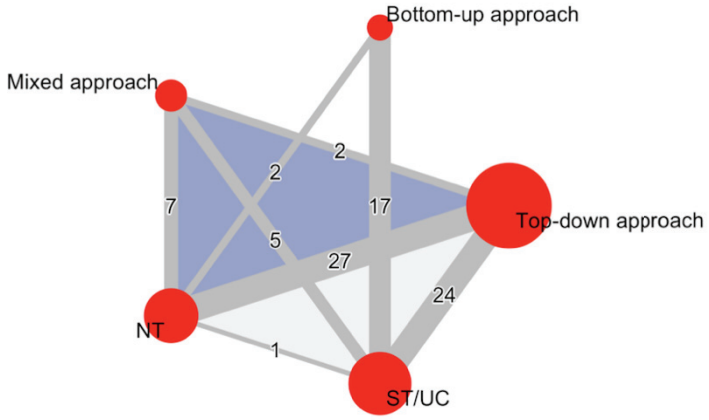


Figure 3. Network meta-analysis of post-intervention effects on balance.

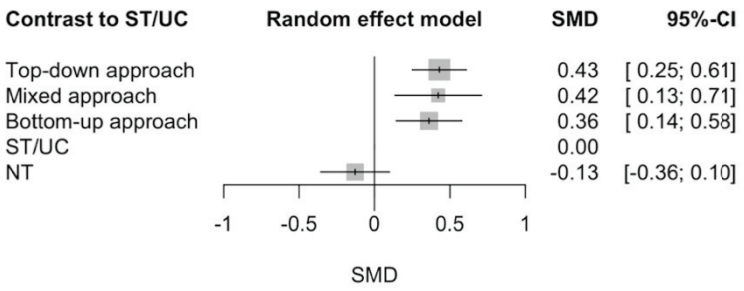
A: Geometry of the network



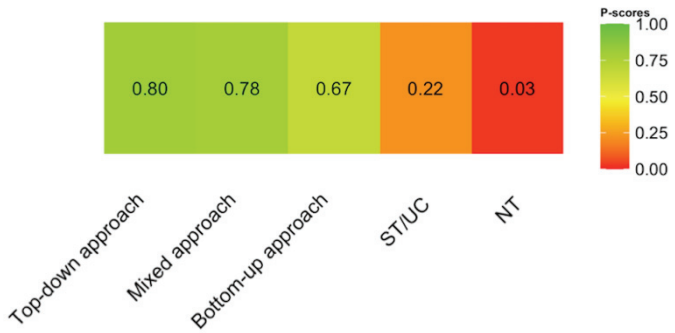
B: Summary of effects

Random effects				
Bottom-up approach	.	0.29 [-0.37; 0.95]	0.39 [0.16; 0.62]	.
-0.06 [-0.41; 0.29]	Mixed approach	0.58 [0.22; 0.93]	0.35 [-0.06; 0.76]	0.03 [-0.59; 0.65]
0.49 [0.19; 0.79]	0.55 [0.27; 0.83]	NT	-0.18 [-1.21; 0.85]	-0.56 [-0.74; -0.37]
0.36 [0.14; 0.58]	0.42 [0.13; 0.71]	-0.13 [-0.36; 0.10]	ST/UC	-0.43 [-0.63; -0.24]
-0.07 [-0.34; 0.20]	-0.01 [-0.29; 0.28]	-0.56 [-0.73; -0.38]	-0.43 [-0.61; -0.25]	Top-down approach

C: Forest-plot of effects



D: Ranking of effects

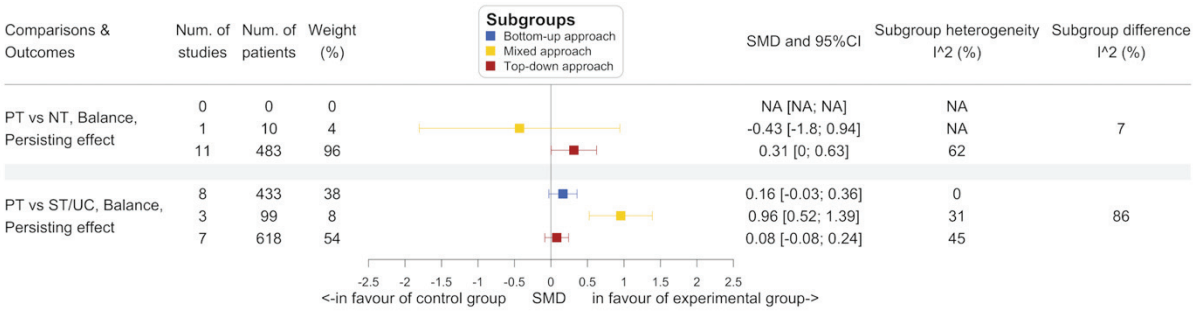


For part A, each node indicates an intervention and the size of node is weighted according to the number of participants who received the intervention. Each line between nodes is proportional to inverse standard error of random effects model comparing two interventions and indicate that there was a direct comparison between

the interventions it connects. Numbers of RCTs investigating the intervention are reported in the line between nodes. Multi-arm studies are marked in the plot by a coloured area. For part B, the treatment effect estimates from the network meta-analysis (indirect and direct comparisons) are reported in the lower triangle whereas in the upper triangle, the table contains treatment effect estimates for direct comparisons. The results are expressed in SMD and 95%CI. For part C, the comparator group is ST/UC. For part D, the treatment ranking indicates the relative effects of treatments. The P-scores measure the certainty that one treatment is better than another treatment, averaged over all competing treatments.

CI, confidence interval; NT, no treatment; SMD, standardised mean difference; STUC, sham treatment and usual care

Figure 4. Summary forest plot of the subgroup meta-analyses for persisting effects on balance according to BU, TD and mixed approaches.



CI, confidence interval; NA, not applicable; Num, number; NT, no treatment; PT, physical therapy; SMD, standardised mean difference; ST/UC, sham treatment and usual care; vs, versus

2.4.5. Chapitre d'ouvrage sur la rééducation

Rééducation de l'équilibre du patient cérébrolésé après AVC

Aurélien Hugues, Thibaut Ferreux et Alain Yelnik

Les chutes sont très fréquentes après un accident vasculaire cérébral (AVC) [1, 2] et leurs conséquences sont graves sur les activités, la participation [3, 4] et la qualité de vie des patients.[5] La rééducation doit donc avoir pour objectif de minimiser ce risque par tous les moyens permettant de renforcer le contrôle de l'équilibre. De nombreuses approches ont été étudiées mais des preuves certaines d'efficacité manquent encore.[6]

1. Principes généraux

1.1. Orientation et stabilisation posturales

Après un AVC, les patients présentent i) une asymétrie des appuis avec une diminution de l'appui du coté hémiplégique [7] et/ou une latéropulsion contralésionnelle pour les atteintes hémisphériques,[8] pouvant s'expliquer par le déficit moteur, la négligence spatiale et les troubles de la cognition spatiale ; ii) une plus grande surface d'oscillation du centre de pression pouvant s'expliquer par les déficits sensitifs et moteurs, la négligence spatiale ou de déficiences neuro-orthopédiques.[9] De plus, les réactions posturales en cas de déséquilibres externes sont précoces et excessives du côté non parétique mais retardées et réduites du côté parétique. Les ajustements posturaux anticipateurs sont retardés et de moindre amplitude.[10–12]

1.2. Objectif : récupération de la fonction par récupération des déficiences ou par compensation ?

Il faut bien savoir dès le départ à quel niveau se situent nos interventions : sur les déficiences pour les réduire, c'est-à-dire que la rééducation vise la récupération de celles-ci, ou plus globalement sur les activités, ici l'équilibre dans toutes ses dimensions, avec ou sans réduction des déficiences. Or, le trouble de l'équilibre est le plus souvent une résultante de plusieurs déficiences. La rééducation doit d'abord comporter un travail analytique sur chacune d'elles, spécifique mais souvent déjà intriqué à un travail global sur l'équilibre. Ce

travail spécifique sur chaque déficience ne sera pas détaillé ici sauf certains aspects dans la partie 3.

La rééducation a d'abord pour but de maximiser ou de solliciter les phénomènes de récupération neurologique. Le pronostic des déficits dépend notamment du siège et de la taille des lésions ainsi que des capacités du parenchyme restant et du délai post AVC. La rééducation vise également à développer les phénomènes de compensation fonctionnelle et, pour ce qui est de l'équilibre, la part des automatismes étant importante, cela rend utile le travail fonctionnel global. L'individualisation de la rééducation est un élément clef de son succès.

1.3. Le travail associe des exercices portant sur l'équilibre statique et dynamique.

Cette distinction est théorique et tout exercice, comme l'exploration de l'espace par le regard et par les membres supérieurs, est déjà un travail dynamique même en position « statique ».

1.4. Travail des ajustements posturaux anticipateurs et rétro-actifs

Les mécanismes d'équilibration diffèrent et se combinent selon que le sujet induit ou subit le déséquilibre et selon que celui-ci a pu être anticipé ou non. Le rôle des ajustements posturaux anticipateurs est de minimiser les perturbations prévues de la posture, alors que les ajustements posturaux réactifs visent à corriger un déséquilibre induit. Il convient donc de créer des situations où le patient doit mobiliser les ajustements posturaux anticipateurs, par des exercices de déstabilisations intrinsèques ou extrinsèques anticipées et les ajustements posturaux réactifs par des exercices de déstabilisations extrinsèques non anticipées.

1.5. Principes de progression et apprentissage moteur

Les modalités de travail en rééducation obéissent aux déterminants de l'apprentissage moteur comme la répétition de la tâche, la diversification, le retour d'information ou la consolidation.[13] La progression peut porter sur l'augmentation de la durée et de l'intensité de la charge de travail, la répétition, la diversification de la tâche (complexification, variabilité) et des conditions (contexte), l'utilisation de stimulations sensorielles, le guidage par des repères et indices, le retour explicite ou implicite d'information ou des résultats

(commentaires, réussite/échec …), la modulation de l'effecteur (contrainte, limitation de compensation), mais aussi sur la cognition (observation, mentalisation, attention).

1.6. A quel stade post AVC : aigu et chronique

La rééducation doit commencer précocement après l'AVC, pour limiter les complications liées à l'immobilité, mais il semble préférable de ne pas solliciter le patient par des efforts trop intenses à la phase aigüe.[14, 15]. La meilleure période pour le travail sur la plasticité cérébrale commence quelques jours après l'AVC, sans doute d'autant plus tard que l'AVC est sévère, et s'étend principalement sur les 3 premiers mois. A un stade chronique s'ajoute le cercle vicieux de la sous-utilisation motrice et du déconditionnement mais les processus de plasticité cérébrale plus réduits existent encore. Même si une rééducation adaptée a été pratiquée dès le début, celle-ci est souvent encore nécessaire à un stade chronique, soit pour gagner en performances globales soit pour au moins entretenir l'état obtenu. Certains patients ont absolument besoin d'un travail de rééducation régulier guidé car ils ne peuvent seuls initier ce travail à un niveau suffisant, que ce soit en raison de troubles cognitifs ou, justement, de la précarité de l'équilibre les mettant en danger. Le maintien des bénéfices de la rééducation nécessite soit un auto-entretien soit la poursuite de la rééducation.[6]

1.7. Quelle intensité et durée de la rééducation

Hormis durant les 24 à 48 premières heures après un AVC, période au cours de laquelle la rééducation ne doit pas être trop intense, nous ne pouvons que recommander de pratiquer le plus possible de rééducation tant en termes d'intensité d'effort et de durée totale, sous réserve de l'état clinique du patient. D'une manière générale, il existe une relation dose-réponse positive en faveur de la rééducation, même à un stade tardif.[16]

2. Travail spécifique sur les déficiences

Rappelons, sans les détailler, les déficiences qui méritent notre attention. La négligence spatiale unilatérale, l'altération de la perception de la verticale gravitaire et la possible dépendance sensorielle ont été traitées dans d'autres chapitres du livre. Le trouble moteur est le plus souvent constitué d'une parésie dite spastique car associée aux troubles du

tonus musculaire de la spasticité. La caractéristique des paralysies par atteinte centrale est la perte de la sélectivité du mouvement. L'objectif de la rééducation est de permettre la récupération d'une commande la plus analytique possible. Toutefois la part d'automatismes étant importante pour ce qui est de l'équilibre et notamment de la marche, un travail sur les automatismes est utile et efficace.

L'hypertonie spastique peut perturber l'équilibre, notamment celle du triceps sural, du quadriceps voire des fessiers. La kinésithérapie permet le plus souvent de l'atténuer transitoirement et surtout d'éviter les rétractions musculaires par des verticalisations ou des postures d'étirement.[17] Mais la dystonie spastique (varus-equin, griffe des orteils), les trépidations en position debout, peuvent nécessiter des traitements médicamenteux, le plus souvent locaux (toxine botulinique), voire chirurgicaux. L'éducation du patient aux auto-étirements quotidiens est essentielle.

L'ataxie cérébelleuse peut être isolée ou associée aux autres déficiences. Elle se caractérise notamment par l'irrégularité du mouvement à l'origine d'embardées dangereuses. L'adjonction d'une charge sur le ou les membres inférieurs peut aider la stabilisation et atténuer la dysmétrie des membres inférieurs. Le travail doit associer toutes les assistances possibles pour une rééducation dans la fonction.

Enfin, insistons sur l'anesthésie et l'ataxie proprioceptive. Le déficit de proprioception a un impact majeur sur la motricité. Il peut justifier précocement l'usage d'une orthèse cruro-pédieuse. S'il persiste, le seul moyen pour le patient de compenser sera d'utiliser la vue mais avec une moindre efficacité. Il ne sera pas traité ici l'ensemble des techniques de rééducation de la sensibilité, mais rappelé quelques points clés impactant l'équilibre. La rééducation proprioceptive ciblera en particulier le tronc, le contrôle du genou et de la cheville. La sensibilité superficielle de la sole plantaire (seul lien avec le sol en l'absence d'aide de marche) retiendra également l'attention des rééducateurs.

3. Principales techniques et justifications

3.1. Le travail du tronc et des transferts

La rééducation spécifique du tronc est une approche multimodale comprenant un travail de stabilisation des parties basses et hautes du tronc, un travail de transfert du poids et un travail des préhensions qui mettent souvent en jeu des mouvements du tronc. Un effet

bénéfique assez large sur l'équilibre assis et surtout debout a été observé.[18] La motricité axiale bénéficie d'une innervation moins latéralisée que celle des membres, ce qui explique souvent la bonne récupération du tronc au point que ce dernier se retrouve souvent négligé dans la rééducation. Il doit être au contraire une cible prioritaire afin d'améliorer l'équilibre. Ses capacités motrices relativement préservées permettent de le solliciter plus aisément lors de tâches fonctionnelles.

Le travail de récupération du tonus axial est essentiel mais il n'est pas besoin que l'équilibre assis soit bon pour travailler la station debout et la marche. Lorsque les déficits sont sévères, l'automatisme de la station debout peut compenser un déficit de tenue du tronc. Le travail de l'équilibre assis et le travail de l'équilibre debout ont tous deux montré des effets positifs sur l'équilibre des patients après un AVC.[19] Le travail assis et debout précoce en recherchant une participation active du patient est une stratégie importante pour lutter contre une latéropulsion controlésionnelle.

Les transferts, en particulier de la position assise à debout, représentent des situations à risque de chute. La rééducation permet d'améliorer leur réalisation et doit être débutée précocement.[20] Le travail du relevé du sol permettrait de diminuer la peur de la chute ou la peur de rester au sol après la chute. Il sera débuté un peu plus tardivement selon les capacités du patient. Sans diminuer spécifiquement le risque de chute, le fait de se savoir en capacité de se relever du sol semble bénéfique pour réduire la peur de chuter.[21]

3.2. La marche

Celle-ci peut être travaillée avec des objectifs qualitatifs (pattern de marche) et/ou quantitatifs (distance parcourue, vitesse de marche, nombre de pas …). Selon le but recherché, elle peut être dispensée selon différentes modalités : utilisation d'indices (visuels, auditifs), avec ou sans perturbations (obstacles, parcours prédéfini avec changement de direction, de nature de sol, de rythme de marche). La marche sur terrain en pente ou dans les escaliers constitue une progression, tout comme l'augmentation de l'intensité de travail et de la difficulté de la tâche d'équilibre. Il est préférable d'entraîner le patient à des situations ressemblant à celles qu'il est susceptible de rencontrer dans son environnement habituel. Le travail des demi-tours est essentiel (cf chapitre 13 du livre). La rééducation de la marche sur

tapis roulant avec support partiel du poids du corps et la rééducation en tâche fonctionnelle ont montré leur efficacité.[22]

3.3. Le renforcement musculaire

Le travail de renforcement musculaire (force, endurance ou puissance) avec ou sans électrostimulation, ou associé à un travail cardiorespiratoire a un effet bénéfique sur l'équilibre.[6, 19, 23] Les modalités du renforcement musculaire peuvent être variées mais il paraît pertinent de se focaliser sur les muscles érecteurs du tronc ou les principaux groupes musculaires des membres inférieurs.

3.4. L'appareillage

L'appareillage vise à stabiliser la station debout en verrouillant le genou (orthèse cruro-pédieuse) et faciliter le passage du pas en luttant contre un pied tombant ou un équin dynamique (orthèse suro-pédieuse). Il est nécessaire lorsque le déficit moteur et/ou sensitif est marqué. Il doit être utilisé précocement pour permettre le travail debout et de la marche sans attendre la récupération des déficits, contribuant ainsi à la récupération précoce de la marche et de l'équilibre du tronc. Il peut aussi contribuer à réduire l'asymétrie posturale médiolatérale.[6] L'orthèse est alors parfois abandonnée après quelques semaines ou mois, après avoir rendu le service immense de permettre la verticalisation précoce.

3.5. Assistance électromécanique et électrostimulation fonctionnelle

L'assistance robotisée de la marche avec allègement du poids du corps a principalement son indication dans les AVC sévères, en permettant le réentrainement des automatismes de marche malgré la sévérité des déficits notamment axiaux.[24] Mais elle ne semble pas plus efficace sur l'équilibre proprement dit que la rééducation de la marche seule lorsqu'elle est possible.[25] Pour améliorer l'équilibre, elle doit être réalisée en complément d'une rééducation conventionnelle fonctionnelle.[26]

La stimulation électrique fonctionnelle, visant à assister la marche en cas de déficit des releveurs du pied, peut être utilisée pour améliorer l'équilibre, notamment pour son effet « orthopédique » sur la cheville. Cependant, peu de patients utilisent ces dispositifs dans la vie quotidienne (coût important, encombrement, installation).

3.6. Double tache

En augmentant la charge attentionnelle par apport de distracteurs, le travail en double tâche permet d'automatiser la tâche motrice. Il ne s'effectuera donc pas en première intention. La deuxième tâche demandée simultanément peut être motrice ou cognitive.

3.7. Dépendance sensorielle

Comme cela est développé dans un autre chapitre du livre, ces patients développent souvent une dépendance visuelle qui peut être une stratégie compensatoire initiale utile mais risque de devenir néfaste à l'équilibre. Une rééducation en privation visuelle améliore l'équilibre à un stade chronique.[27] Précocement, la progression de la rééducation par tâche orientée de l'équilibre peut impliquer de réaliser celle-ci en privation visuelle.[27] ou avec un accroissement des perturbations sensorielles (suppression ou perturbation des entrées visuelles par flux optocinétique, introduction d'une surface instable, puis ajout des mouvements de la tête) avec un bénéfice sur l'indépendance fonctionnelle.[28]

3.8. Feedback, réalité virtuelle et imagerie motrice

Les techniques de biofeedback et de réalité virtuelle sont traitées dans les chapitres du livre spécifiquement dédiés. Le recours à des techniques d'imagerie motrice pour améliorer l'équilibre n'a pas montré à ce jour des résultats clairs : positifs pour certains [29] mais pas pour d'autres.[30] Il semblerait préférable de recourir à des tâches d'imagerie motrice plus fonctionnelles en association avec une rééducation de tâche orientée. De manière similaire, pour améliorer la stabilité posturale des patients, l'observation puis l'imitation de tâches fonctionnelles (se lever, marcher, s'asseoir avec une progression) devrait être associée à une rééducation par tâche orientée (équilibre, assis-debout, marche).[31]

3.9. Réentrainement cardio-respiratoire

Les effets de l'entraînement cardio-respiratoire sur l'équilibre semblent contradictoires. L'entraînement aérobie seul n'améliorerait pas l'équilibre.[32, 33] Mais réalisé en situation de marche ou associé à un renforcement musculaire, il améliorerait l'équilibre.[23] Le mécanisme d'action du travail cardiorespiratoire sur l'équilibre ne semble pas direct mais agirait en luttant contre la désadaptation à l'effort.

3.10. Approches complémentaires

Les mises en situation (cuisine, courses en extérieur, utilisations des transports en commun ...) en ergothérapie participent à la rééducation de l'équilibre. La rééducation en groupe comme source d'émulation, la pratique alternée de différentes tâches motrices en « circuit training », du yoga ou tai-chi comme approche globale peuvent être proposée en complément de la rééducation habituelle.

Conclusion

La rééducation de l'équilibre d'un patient cérébrolésé nécessite une analyse des mécanismes à l'origine du trouble de l'équilibre. Selon le stade, l'association des déficiences et leur sévérité, le kinésithérapeute choisira dans une large palette les techniques les plus adaptées à chaque patient et saura les faire évoluer.

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3. RELATION AVEC LES DEFICITS DE LA COGNITION SPATIALE

Dans ce chapitre, nous nous sommes intéressés aux relations existantes entre les troubles posturaux, que sont l'asymétrie d'appui et l'instabilité posturale, ou les troubles de l'équilibre après AVC, et les déficits de la cognition spatiale, tels que les perturbations des cadres référentiels spatiaux ou la négligence spatiale unilatérale.

3.1. LES DEFICITS DE LA COGNITION SPATIALE APRES AVC

3.1.1. Perception de la verticalité

Après un AVC, la perception des différents cadres référentiels spatiaux évoqués dans le sous-chapitre 1.4 peut être perturbée. En effet, plusieurs études ont rapporté des biais dans l'estimation de la verticale, sous forme d'une déviation par rapport à la normale et/ou d'une incertitude dans la perception.[14,15,190–193] La modalité visuelle est la plus fréquemment évaluée. Entre 46% et 63.3% des patients présentaient une perception déviée de la verticale visuelle après un AVC par rapport aux sujets sains selon les études.[15,190–192] Après une lésion hémisphérique, ces biais se caractérisaient le plus souvent par une déviation dans l'espace controlésionnel. Une méta-analyse a montré qu'après un AVC les patients présentaient en moyenne une déviation significative de la verticale visuelle par rapport aux sujets sains (différence moyenne standardisée 1.35, intervalle de confiance à 95% [1.02, 1.68]).[193]

Sur l'inclinaison anormale de la verticale visuelle, Bonan *et al.*[190] ont rapporté que les prévalences étaient comparables selon le coté de la lésion à 45 jours post-AVC mais qu'à 3 et 6 mois, la prévalence était plus élevée après une lésion droite que gauche. L'amplitude de la déviation présentait cette même caractéristique : alors que l'inclinaison de la verticale visuelle n'était pas différente selon le coté de la lésion à 45 jours post-AVC, elle était plus déviée après lésion droite que gauche à 3 et 6 mois. En revanche, l'incertitude dans l'estimation de la verticale visuelle était plus importante et plus fréquente après lésion droite qu'après lésion gauche à 45 jours, 3 et 6 mois post-AVC. Si pour l'ensemble des patients avec une perception

anormale de la verticale visuelle ces auteurs notaient une réduction significative de l'amplitude de la déviation au cours des 3 premiers mois après l'AVC sans modification de l'incertitude dans l'estimation, les patients avec une lésion gauche semblent mieux récupérer de leur perturbation de la verticale visuelle que ceux avec une lésion droite. Par ailleurs, Bonan *et al.*[190] ont montré qu'alors que les patients présentant une négligence spatiale unilatérale estimaient leur verticale visuelle plus déviée que ceux sans négligence, des biais dans la perception de la verticale visuelle étaient également retrouvés chez des patients non négligents, suggérant une possible dissociation entre ces deux déficits.

Quant aux autres modalités sensorielle, la verticale haptique et la verticale posturale étaient également perçues comme significativement déviées par rapport aux sujet sains.[15] Contrairement aux modalités visuelle et haptique, les biais de la verticale posturale étaient toujours controlésionnels après un AVC hémisphérique. Pérennou *et al.*[15] ont montré que la déviation de la verticale posturale était plus importante après un AVC droit que gauche ; et qu'en cas de lésion droite, la déviation était influencée par la taille de la lésion. Une atteinte transmodale (c'est à dire touchant les 3 modalités visuelle, haptique et posturale) de la perception de la verticalité n'était retrouvée quasi-exclusivement qu'après lésion droite. De plus, les patients estimant sans biais les verticales subjectives avaient des lésions cérébrales plus petites que ceux présentant des perturbations dans l'estimation des verticales.[15]

3.1.2. Axe corporel longitudinal et droit devant

Concernant le référentiel égocentré, les perturbations peuvent concerner la perception de l'axe corporel longitudinal et celle du droit devant. Après une lésion hémisphérique, la perception de l'axe corporel longitudinal est significativement déviée vers l'espace controlésionnel et/ou significativement plus incertaine par rapport aux sujets sains. Ces biais n'étaient pas systématiquement retrouvés après un AVC.[121,136] De plus, ils concernaient plus fréquemment les patients avec lésion droite que ceux avec lésion gauche,[121,151] et l'amplitude de la déviation était plus importante après une atteinte de l'hémisphère droit ou en cas de lésion cérébrale étendue.[121]

Des biais dans la perception du droit devant sont également rapportés après un AVC. La modalité proprioceptive avec le droit devant manuel est la plus fréquemment évaluée dans la littérature.[135,136,194–204] La modalité visuelle est évaluée à travers le droit devant visuel.[135,199,205–207] Les biais dans l'estimation du droit devant se caractériseraient par une déviation ipsilésionnelle chez les patients avec négligence spatiale unilatérale par rapport à ceux non négligents et les sujets sains.[113,194,196–198,200,207] Cependant, cette déviation ne semble pas systématiquement retrouvée chez les patients négligents et il existe une importante dispersion interindividuelle des estimations du droit devant.[197,202,203,208] Plusieurs études n'ont pas montré de différence significative entre les groupes de patients négligents, non-négligents et contrôles sains.[199,202–204,208] Chez Farnè *et al.*, la proportion entre déviations ipsi et contro-lésionnelles était similaire chez les sujets sains, les patients AVC droits négligents et ceux non négligents.[199]

Les sujets sains et les patients non négligents (que ce soit après lésion gauche ou droite) ne percevaient pas, en moyenne, le droit devant significativement dévié.[136,194,196,197,199,205,206] Pour autant, certains des patients non négligents après lésion droite ont montré, individuellement, une déviation du droit devant.[203] De plus, les patients AVC droits bien que non-négligents présentaient des biais significatifs dans la perception du droit devant, sous la forme d'une incertitude dans l'estimation, par rapport aux sujets sains.[199] Il apparaît donc que la perception du droit devant est perturbée après lésion droite, avec une plus grande imprécision que les sujets sains, indépendamment de la présence ou non d'une négligence spatiale unilatérale.

L'ensemble de ces éléments suscités ne plaideraient pas en faveur d'une relation causale entre négligence spatiale unilatérale et perturbations du droit devant. Les résultats des études corrélationnelles sont d'ailleurs contradictoires.[194,197,199,202,203,208] De plus, les résultats d'une étude expérimentale montrant une double-dissociation des effets observés (entre patient et chez chaque patient) sur le droit devant manuel et la bissection des lignes, évaluant la négligence spatiale unilatérale, à la suite d'une intervention par adaptation prismatique chez des patients AVC droits négligents renforcent cette hypothèse.[209] Alors qu'historiquement, il avait été suggéré que la négligence spatiale unilatérale soit une conséquence de la perturbation du référentiel égocentré évaluée par le droit devant,[113,210] il

apparaît maintenant au vue des différents faits présentés que ce sont deux phénomènes, certes probablement proches, mais distincts.[199,208,209]

3.1.3. Négligence spatiale unilatérale

La négligence spatiale unilatérale est un syndrome polymorphe complexe qui est à distinguer des atteintes sensori-motrices consécutives de l'AVC. Elle se définit par la présence d'un biais comportemental ipsilésionnel et un défaut de conscience de l'hémi-espace controlésionnel, conséquences d'un déficit d'orientation de l'attention dans l'espace opposé à la lésion et d'une altération de l'exploration et/ou de la construction de l'espace de représentation mentale.[113,211–213] La négligence spatiale unilatérale est un déficit de la cognition spatiale qui s'ajoute aux déficits sensori-moteurs bien connus après un AVC.

La négligence spatiale unilatérale peut concerner différents espaces : l'espace personnel (corporel), l'espace extra-personnel (proche ou péri-personnel atteignable par préhension, et lointain atteignable que par déplacement locomoteur du sujet) et l'espace représenté. Les manifestations de la négligence spatiale unilatérale dans l'espace personnel se caractérisent par rapport au plan sagittal médian séparant le corps en deux parties égales (droite-gauche ; voir partie 1.4.2). En revanche, dans l'espace extra-personnel, la négligence spatiale unilatérale est caractérisée dans un référentiel définit par rapport à l'objet ou l'environnement, indépendamment de la position du sujet. L'espace représenté est une construction mentale imaginée par le patient.[113,211,213]

Le syndrome de négligence spatiale unilatérale peut aussi être décrit en fonction des manifestations cliniques du patient : On parle de la négligence sensorielle, motrice, corporelle, égocentrique, allocentrique ou représentationnelle. Une présentation de la sémiologie, ainsi que des évaluations selon ces différents sous-types de négligence spatiale unilatérale se trouve dans la revue narrative de littérature figurant en partie 3.2.1.

Une revue systématique de la littérature récente a estimé la prévalence moyenne de la négligence spatiale unilatérale autour de 30%, indépendamment de la localisation de la lésion, du délai post-AVC et de la méthode d'évaluation utilisée.[214] Ces auteurs ont rapporté que la prévalence était bien supérieure (53%) en cas d'évaluation écologique, suggérant une

sous-évaluation par les tests conventionnels « papier-stylo ». La prévalence de la négligence spatiale unilatérale tendait à diminuer dans le temps (entre le stade subaigu et chronique de l'AVC).[214] Par ailleurs, elle était plus élevée après une lésion droite qu'après une lésion gauche, particulièrement aux stades aigu (45% vs 23%) et subaigu (40% et 19%). Quant au stade chronique, il semblerait que le ratio droite/gauche de prévalence diminue (20% vs 13%) même si cela reste à démontrer compte tenu du nombre très réduit d'études l'évaluant à ce stade (une seule étude incluse dans leur revue de littérature).[214]

Dans une large cohorte comprenant 335 patients négligents et non négligents post-AVC entre 2011 et 2014,[215] la négligence spatiale unilatérale concernait à 37% l'hémi-espace droit (en majorité après lésion gauche) et à 63% l'hémi-espace gauche (en majorité après lésion droite). Il n'y avait pas de différence significative entre ces deux groupes de patients négligents, ni avec les patients non-négligents, en ce qui concerne l'âge, le sexe, la latéralité manuelle, le nombre d'AVC et l'étiologie de l'AVC. Les manifestations cliniques concernaient l'espace ispilésionnel pour 17% à 35.5% des patients négligents, indiquant que dans la grande majorité des cas, la négligence spatiale unilatérale concerne l'espace controlésionnel. La sévérité de la négligence aux tests de bissection de lignes et de barrages était plus importante chez les négligents gauches que chez les négligents droits. Bien que la négligence comportementale ne fût pas significativement différente selon l'hémi-espace touché, elle était significativement plus sévère chez les patients négligents gauches comparativement aux patients non négligents. L'atteinte simultanée des espaces péri-personnel (proche) et extra-personnel (lointain) était plus fréquemment retrouvée en cas de négligence gauche que droite, ce que les auteurs expliquaient par la présence de lésions cérébrales plus étendues chez ces patients négligents gauches comparativement aux patients AVC non négligents (mais sans différence avec les patients négligents droits). Quant à l'autonomie dans les activités de la vie quotidienne, mesurée par l'échelle de « Barthel », elle était globalement comparable entre patients négligents gauches et droits, mais significativement plus faible par rapport aux patients non négligents après AVC.[215] La négligence spatiale unilatérale impacte le niveau d'activité et de participation des patients.[216–219]

3.1.4. Latéralisation de la cognition spatiale

Comme nous avons pu le constater dans les paragraphes précédents, de nombreux arguments plaident en faveur d'une prédominance de l'hémisphère droit dans la cognition spatiale. En effet, les biais dans l'estimation des cadres référentiels spatiaux sont généralement plus importants et/ou plus fréquents après une lésion droite qu'après une lésion gauche.[15,121,151,190,191,220] Il en est de même pour la prévalence et la sévérité des manifestations cliniques de la négligence spatiale unilatérale, généralement plus élevées après lésion droite.[214,215] La cognition spatiale est une fonction cérébrale latéralisée comme l'est le langage au niveau de l'hémisphère gauche, en particulier chez le sujet droitier.

Malgré que les perturbations des cadres référentiels spatiaux et de la négligence spatiale unilatérale puissent relever de phénomènes distincts, la latéralisation hémisphérique de la cognition spatiale pourrait expliquer que ces déficits spatiaux soient retrouvés fréquemment associés,[121,190,192,194] probablement en raison d'une atteinte de réseaux neuronaux communs.

3.2. DEFICITS DE LA COGNITION SPATIALE ET TROUBLES POSTURAUX APRES AVC

Compte tenu de la prédominance de l'hémisphère droit dans la cognition spatiale (présentée précédemment), et de la majoration des troubles posturaux après un AVC hémisphérique droit par rapport à un AVC hémisphérique gauche (présentée en sous-chapitre 2.2), il est raisonnable de penser que les déficits de la cognition spatiale puissent être un facteur contribuant à ces troubles posturaux. Ceci s'inscrit de façon cohérente dans le cadre théorique du contrôle postural, reposant sur des modèles internes impliqués dans la construction des représentations spatiales à partir d'une intégration multi-sensorielle afin de prédire, réaliser et adapter une action motrice.

Ce lien entre troubles posturaux et cadres référentiels spatiaux est retrouvé en ce qui concerne l'orientation posturale par rapport à la gravité. Pérennou *et al.* et Dai *et al.* ont montré que la latéropulsion (regroupant sous une même entité trois manifestations cliniques :

l'inclinaison posturale, le « pushing » et la résistance active à la correction) est un comportement postural contre la gravité mis en œuvre par le patient pour faire correspondre son orientation posturale avec la perception erronée qu'il se fait de la verticale dans le plan frontal.[14,15] En effet, alors que l'orientation des verticales était principalement dans la normalité chez les patients sans latéropulsion, elle était significativement déviée (principalement dans l'espace controlésionnel) chez les patients présentant une latéropulsion. L'amplitude de la déviation était d'autant plus grande que la latéropulsion était sévère.[14,15] Et ce quelle que soit la modalité sensorielle (haptique, visuelle et posturale) utilisée.[15] Chez les patients avec une latéropulsion sévère (considérés comme « Pushers » sur l'échelle « Scale for Contraversive Pushing »), la verticale posturale était plus inclinée que les verticales haptiques et visuelles.[15] Par ailleurs, la corrélation statistique entre le degré de latéropulsion et les biais des verticales était faible pour la verticale visuelle, moyenne pour la verticale haptique et forte pour la verticale posturale.[15] Plus facile d'exploration en pratique courante, la verticale visuelle était retrouvée faisant partie d'une même dimension, l'orientation posturale par rapport à la gravité, au même titre que la latéropulsion.[14] Ainsi, il apparaît que la latéropulsion est causée par une perception graviceptive altérée. Dai *et al.* ont également suggéré que la latéropulsion puisse être une forme de négligence graviceptive.[14]

Si le lien entre la perturbation du cadre référentiel gravitaire et la latéropulsion paraît bien documenté, cela ne semble pas le cas pour l'asymétrie d'appui après AVC. Une corrélation a été mise en évidence entre l'asymétrie d'appui et la déviation de l'axe corporel longitudinal au stade subaigu et chronique d'un AVC, sans corrélation avec la verticale visuelle.[136,151] Ces études portaient sur des corrélations univariées comprenant respectivement 30 et 22 patients. Ces résultats plaident en faveur d'une origine égocentrée, plutôt qu'allocentrée, à l'asymétrie d'appui.

Concernant l'influence de l'autre cadre référentiel égocentré qu'est le droit devant sur l'asymétrie d'appui après un AVC, une seule étude a investigué cette relation statistique sans mettre en évidence de corrélation significative.[136] Pour autant, plusieurs études interventionnelles semblent suggérer l'influence du droit devant sur l'asymétrie d'appui. En effet, une réduction de l'asymétrie d'appui chez des patients avec lésion droite a été observée après adaptation prismatique (déviant l'axe optique vers la droite).[135,221–224] Compte tenu que

l'adaptation prismatique puisse induire une déviation du droit devant manuel vers la gauche après AVC droit,[198,225] il est possible de suspecter un lien entre ce cadre référentiel spatial égocentré et la distribution du poids du corps sur les membres inférieurs. Dans l'étude pilote présentée plus loin (chapitre 4), nous avons pu constater une déviation conjointe et comparable du droit devant manuel à la réduction de l'asymétrie d'appui après adaptation prismatique chez des patients avec lésion droite chronique. Il apparaît donc pertinent d'explorer la possible relation entre le droit devant et l'asymétrie d'appui après AVC.

Par ailleurs, Genthon *et al.* ont montré que la négligence comportementale était un prédicteur de l'asymétrie d'appui post-AVC, après ajustement par le déficit moteur, la spasticité et le déficit sensitif, tous non significatifs.[139] La négligence spatiale unilatérale, notamment par sa composante concernant l'espace personnel, est ainsi fortement suspectée de participer aux troubles posturaux, et particulièrement à l'asymétrie d'appui. Pour autant, les autres paramètres de la cognition spatiale n'ont pas été pris en compte dans l'analyse multivariée. Cette influence de la négligence spatiale unilatérale pourrait expliquer la potentielle action de l'adaptation prismatique sur l'asymétrie d'appui, compte tenu de sa proximité physiopathologique avec le droit devant. En effet, l'adaptation prismatique réduirait certaines manifestations cliniques de la négligence spatiale unilatérale, conjointement avec une modification du droit devant manuel.[198,225–228]

Il apparaît donc approprié d'étudier les relations entre les cadres référentiels spatiaux égocentrés et l'asymétrie d'appui après AVC dans une analyse multivariée. Si l'effet de l'axe corporel longitudinal semble attendu, l'effet du droit devant reste inconnu. En plus des cadres référentiels spatiaux égocentrés, l'influence de la négligence spatiale unilatérale, autre déficit de la cognition spatiale, semble à considérer, pour son rôle propre sur l'asymétrie d'appui ou bien pour un possible effet de confusion avec le droit devant.

En ce qui concerne les troubles posturaux relatifs à la stabilisation posturale, une relation entre certains paramètres de stabilité posturale et la négligence spatiale unilatérale a pu être trouvée[157] mais aucune étude n'a, à notre connaissance, investigué les relations avec les cadres référentiels spatiaux après un AVC.

Les relations entre les déficits de la cognition spatiale et les troubles posturaux post-AVC ont été abordés à travers :

1. Une revue narrative sur la relation entre la négligence spatiale unilatérale et les troubles posturaux et de l'équilibre après un AVC, conduite sous la supervision du directeur de thèse, le Pr Gilles Rode, et du Pr Dominic Pérennou (PU-PH, Médecine Physique et de Réadaptation, Centre Hospitalier Universitaire de Grenoble). Cette revue doit figurer comme chapitre d'un ouvrage (intitulé « Troubles de l'équilibre : aspects sensoriels ») dirigée par le Pr Alain Yelnik (PU-PH, Médecine Physique et de Réadaptation, Assistance Publique des Hôpitaux de Paris). Cette revue a été soumise et acceptée par le Pr Alain Yelnik. L'ouvrage est actuellement sous presse (éditeur : Masson).

2. Une étude transversale sur l'influence du droit devant manuel, de l'axe corporel longitudinal et de la négligence spatiale unilatérale sur l'asymétrie d'appui après un AVC droit, issue d'un essai clinique contrôlé randomisé multicentrique « AVCPOSTIM » (PHRC national, promoteur : CHU de Rennes, 8 centres investigateurs, investigatrice principale : Pr Isabelle Bonan).

3. Issue de cette étude transversale, une analyse complémentaire sera présentée dans la thèse portant sur l'influence du droit devant manuel, de l'axe corporel longitudinal et de la négligence spatiale unilatérale sur l'instabilité posturale à partir de cette même population de patients.

Les tables, les figures et les références bibliographiques mentionnées dans le texte du chapitre d'ouvrage et de l'étude transversale sont répertoriées à la fin de chacun. Le matériel supplémentaire de l'étude transversale est reporté en annexe de la thèse.

3.2.1. Chapitre d'ouvrage sur la négligence spatiale unilatérale et l'équilibre

Négligence spatiale unilatérale et équilibre

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Après un accident vasculaire cérébral (AVC), les patients peuvent présenter, en plus des déficits sensori-moteurs « habituels », des déficits cognitifs à l'instar du syndrome de négligence spatiale unilatérale (NSU). Avec une prévalence moyenne autour de 30% diminuant avec le temps,[1] la NSU est plus fréquente après une lésion droite qu'après une lésion gauche chez le droitier même si sa sévérité, lorsqu'elle est présente, est similaire quel que soit le coté de la lésion.[2]

1. La négligence spatiale unilatérale : un trouble des comportements moteurs orientés dans l'espace

1.a. Un syndrome complexe associant 2 composantes

Le syndrome de NSU est à distinguer des déficits moteurs et sensitifs du patient après un AVC. Il s'agit d'un déficit de la cognition spatiale caractérisé par deux composantes associées : un biais comportemental vers le coté de la lésion et un défaut de conscience de l'hémi-espace controlésionnel.[3–5] La première composante se manifeste par une déviation occulo-céphalique et des membres vers le coté de la lésion. La motricité spontanée est orientée préférentiellement vers l'espace ipsilésionnel. Contrairement aux atteintes vestibulaires, cérébelleuses ou aux ataxies optiques qui peuvent également provoquer un biais comportemental ipsilésionnel, la NSU est également associée à défaut de conscience de l'hémi-espace controlésionnel. Cette seconde composante rend difficile toute compensation du biais comportemental par le patient. C'est l'association de ces deux composantes qui est

responsable des principales manifestations du syndrome de NSU : absence de prise en compte des informations sensorielles provenant de l'hémi-espace controlésionnel (négligence sensorielle), réduction de la motricité dans ce même espace caractérisée par une sous-utilisation des membres parétiques mais aussi une lenteur d'initiation et d'exécution des mouvements (négligence motrice), et enfin une hyper-attention ipsilésionnelle (négligence représentationnelle).

Le biais comportemental vers le coté de la lésion et le défaut de conscience de l'hémi-espace controlésionnel ne sont pas dus aux déficits moteurs et sensitifs secondaires à l'AVC. Le premier est la conséquence d'un déficit d'orientation de l'attention dans l'espace controlésionnel alors que le second est induit par une altération de l'exploration et/ou de la construction de l'espace de représentation mentale.[3–5]

1.b. Observé dans différents espaces (personnel, extra-personnel et représenté)

La NSU peut se manifester dans les différents espaces d'action et de représentation : l'espace personnel ou corporel, l'espace extra-personnel (ou de préhension) et l'espace représenté. Quel que soit l'espace concerné, la NSU se définit par rapport au plan sagittal médian de l'objet ou du sujet.

Dans l'espace personnel, le plan sagittal médian du corps du sujet sert de référentiel en définissant l'hémi-espace ispi et controlésionnel. Les manifestations de la NSU se caractérisent par rapport au référentiel du patient. Lors d'un test de barrage, le patient va correctement identifier tous les objets présents dans l'hémi-champ ipsilésionnel en négligeant ceux situés dans le champ opposé à la lésion.[3] Lors du test de copie d'une frise, le patient va recopier seulement les éléments de la frise situés dans son champ ipsilésionnel.[3] La dictée sur une feuille blanche avec un décalage du texte vers le coté de la lésion met en évidence une négligence de l'espace personnel.[3] La déviation occulo-céphalique, la sous-utilisation motrice des membres parétiques sont également des manifestations dans l'espace personnel ainsi que la négligence somatosensorielle.[3] Lors d'une tache de pointage avec le membre supérieur sain du « droit devant » dans l'obscurité ou avec les yeux fermés, le patient présente une déviation vers le coté de la lésion.[5] La distorsion, l'omission ou la non-reconnaissance de tout ou partie de l'hémi-corps parétique relèvent également de manifestations de la NSU dans l'espace personnel.[3]

Dans l'espace extra-personnel, l'environnement/l'objet est le référentiel indépendamment de la position du sujet. On distingue parfois l'espace proche (également appelé espace de préhension) et l'espace lointain. Classiquement, la NSU dans l'espace extra-personnel se manifeste lors du dessin de mémoire, la copie d'une frise ou la lecture de mots par une omission partielle ou totale de la partie controlésionnelle des objets. La NSU dans l'espace extra-personnel est également mise en évidence par un test de bissection de ligne dans lequel le point de bissection est dévié vers le coté de la lésion. L'exploration visuelle des objets est préférentiellement réalisée sur le côté ipsilésionnel des objets.[3] Le déficit peut également concerner l'espace extra-personnel éloigné. Il est mis en évidence en demandant au patient de réaliser un test d'exploration visuelle, un test de bissection de ligne ou d'appréciation de la référence égocentrique avec un pointeur laser. On constate alors un défaut d'exploration ou un biais directionnel du côté de la lésion cérébrale. La réalisation concomitante des tests dans l'espace proche et éloigné peut révéler des doubles dissociations (tests et espaces), suggérant ainsi que les informations spatiales issues de ces parties différentes de l'espace extra-personnel sont traitées par des réseaux neuronaux distincts comme cela a été démontré chez le singe. Cette distinction est pertinente à connaître en clinique car le cadre référentiel éloigné est pris en compte pour l'orientation de la marche et l'équilibre dynamique.

Enfin l'espace représenté est l'espace mental imaginé. Il est le fruit d'une construction mentale. Il peut être exploré par une tache d'imagerie mentale non motrice comme la description mentale d'une carte géographique. En cas de NSU, le sujet va présenter des omissions ou déformations des représentations mentales.[3]

1.c. Un syndrome complexe polymorphe avec différents sous-types cliniques

La NSU n'est pas un syndrome unique et uniforme mais regroupe des tableaux cliniques différents selon les symptômes exprimés. On parle de négligence sensorielle (qu'elle soit visuelle, auditive ou somatosensorielle), motrice, corporelle, egocentrique, allocentrique ou représentationnelle. Parmi tous ces sous-types de négligence dont nous avons décrit la sémiologie,[3] plusieurs sous-types pourraient être par leur nature impliqués dans la posture et l'équilibre.

Parmi la négligence sensorielle, la négligence visuelle est l'incapacité de détecter et de réagir à un stimulus visuel présent dans l'hémi-champ visuel controlésionnel.[6] Elle concerne l'espace extra-personnel, notamment lointain, et comprend une composante visuo-motrice (lésion frontale) mise en évidence par un test de barrage mais aussi une composante visuo-perceptive (lésion occipitale) mise en évidence par une bissection des lignes.[7] La négligence somato-sensorielle est un autre sous-type de négligence sensorielle qui concerne pour sa part l'espace personnel. Elle se manifeste par des omissions ou des erreurs de localisation lors d'une stimulation tactile, thermique ou nociceptive ainsi que des erreurs de perception de la position et des mouvements des segments du corps (proprioception). Ce sous-type de négligence est indépendant des troubles somato-sensoriels primaires et semble lié à des biais de la représentation spatiale egocentrique.[8]

La négligence motrice est une réduction des mouvements spontanés, volontaires ou non, des membres du côté opposé à la lésion en dehors d'un déficit moteur ou sensitif.[9] La réalisation des mouvements est également plus lente. Ce sous-type de négligence concerne l'espace personnel. La négligence motrice se caractérise par une atteinte plus ou moins complète de l'hémicorps touchant à la fois les mouvements proximaux et distaux, et est le plus souvent régressive et transitoire. Son expression tend à se réduire en cas de stimulation verbale soutenue.[9]

La négligence corporelle peut-être définie comme un déficit d'exploration et de conscience de l'hémicorps controlésionnel.[6,10] Cela peut se manifester par une omission partielle ou totale de l'hémicorps et/ou par des distorsions de représentation corporelle. L'évaluation d'un tel sous-type de négligence est possible par le « Fluff test » dans lequel le patient doit enlever le plus de marqueurs préalablement disposés sur son hémicorps controlésionnel sans l'aide de la vision.[10] Après une lésion droite, 44% des patients ont oublié des marqueurs sur leur hémicorps gauche lors du « Fluff test », suggérant une perturbation de la représentation spatiale égocentrée.[10]

La négligence égocentrique et allocentrique sont respectivement des sous-types de négligence relatives à l'espace personnel et à l'espace extra-personnel, dont les manifestations ont été décrites précédemment (cf partie 1.b. de ce chapitre d'ouvrage).

Ces différents phénotypes cliniques de la NSU peuvent être associés ou dissociés, et avoir des impacts différents sur le niveau d'activité ou la participation des patients. La NSU ne

peut-être résumé à la seule la négligence visuelle, celle la plus fréquemment évaluée dans les études. L'évaluation clinique des sous-types de NSU repose souvent sur des tests conventionnels « papier-crayon » mais aussi sur des évaluations en situation réelle dont les performances psychométriques sont meilleures.[11]

2. Modèle théorique du contrôle postural et de l'équilibre

2.a. Chez le sujet sain

La posture est une attitude caractérisée par la position relative des segments les uns par rapport aux autres mais également par leur orientation respective dans l'espace. Le contrôle postural vise à assurer 3 objectifs : antigravitaire pour assurer l'équilibre, fournir une base de stabilité pour réaliser des mouvements, et contribuer à la constitution de représentations spatiales.[12,13]

En tenant compte des contraintes internes (biomécanique corporelle) et externes (gravité, perturbations et support), le contrôle postural cherche à maintenir la posture de référence ou à adapter la posture à l'environnement. En plus de la participation active des muscles posturaux anti-gravitaires par un tonus musculaire, cela implique une connaissance de la position du corps dans l'environnement (représentation) reposant sur la constitution de référentiels spatiaux (égocentré et allocentré) à partir de la position et de l'orientation des différents segments du corps dans l'espace. La fonction posturale est donc constituée de deux composantes distinctes, l'orientation posturale et la stabilisation posturale, afin de maintenir une position donnée et permettre de réaliser des mouvements en fournissant une base stabilisée. Le but final est la recherche de l'équilibre qui est défini comme le maintien de la projection du centre de masse dans le polygone de sustentation.[12–14] Ceci implique parfois des compromis entre orientation et stabilité. Lors de la réalisation d'un mouvement, le contrôle postural implique la mise en jeu de stratégies anticipatrices (ajustements posturaux anticipateurs et accompagnateurs) et réactives (réactions posturales). Le contrôle postural est construit à partir d'informations sensorielles multiples (visuelles, graviceptives, vestibulaires, proprioceptives et cutanées) dont l'intégration est réalisée par les modèles internes.[13] En position debout ou assise, l'orientation par rapport à la gravité est fortement liée à la verticalité pour laquelle la contribution des afférences graviceptives somesthésiques et des afférences proprioceptives est majeure.

2.b. Après un AVC

Selon le modèle théorique du contrôle postural présenté plus haut, l'orientation médiolatérale et la stabilisation sont toutes deux altérées après un AVC. Dans le plan frontal, le patient présente une inclinaison controlésionnelle appelée latéropulsion. Cette perturbation de l'orientation posturale par rapport à la gravité est corrélée avec la déviation controlésionnelle de la verticale posturale subjective.[15] Le patient s'incline pour atteindre l'alignement avec son référentiel vertical qui est incliné. Cette latéropulsion est la principale cause des troubles de l'équilibre et la marche après un AVC au stade subaigu.[16] La stabilisation altérée par rapport au support est l'autre composante des troubles posturaux après un AVC. Les déficits sous-tendant cette instabilité seraient multiples : déficit moteur [17] ou sensitif, négligence spatiale ou trouble orthopédique.[16]

L'asymétrie d'appui du poids du corps sur les membres inférieurs en faveur du membre non parétique est un déficit latéralisé commun après un AVC.[18] Un débat existe sur le fait de considérer ou non cette asymétrie comme une perturbation de l'orientation posturale dans le plan frontal. Alors que cela l'a été historiquement, certains auteurs ont suggéré plus récemment que cette asymétrie serait le résultat d'une stratégie compensatoire active des patients pour améliorer leur instabilité posturale.[19] Les mécanismes de cette asymétrie d'appui sont probablement complexes et intriqués, impliquant en partie les référentiels égocentrés.[18,20]

3. Association entre négligence spatiale unilatérale et troubles posturaux et de l'équilibre

3.a. Négligence spatiale unilatérale et orientation posturale

En 2007, Lafosse *et al.* [21] ont mis en évidence, au moyen d'une analyse par classification hiérarchique, qu'il existait 3 groupes distincts de sujets parmi les 37 évalués en fonction de leurs troubles posturaux assis : le premier groupe comprenait les sujets sains (36%) et les patients avec un AVC ne présentant pas de troubles posturaux assis (lésion gauche 50%, lésion droite 14%); le second groupe était constitué des patients avec un AVC (lésion droite 71%, lésion gauche 29%) présentant une NSU, une déviation ipsilésionnelle médiolatérale du centre de gravité assis mais aussi une inclinaison controlatérale et une rotation ipsilésionnelle de la tête; enfin le dernier groupe regroupait les patients présentant tous, une lésion droite, une NSU et pour 88% d'entre eux un syndrome de « pushing »

(latéropulsion avec une résistance à la correction passive). Pour ce dernier groupe, la station assise était marquée par une déviation controlésionnelle du centre de gravité ainsi que par une rotation ipsilésionnelle et une tendance à l'inclinaison ipsilésionnelle de la tête. On peut ainsi suspecter la NSU d'être un facteur impliqué dans les troubles posturaux.

De la même manière, Pérennou *et al.* [22] ont utilisé le paradigme de la plateforme à bascule pour évaluer l'orientation posturale par rapport à la gravité de patients assis sur une plateforme instable basculant librement dans le plan frontal. Les patients AVC droits négligents inclinaient significativement plus leur bassin vers la gauche que les patients AVC droits non négligents, que ceux avec une lésion gauche, ou que les sujets sains. Des résultats semblables ont également été obtenus chez des patients « pushers » après lésion droite comparativement aux sujets sains ou aux patients AVC droits non « pushers ».[23] Dans ces deux dernières études,[22,23] l'orientation de la tête n'était pas modifiée par la présence de la NSU et la contribution de la vision était négligeable. L'orientation du tronc par rapport à la verticale étant assurée par des informations graviceptives d'origine somesthésique et celle de la tête par les informations graviceptives d'origine vestibulaire, ces résultats suggèrent une intégration asymétrique des informations somesthésiques graviceptives au niveau des centres supérieurs chez les patients négligents ou « pushers » après lésion droite. Ces constatations plaident en faveur de l'effet d'une négligence graviceptive sur l'orientation posturale médiolatérale. L'hypothèse d'un lien entre la NSU et la latéropulsion est renforcée par la similarité des ratio droite/gauche de récupération après AVC. En effet, la NSU et la latéropulsion sont présentes dans des proportions comparables entre les patients avec une lésion droite et ceux avec une lésion gauche à un stade très précoce après l'AVC ; puis la prédominance de la NSU et de la latéropulsion chez les patients avec lésion droite augmente dans des proportions comparables au stade aigue et subaiguë.[24–26] Par ailleurs, plusieurs études ont rapporté une corrélation statistique entre les perturbations de la verticale subjective et la NSU.[27,28]

A un degré plus important, la latéropulsion se caractérise par une résistance à la correction passive, aussi appelée syndrome de « pushing ». Même si aucune corrélation statistique n'a été mis en évidence entre la NSU et la syndrome de « pushing »,[29] 80% des patients ayant un syndrome de « pushing » après AVC présentent également une NSU.[30] Chez ces patients, la NSU se manifestait par un biais comportemental orienté plus vers

l'espace controlésionnel comparativement aux patients négligents sans syndrome de « pushing » avec un biais comportemental plus ipsilesionnel, suggérant l'influence d'un phénomène sur l'autre.[31] La nature de la relation reste incertaine mais les bases neurales du syndrome de « pushing » et de la NSU paraissent identiques.[32] Dans cette étude, le cortex insulaire était impliqué à la fois dans la NSU, le syndrome de « pushing » mais aussi dans les perturbations de la perception des verticales (visuelle et haptique) et dans l'anosognosie. Déjà en 2006, Karnath et Dieterich ont montré que les régions cérébrales associées à la NSU participaient au système « vestibulaire », responsable de l'intégration multimodale des informations vestibulaires, visuelles et proprioceptives.[33]

En ce qui concerne l'association entre la NSU et l'asymétrie posturale, les résultats sont plus contradictoires en position assise.[34] D'un côté, Nijboer *et al.* [35] ont montré une asymétrie médiolatérale en position assise majorée chez les patients présentant une négligence visuelle extra-personnelle de l'espace proche après un AVC par rapport à ceux sans négligence visuelle mais aussi par rapport à ceux présentant une négligence visuelle extra-personnelle de l'espace lointain, indépendamment de la position d'ouverture des yeux. De l'autre côté, Bonan *et al.* [36] n'ont pas retrouvé d'association significative entre déviation posturale médiolatérale en position assise et la négligence visuelle chez 30 patients après AVC droit ou gauche en phase subaiguë. Tout comme Yelnik *et al.* [37] entre la négligence visuelle et l'inclinaison corporelle médiolatérale sous stimulation optocinétique chez 25 sujets avec un AVC droit ou gauche en phase aiguë. Toujours en position assise, il semblerait que les patients avec une négligence visuelle droite présentent, les yeux fermés, une asymétrie médiolatérale plus importante que les patients avec ce même sous-type de négligence mais touchant l'espace gauche.[2] En position debout statique, les résultats étaient plus convergents,[34] arguant en faveur d'une association entre NSU et asymétrie d'appui. L'évaluation portait sur différents sous-type de négligence : l'asymétrie d'appui sur les membres inférieurs en position statique n'était pas corrélée avec la négligence visuelle [20,38] mais l'était avec la négligence comportementale évaluée par l'échelle de Catherine Bergego.[20,39] D'ailleurs, Genthon *et al.* [39] ont montré que seule la négligence comportementale était corrélée à l'asymétrie d'appui en analyse multivariée incluant la parésie, la spasticité et le déficit sensitif. En dynamique, les capacités de transfert du poids du corps sur les membres inférieurs étaient

retrouvées corrélées négativement avec la négligence visuelle par De Haart *et al.* [40] mais pas par Ishii *et al.*.[38]

Ainsi, l'impact de la négligence visuelle sur l'asymétrie posturale ne semble pas établi. Il est en revanche permis de penser que la négligence comportementale, impliquant des composantes personnelle et extra-personnelle, joue un rôle dans l'asymétrie d'appui médiolatérale.[34]

3.b. Négligence spatiale unilatérale et stabilité posturale

La stabilité posturale est évaluée instrumentalement sur plateforme de force. En position assise, certains auteurs n'ont pas retrouvé de corrélation entre la négligence visuelle (péri ou extra-personnelle) et l'instabilité posturale.[35,36] Pour autant, plusieurs résultats expérimentaux semblent accréditer l'hypothèse d'un lien entre NSU et l'instabilité posturale. Pérennou *et al.* [41] ont mis en évidence au moyen du paradigme de la plateforme à bascule que les patients négligents présentaient une instabilité posturale assise plus importante que les patients non négligents. De plus, l'application de stimulations électriques transcutanées (TENS) sur les muscles cervicaux controlésionnels avait pu réduire significativement l'instabilité posturale des patients AVC négligents, mais pas celle des patients non négligents.[41] Cette différence d'effet selon la présence ou non d'une négligence mais aussi l'existence d'une association statistique entre les effets de stimulations optocinétiques sur les réactions de stabilisation posturale en position assise et la négligence visuelle [37] plaident en faveur d'un lien entre NSU et l'instabilité posturale assise.

En position debout, l'instabilité posturale médiolatérale paraitrait associée à la négligence comportementale. Cette dernière est d'ailleurs le seul facteur significativement associé après une analyse multivariée incluant la parésie, la spasticité et le déficit sensitif.[39] L'instabilité posturale médiolatérale semble également corrélé avec la négligence visuelle : Bonan *et al.* [27] ont observé en 2007 une corrélation entre la négligence visuelle et l'instabilité posturale dans le plan frontal et dans le plan sagittal. Cependant, aucune analyse multivariée n'a été réalisée.

3.c. Négligence spatiale unilatérale et équilibre

L'équilibre est évalué dans sa dimension fonctionnelle et clinique. Pour le tronc, il semble exister une relation négative entre l'équilibre du tronc évalué par le « Trunc Control Test » ou la « Trunk Impairment Scale », et la négligence visuelle lors de tests de barrage. La négligence visuelle était le facteur le plus fortement associé lors d'une analyse multivariée.[42] Concernant l'équilibre fonctionnel, les résultats semblent plus contradictoires, laissant apparaître une relation plus complexe. En effet, une corrélation statistique significative négative entre la négligence visuelle et l'équilibre (évalué par la « Berg Balance Scale » ou la « Postural Assessment Scale for Stroke ») est retrouvée chez des AVC aigus ou subaigus, tant à un instant donné [27,28,42] que longitudinalement.[43] Même si 2 de ces études n'ont pas réalisé d'analyses multivariées permettant de prendre en compte d'éventuels co-facteurs, les 2 autres [42,43] ont montré que la négligence visuelle était un facteur indépendant expliquant l'équilibre tant transversalement que longitudinalement, et qu'il était le facteur prédictif le plus fort. En revanche, plusieurs autres études ne retrouvent pas d'association entre la négligence visuelle et l'équilibre.[36,44] Malgré une corrélation univariée significative avec la négligence visuelle, seuls le déficit sensitif et le déficit moteur étaient des facteurs indépendants associés avec l'équilibre aux stades aigu et subaigu de l'AVC.[44] Plus récemment, Dai *et al.* ont certes confirmé la contribution indépendante du déficit moteur et du déficit sensitif (sévère) sur l'équilibre mais ils ont également mis en évidence que la NSU n'était pas un déterminant indépendant de l'équilibre et que c'était la latéropulsion qui était le facteur indépendant le plus fortement associé avec l'équilibre aux stades aigu et subaigu.[16] Dans cette étude, les différents sous-types et différents espaces de NSU étaient évalués, permettant une meilleure détection,[11] contrairement aux autres études évaluant seulement la négligence visuelle qui concerne l'espace extra-personnel. Les déficits sensori-moteurs et la NSU sont ainsi moins déterminants que les troubles d'orientation posturale en rapport avec la gravité au stade subaigu de l'AVC. Dans l'hypothèse où la latéropulsion serait une manifestation posturale de NSU (cf partie 3. de ce chapitre d'ouvrage), la question de l'impact de la NSU sur l'équilibre reste ouverte.

Par ailleurs, la NSU pourrait être aussi un facteur explicatif de l'incidence des chutes en raison d'une corrélation univariée significative mais à la limite de la significativité en analyse multivariée avec l'âge comme facteur significatif.[45]

Même si l'équilibre n'est pas la seule activité mise en jeu lors d'un transfert assis-debout, elle en est une composante déterminante. L'influence de la NSU n'est pas clairement établie dans ce type de transfert.[34] Il semble que la négligence visuelle soit associée significativement à la mise en charge sur le membre inférieur parétique lors du lever [46] mais aussi avec l'indépendance dans la mise debout depuis les toilettes. Cependant, ni l'indépendance dans le lever depuis le fauteuil roulant qui peut est considérée comme une situation très proche, ni le niveau d'assistance nécessaire pour un transfert assis-debout depuis une chaise ne sont corrélés avec la négligence visuelle.[34]

3.d. Négligence spatiale unilatérale et marche

Bonan *et al.* [27] ont trouvé une corrélation positive entre la négligence visuelle dans les 3 premiers mois post-AVC et la vitesse confortable de marche 6 mois après l'AVC. Mais d'autres études n'ont pas observé de corrélation entre la négligence visuelle au cours du premier mois post-AVC et la vitesse de marche à distance (8 semaines et 6 mois après) [46,47] ni avec le changement de vitesse de marche à 8 semaines.[47] A un stade chronique, les patients ne présentaient pas une vitesse de marche significativement différente qu'ils soient négligents ou non.[48] La vitesse de marche n'était pas corrélée avec la négligence visuelle mais avec le déficit moteur et le niveau de déficiences neurologiques évalué par la « National Institutes of Health Stroke Scale ».[49]

En ce qui concerne l'analyse temporo-spatiale de la marche, il semble que la négligence visuelle impacte négativement la trajectoire de la marche.[48] Cependant, il n'est pas retrouvé de corrélation entre l'asymétrie temporelle de la marche et la NSU. Là encore, cette asymétrie est expliquée par l'influence du niveau de déficiences neurologiques et le déficit moteur.[49]

A l'image des résultats relatifs à la vitesse de marche et l'analyse temporo-spatiale, il semblerait que la NSU n'influence pas le niveau fonctionnel de marche. Ici encore, les études s'appuient presque toutes sur la seule composante visuelle de la NSU.[34] Par exemple, chez Van Nes *et al.*, la NSU était le facteur le plus fortement corrélé avec la fonctionnalité de la marche évaluée sur l'échelle « Functional Ambulation Categories » (FAC) dans les 2 semaines qui suivirent l'AVC.[42] Longitudinalement (de 6 à 12 semaines après l'AVC), le niveau de NSU n'était pas retrouvé comme un facteur indépendamment associé à la fonctionnalité de la

marche (FAC) après ajustement par l'âge et le déficit moteur.[43] En revanche, Kollen *et al.* [50] ont montré que l'évolution de la NSU dans le temps était corrélée négativement avec celle du score FAC dans une analyse multivariée, mais très faiblement (-0.01). Avec une évaluation de plusieurs sous-types et des différents espaces (personnel et extra-personnel) de NSU comme chez Dai *et al.*, celle-ci n'apparaît pas comme un facteur indépendant associé aux troubles de la marche. En revanche, la latéropulsion et le déficit moteur sont les deux seuls facteurs explicatifs au stade subaigu d'un AVC.[16] Les troubles de la marche étaient principalement dus aux troubles de l'orientation posturale par rapport à la gravité.

Sur le plan de l'indépendance de la marche, l'absence de négligence visuelle dans les 30 premiers jours après un AVC constitue un facteur significatif prédictif de la capacité de marcher à l'intérieur sans aide ni supervision à la sortie d'hospitalisation. En revanche, sa présence est un facteur significatif prédictif du besoin d'un fauteuil roulant pour se déplacer à la sortie d'hospitalisation. Après un AVC, l'obtention d'une marche indépendante nécessite plus de temps en cas de négligence, mais également en cas d'incontinence urinaire, de déficit cognitif, et d'incapacité à tenir l'équilibre assis dynamique ou l'équilibre debout.[34]

4. Hypothèses explicatives de l'association entre négligence spatiale unilatérale et les troubles posturaux.

Plusieurs hypothèses pourraient expliquer les relations de ces déficits, se référant à des plans et des espaces différents. Comme énoncé plus haut, la NSU est un biais comportemental vers le coté de la lésion et un défaut de conscience de l'hémi-espace controlésionnel, et donc en lien avec la référence sagittale, alors que l'orientation posturale se définit par rapport à la gravité, représentée par l'axe vertical. Ainsi la première hypothèse serait que la NSU et la latéropulsion sont deux déficits causés par l'atteinte d'une structure ou un réseau neuronal commun et responsable d'un codage de l'espace en trois dimensions. Une lésion cérébrale concernant cette structure entrainerait la manifestation conjointe de la NSU et de la latéropulsion. La NSU serait la conséquence d'un biais de codage de la référence sagittale et la latéropulsion celle d'un biais du référentiel vertical.

Cependant, Pisella *et al.* [51] ont démontré que les biais du référentiel sagittal, représenté par le droit devant manuel, étaient à distinguer de la NSU, car relèvent de mécanismes différents. Alors que la latéropulsion est, quant à elle, bien liée à des biais des

verticales subjectives, représentant le référentiel gravitaire,[15] il serait possible d'expliquer l'association entre NSU et latéropulsion par une seconde hypothèse : celle d'une atteinte de structures ou réseaux neuronaux distincts mais anatomiquement proches ou inter-connectés. Les données des études neuro-anatomiques plaident en ce sens. La construction du référentiel sagittal qu'est le droit devant et des verticales subjectives implique des aires cérébrales partiellement communes : lobe pariétal antérieur, partie antérieure du lobe pariétal inférieur, sulcus intra-pariétal, partie moyenne du gyrus temporal supérieur et dans une moindre mesure la partie postérieur du gyrus frontal supérieur pour le droit devant ; partie postérieure du lobe pariétal inférieur, partie postérieure du segment horizontal du sulcus intrapariétal, gyrus temporal supérieur postérieur, gyrus temporal moyen postérieur et dans une moindre mesure le lobe occipital dorsolatéral adjacent pour les verticales subjectives. Et dans les deux cas, le faisceau longitudinal supérieur serait également impliqué.[28] Certaines des régions impliquées dans la NSU sont soit situées à proximité, soit partiellement communes.[3,7] De plus, les données récentes de neuro-anatomie fonctionnelle suggèrent que l'origine de la NSU résiderait peu dans l'atteinte de structures cérébrales mais essentiellement dans les dysconnexions de réseaux neuronaux impliquant plusieurs aires cérébrales distinctes.[52,53] Karnath *et al.* [54] avaient déjà montré qu'une lésion des ganglions de la base droits après un AVC chez des patients présentant un tableau de NSU avait entrainé un dysfonctionnement dans 3 régions cérébrales (gyrus temporal supérieur, lobule pariétal inferieur et gyrus temporal supérieur) bien que structurellement intactes, et connues pour être responsables d'une NSU en cas d'atteinte structurelle.

L'hypothèse d'une atteinte conjointe par une même lésion cérébrale est renforcée par le fait que les patients négligents présentent des lésions de plus grande taille que celles des patients non négligents,[55] et que la fréquence de la NSU est positivement associée à la taille de la lésion cérébrale.[56] Il a également été suggéré, sur la base de données neuro-anatomiques, que les structures cérébrales impliquées dans le syndrome de « pushing » soient situées à proximité des régions impliquées dans l'aphasie en cas de lésion gauche ou de celles impliquées dans la NSU en cas de lésion droite.[57] Car quand bien même 80% des patients avec un syndrome de « pushing » présentent une NSU, ce syndrome se manifeste également après une lésion gauche, sans NSU, mais toujours associée dans ce cas à une aphasie.[30] Il est donc raisonnable de penser qu'une lésion étendue pourrait toucher à la fois les structures

responsables de la motricité, de la sensibilité et des représentations spatiales entrainant des troubles posturaux et de l'équilibre mais pourrait aussi engendrer concomitamment des dysconnexions neuronales à l'origine d'une NSU.

Contrairement aux deux autres hypothèses, relevant d'une concurrence ou co-occurence entre les déficits, une troisième hypothèse, reposant sur la dépendance de l'un par rapport à l'autre, pourrait expliquer la relation entre NSU et des troubles de l'orientation posturale. Comme évoqué en partie 3.a., la latéropulsion pourrait être une forme de négligence somesthésique graviceptive.[22,23] En effet, la présence d'une NSU après un AVC entraine une inclinaison du tronc que ne présentent pas les patients sans négligence ou les sujets sains. Mais comme l'orientation de la tête reste préservée, il est permis de penser qu'après une lésion hémisphérique, l'intégration des informations somesthésiques graviceptives serait asymétrique en raison de la NSU. Ces afférences graviceptives provenant de l'hémi-tronc controlésionnel, nécessaire à la construction de la représentation de la verticalité,[58] seraient « négligées » conduisant à une déviation controlésionnelle de la verticale subjective. Les patients chercheraient en position debout à aligner leur axe corporel longitudinal avec cette représentation erronée de la verticale, d'où la latéropulsion. De plus, l'évolution du gradient de récupération de la latéropulsion se fait selon le même modèle que celui de la NSU. Les études de neuro-anatomie montrent également que les bases neurales du syndrome de « pushing » comme celles du cortex « multi-sensoriel » en charge de l'intégration des différentes afférences sont des aires cérébrales correspondant à des localisations responsables de NSU.[32,33]

L'implication de la NSU dans les troubles de stabilité posturale pourrait s'expliquer par l'impossibilité de constituer une représentation complète et non-baisée du corps. Comme capacité de stabiliser les segments corporels les uns par rapport aux autres, la stabilité posturale se conçoit comme multi-segmentaire et implique une représentation du schéma corporel.[59] En raison du biais comportemental ipsilésionnel et du défaut de conscience controlésionnel constitutifs de la NSU, cette représentation est altérée, rendant difficile le contrôle multi-segmentaire.

Conclusion : Impact dans la rééducation des patients post-AVC

La relation entre la NSU et les troubles de la posture et de l'équilibre doit amener à penser la rééducation des troubles de la posture et de l'équilibre consécutifs à un AVC comme une prise en charge multidisciplinaire associant les aspects cognitifs et sensori-moteurs. L'évaluation et la rééducation de la NSU doit être un des constituants de la rééducation des troubles posturaux et de l'équilibre. Les manifestations de la NSU ne se limitent pas aux seules déficiences neuropsychologiques mais impactent globalement le patient en s'exprimant au cours de l'écriture,[60] la navigation, la marche, les interactions sociales [61] … Un travail collaboratif multidisciplinaire est donc essentiel associant médecins, masseur-kinésithérapeutes, ergothérapeutes, orthophonistes, neuropsychologues et psychomotriciens. Cette prise en charge doit débuter le plus tôt possible après l'AVC et se poursuivre dans le temps y compris au stade chronique, durant lequel la prévalence de la NSU est souvent sous-estimée.[1]

Pour cela, il est nécessaire de procéder à une évaluation complète des différents sous-types de NSU et des différents espaces concernés. Le polymorphisme de ce syndrome implique de ne pas limiter l'évaluation à la seule négligence visuelle touchant l'espace extra-personnel au moyen des tests conventionnels « papier-crayon », mais d'évaluer également les autres composantes de la NSU (corporel, comportemental, motrice …).[61]

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3.2.2. Manuscrit d'article en format « pré-soumission » 2

Contribution of spatial reference frames and unilateral spatial neglect on weight bearing asymmetry after right stroke. A cross-sectional study.

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Abstract

Background: After right stroke, patients frequently suffer from weight-bearing asymmetry (WBA). The influence of misperceptions of egocentric spatial reference frames such as longitudinal body axis (LBA) and subjective straight-ahead (SSA), but also of unilateral spatial neglect (USN) on WBA are strongly suspected. The aim of this study was to determine the independent contribution of LBA, SSA, and USN on WBA, and to explore a potential interaction effect between spatial reference frames and USN.

Methods: A cross-sectional study from the AVCPOSTIM multicentric RCT including patients with a right unilateral sustentorial stroke dating from less than 9 months and having a weight-bearing on the paretic lower limb ≤40% was conducted. The main outcomes included the type of stroke lesion, motor weakness, spasticity, superficial and kinaesthetic sensibility, lateral homonymous hemianopia, WBA and body sway assessed in standing position with eyes open (EO) and eyes closed (EC), lateropulsion, SSA, LBA, and different components of USN. Linear and non-linear models were used in univariate and multivariate regressions.

Results: A total of 86 patients (mean age: 59.4 years, median delay post-stroke: 78 days) were recruited. The mean±standard deviation WBA was 18.4±10.0 in EO condition and 17.7±9.7 in EC condition. Multivariate regressions found that the time post-stroke ($p<0.001$) was a significant predictor of WBA in EO condition, while anosognosia ($p=0.52$) and kinaesthetic sensibility ($p=0.10$) were non-significant predictors (adjusted $R^2=0.22$). The time post-stroke ($p<0.001$), LBA ($p=0.02$), and the interaction between LBA and behavioural neglect ($p=0.04$) were significantly associated with WBA in EC condition (adjusted $R^2=0.32$).

Conclusion: After subacute right stroke, findings suggest a modulating effect of behavioural neglect on the influence of LBA on WBA in EC condition; and no contribution of spatial reference frames and USN on WBA in EO condition. The time post-stroke independently contributes to WBA.

Keywords: stroke; postural disorders; body sway; weight-bearing asymmetry; spatial reference frames; hemineglect.

Introduction

Background

After stroke, patients frequently suffer from postural disorders, among which a weight-bearing asymmetry (WBA) towards the non-paretic side (ipsilesional) assessed using posturographic platform.[1–4] Although WBA is improved during the acute or subacute stage, it remains during chronic stage.[5–7] Because it is correlated with gait disorders, a reduced independence in daily living activities and a lower quality of life,[8–12] WBA is therefore regarded as one of main concerns in rehabilitation after stroke. Up to now, the efficacy of rehabilitation on WBA after stroke is however limited or not evidenced.[13] While the determinants of WBA post-stroke are incompletely known, a better knowledge of these could help to develop effective rehabilitation strategies.

Justification of the research

Sensory-motor deficits such as motor weakness,[3,8,11,14] somatosensory deficits,[3,11] and spasticity [11,15] may be associated to WBA. Some authors have suggested that WBA would be a compensatory strategy of the non-paretic lower limb for the loss of postural control from the paretic lower limb.[3,16–18]

Furthermore, the misperceptions of spatial reference frames may be involved in WBA after stroke. Patients with stroke could perceive their verticality,[19–23] longitudinal body axis (LBA)[24] and straight-ahead [25–30] with a deviation and/or an uncertainty in the estimation. Even though these bias of spatial reference frames have been observed in patients with either left or right stroke lesion,[19,22,24,31] having or not an unilateral spatial neglect (USN),[19,28–31] the frequency and/or the magnitude of these biases were higher after right

lesion than left lesion,[20,22,24,31] or in case of USN,[19,20,24,28,30,31] in accordance with the predominance of the right hemisphere in spatial cognition. Patients with a right stroke had also an greater WBA compared to those with a left lesion.[1] In addition, WBA was correlated with a contralesional deviation of LBA.[11,32] In the same way that patients' lateropulsion after stroke is a postural behaviour aiming at orientating the body against gravity based on an impaired perception of verticality,[22,33] the misperceptions of spatial reference frames may also explain the WBA as they can generate biased coordinates for the distribution of loading on lower limb during upright stance.[11]

While WBA could be more closely linked to biased egocentric coordinates than to biased allocentric coordinates,[11,32] the influence of two egocentric spatial reference frames that are LBA (in frontal plane) and SSA (in horizontal plan) could be different. To our knowledge, two studies reported a significant correlation between WBA and the deviation of LBA in 22 and 30 patients after stroke respectively.[11,32] Only Jamal *et al.*[32] have investigated the association between SSA and WBA, and failed to find one in patients at chronic stage. Nonetheless, findings from several experimental studies suggest that the use of prismatic glasses with an optical deviation towards the right side producing a shift of SSA to the left side,[26] was likely to reduce WBA in patients with right stroke.[34–37] This could indicate an involvement of SSA in WBA of patients with right stroke, the nature of this involvement remains unclear.

In addition to the potential involvement of spatial reference frames, WBA in patients after stroke may be linked to USN.[3,11,38] Even if the frequency and magnitude of misperceptions of spatial reference frames are higher in case of USN than without,[19,20,24,28,31] these misperceptions of spatial reference frames can also be encountered in patients without USN,[19,28,31,32,39,40] suggesting a dissociation between these spatial cognition deficits. While USN was previously considered as the result of egocentric spatial orientation bias characterized by an ipsilesional deviation of SSA,[41,42] later findings suggested that USN and SSA are different deficits related to distinct but close mechanisms.[30,39,40,43,44]

Considering current theoretical frameworks in favour of the involvement of mental representations generated from multiple sensory inputs by internal models to perform a motor action and especially postural control,[45–50] the question of influence of the misperceptions of spatial reference frames and of USN on WBA is relevant. Consequently, the

aim of the present study was to determine the independent contribution of LBA, SSA, and USN on WBA taking into account demographic and clinical covariates in a larger sample of patients. In addition, a potential interaction effect between LBA on the one hand, and USN or SSA on the other hand on WBA was explored. Because factors explaining contralesional WBA are likely to be different, the present study investigated only patients with an ipsilesional WBA after right stroke.

Materials and methods

Design

The study presented herein is an observational cross-sectional study based on a multicentric randomised controlled trial (RCT; AVCPOSTIM) assessing the effects of prism adaptation and neck-muscle vibrations on WBA in patients with right stroke. This RCT, registered under the number NCT01677091 on Clinicaltrials.gov, was conducted in the adult physical and rehabilitation medicine units of 8 hospitals in France (The University Hospital Centres of Rennes, Lille, Grenoble, Lyon, Reims, Nancy, Reims, and Paris, and the rehabilitation centre of Kerpape). For the cross-sectional study presented herein, only data from the AVCPOSTIM RCT collected during the baseline or pre-intervention assessment were analysed. The reporting follows recommendations of STROBE guidelines for cross-sectional studies.[51]

Participants

All patients admitted after a stroke in the participating physical and rehabilitation medicine units were eligible for inclusion. The inclusion criteria were: being aged between 18 and 80 years; having a first right unilateral sustentorial stroke defined using a computed tomography or a magnetic resonance imaging; having an ischemic or haemorrhagic stroke within 9 months before study inclusion; being able to stand upright without any help for at least 30 seconds; and having a bearing on the paretic (left) lower limb ≤40% of body weight during a posturographic assessment in quiet standing position with eyes closed (EC).[52] The exclusion criteria were: having any orthopaedic, rheumatologic, or visual disorders affecting the distribution of the centre of pressure (COP) during posturographic assessment; having any visual disorders limiting the assessment of LBA; having any brainstem or cerebellum stroke

lesion; and presenting any limits preventing the understanding of instructions. The presence of an USN or a lateral homonymous hemianopia (LHH) was not an exclusion criterion.

During the inclusion visit, eligible patients who fulfilled the above inclusion criteria and who were willing to participate in the study provided a free, informed, and written consent. The ethical approval was obtained from the ethics committee Institutional Review board of Poitiers-France III West N°05/12/16 on the 30th July 2012. The study was performed in accordance with the Declaration of Helsinki. A sample size of 114 participants to include was estimated for the AVCPOSTIM RCT.

Outcomes

The following data were extracted from medical records: age, sex (male/female), the manual laterality (left/right), the time post-stroke (in days), the type of stroke lesion (ischemia/haemorrhage), and the presence or absence of a LHH (yes/no). In addition, the motricity index was used to assess the motor weakness of the paretic lower limb during a hip flexion, a knee extension, and an ankle dorsiflexion.[53] The total motricity index score ranges from 0 to 100 points, and a better score indicates better abilities. The spasticity of paretic quadriceps, adductor, and triceps surae were assessed according to the modified Ashworth scale.[54] The spasticity of the paretic lower limb was calculated by adding these 3 individual spasticity scores. The epicritic sensibility of the paretic thigh, calf, and big toe were measured by light touch; also, the kinaesthetic sensibility of the paretic knee, ankle, and big toe were assessed by asking patients to indicate when they feel the joint motion mobilised by the therapist. For these 2 types of sensibility, anaesthesia was scored as 0, disturbed perception as 1, and normal perception as 2, after comparison with the non-paretic side. A total paretic lower limb score was calculated for the epicritic sensibility and the kinaesthetic sensibility by adding their 3 sub-scores respectively. All patients underwent a magnetic resonance imaging (MRI) scan or a computed tomography scan (CT) in case of MRI contraindication. Images were centralised using the Shanoir server.[55] Lesion delineation was performed using ITK-SNAP,[56] by a trained medical doctor supervised by an expert neuroradiologist.

Postural disorders were quantified by means of posturographic assessments in quiet upright position. A dual force plate (Feetest6© from Techno Concept) recorded the spatial and temporal evolution of centre of pressure (COP) while the patient stood quietly and upright for

30 seconds without any help. Patients were asked to look straight ahead. Foot pads were parallel and separated by 14cm. We performed 2 trials with eyes open (EO) and 2 others with EC. The measured parameters were: the mean mediolateral position of COP (mm), the mean anteroposterior position of COP (mm), the sway area of COP (mm^2), the standard deviation of the mediolateral and anteroposterior positions of COP, and the percentage of body weight bearing on the paretic lower limb. Each parameter was expressed as the mean of 2 trials with EO and the mean of 2 trials with EC. WBA was defined as: 50 minus the percentage of body weight bearing on paretic lower limb. Regarding postural disorders, we also assessed lateropulsion and pushing using the scale for contraversive pushing (SCP).[57] This scale assessed: i) the symmetry of spontaneous posture, ii) the use of the leg or the arm to extend the base of support, and iii) the resistance during a passive correction of posture. Each of these 3 items, scored between 0 and 1 point, was measured while sitting and standing. The total score was thus between 0 and 6 points. As proposed by Karnath *et al.*[57] and Perennou *et al.*,[22] patients with a score on total SCP score >0.5/6 were considered as having lateropulsion, and those with a score reaching at least 1 on each of the 3 items as having contraversive pushing.

LBA was assessed in accordance with the method used in Barra *et al.*[11,24] LBA reflects the body spatial reference frame, without graviceptive sensorial input. Patients were lying on an examination table, with the head, trunk, pelvis, and legs strictly aligned. The head and legs were laterally constrained to keep the alignment during the time of assessment. A rolling device was composed of a half protractor with a fluorescent rod fixed in its centre and oriented towards the outside. The centre of the protractor was placed at approximately 25-30cm above the patient's navel and the fluorescent rod above the body top. In complete darkness, the assessor moved slowly the fluorescent rod from extreme left or right position in the patient's visual field towards the opposite extreme position. Patients were asked to indicate when the fluorescent tube reached the position they perceived as overlapping with their LBA. Six trials were performed, the departure positions of the rod were in the following order: 30°/20°/-30°/10°/-20°/-10°. Between each trial, patients were asked to close their eyes to remove any feedback or cue. A mean of 6 trials was calculated.

We also assessed manual SSA, which reflects the peri-personal spatial reference frame based on proprioceptive inputs, in accordance with the method already described

elsewhere.[29,32,44,58] Patients were seated in front of a table, on which was drawn a half protractor. The navel aligned with the centre of the half protractor and patients, blindfolded, were asked to point “straight-ahead” using the right hand. Six trials were performed with a departure position of the hand in the following order: 30°/-20°/10°/-30°/20°/-10°. A mean of 6 trials was calculated. For both SSA and LBA, a negative value means a position on the left hemi-space while a positive value means a position on the right hemi-space.

USN is a heterogenous syndrome involving different components.[59,60] We explored the exploratory/visuo-motor component using the bells test.[61–63] The variables recorded were the total number of omissions (/35), the column number of the first bell circled (1 to 7), the difference between left-side and right-side omissions, and the duration to complete the test. Patients were considered as neglect for the exploratory/visuo-motor component if the total number of omissions was >6, the column number of the first bell circled was >5, the left minus right omissions was >2, or the duration was <183sec. A correction was applied to take into account the age and the educational level.[62] The perceptive/visuo-spatial component was assessed using a line bisection test.[62, 63] We measured the deviation in mm from the true middle. The test was performed on a 20cm line. A mean of 3 trials was calculated. A negative value indicates a deviation towards the left side while a positive value indicates a deviation towards the right side. Patients were considered as neglect for the perceptive/visuo-spatial component if the absolute value of deviation was ≥7mm.[62] The personal neglect was assessed using a fluff test.[64] In this test, patients were required to remove all the targets attached to their body on both right and left sides while being blindfolded. We quantified the number of targets omitted on the paretic body (/15). Patients were considered as having a personal neglect if the omissions were <13.[64] Lastly, the behavioural neglect was assessed using the Catherine Bergego Scale (CBS).[62,65] This scale appraises the presence and the severity of USN in daily living situations but also of anosognosia. The score of the evaluation by the therapist (/30) was used to determine the presence (*i.e.* CBS score >0) and the severity of USN, and the difference of scores between the self-evaluation by the patient (/30) and the evaluation by the therapist was used to determine the anosognosia. Patients were considered as having an anosognosia if the anosognosia score was >0.

Balance was assessed by Berg balance scale (BBS) and postural assessment scale for stroke (PASS) while gait was assessed by timed up and go test (TUG).[66–68] By a score range

between 0 and 56 points and between 0 and 36 points respectively, BBS and PASS reflects functional abilities of balance in patients after stroke. The time required to complete a TUG (to stand-up from a chair, to walk 3 meters, to turn around, to return to the chair and to sit down) was recorded. BBS, PASS and TUG were only used to describe participants included in the study, but they were not considered as covariates in statistical analyses.

Except for data extracted from medical records (*i.e.* age, sex, manual laterality, the time post-stroke, the type of stroke lesion, and the presence or absence of a LHH), all other outcomes were assessed between the inclusion visit and the beginning of interventions in AVCPOSTIM RCT (15 days later approximately). RMI (or CT) scan was performed in a delay less than 8 weeks post-stroke.

Statistical analysis

Variables were expressed as mean±standard deviation (SD) in case of a normal distribution or median [interquartile range, IQR] for discrete or continuous variables, or count (percentage) for categorical variables. Missing data were not imputed. The categorisation of quantitative variables (*e.g.* USN) were only used for the description of participants.

First, univariate linear regressions were performed to explain WBA, and select the variables with a p-value≤0.1. Non-linear effect of LBA and SSA were considered using natural cubic splines. To reduce the number of USN and other demographic and clinical variables selected using the aforementioned method, intermediary multivariate regressions were performed using a both forward and backward stepwise Akaike Information Criterion (AIC) selection (this procedure was done twice, once with USN variables and the second time with other demographic and clinical variables). Finally, multivariate analyses were conducted with: i) variables with a p-value≤0.1 from univariate regressions for SSA or LBA, and ii) variables from intermediary stepwise multivariate regressions for USN and other demographic and clinical variables.

Generalised additive models (GAM) assuming a gaussian distribution were used.[69] These are flexible statistical models that allow to model non-linear relationship using smooth functions of covariates. The interaction effect between LBA and USN or LBA and SSA on WBA was assessed in the multivariate GAM, if the effect of each explicative variable was significant at the end of the previous univariate or stepwise multivariate regressions. Smoothing

parameter estimation was performed using restricted maximum likelihood. Several models were considered with increasing complexity in terms of non-linearity and interaction structure (tensor product splines were used to model interactions between continuous variables). A double penalty approach was also used that allowed not only to smoothen certain effects but also to remove them completely from the model.[70] The final model was the one with the smallest AIC score (AIC corrected for smoothing parameter uncertainty).[71] Keeping in mind the risk of overfitting with GAMs, we finally graphically examined each model but also checked the effective degrees of freedom (edf), with the aim of limiting the "wiggliness" of the curve. If necessary, an additional penalty was used to limit the "wiggliness".[69] Adequacy plots of the final model were built to check the validity of the model.

We considered as statistically significant p-values≤0.05. All statistical analyses were performed using R software (version 4.0.0) with, among others, the R packages "MASS", "splines", and "mgcv".

Data availability statement

The data supporting the study presented herein and statistical analyses will be available upon reasonable request to the corresponding author and Prof. Isabelle Bonan.

Results

Participants

The enrolment of participants run from May 2013 to May 2018 (Fig. 1). Despite a sample size to include of 114 participants, the enrolment was stopped earlier due to difficulties in the recruitment and the workload induced by the RCT for caregivers. A total of 86 participants from 8 hospitals was recruited (Rennes: n=32, Lille: n=12, Kerpape: n=10, Grenoble: n=10, Lyon: n=8, Reims: n=6, Nancy: n=6, and Paris: n=2). There were 59 (69%) males. The mean age of participants was 59.4±10.4 years, and the median [IQR] post-stroke delay was 78 [74.8] days. Eighty participants (95%) were right-handed. The mean motor weakness of the paretic lower limb was moderate. A total of 70 (84%) patients had a spasticity of the paretic lower limb, 50 (60%) epicritic sensibility deficits, 42 (51%) kinaesthetic sensibility deficits, and 32 (45%) a LHH. A total of 67 (94%) patients had at least 1 component of USN, the most frequent

one was the behavioural neglect which was encountered in 66 (89%) patients. Anosognosia was found in 46 patients (62%; Table 1).

Seventy scans were analysed. For 16 subjects, missing or low-quality data did not allow the processing of data (missing T1 weighted or flair images in case of MRI data, motion artifacts, low intensity CT images). The individual stroke lesions maps were overlaid on a T1-template in the Montreal neurological institute template space (Fig. 2). Colour scale indicates the number of patients for which the lesion extended in this voxel. Most frequent lesioned voxels (49%) were found in the frontal lobe (precentral gyrus, middle and inferior frontal gyrus), 19% in the parietal lobe (inferior parietal lobule and postcentral gyrus), 9% in the superior temporal gyrus, 7% in the insula.

Missing data

The total number of missing data represented 6.0% of the dataset. Data for WBA were missing for 3 participants (3.5%) due to: technical problem during posturographic assessment (n=1), organisation error (n=1), and withdraw before assessments (n=1). Missing data for other variables were due to withdraws before the achievement of all or parts of assessments, technical issues, and organisation errors. No missing data were imputed.

Postural disorders

The mean±SD weight bearing on the paretic lower limb was 31.6±10.0% with a range between 7.9% and 52.0% in EO condition and 32.3±9.7% with a range between 10.6% and 52.4% in EC condition. Six participants were considered as symmetric (weight bearing on the paretic lower limb between 47 and 53%)[7] according to EO or EC condition. All other participants had a WBA towards the non-paretic (right) lower limb (Fig. 3). There was no significant difference between EO and EC condition for WBA (Table 1).

The sway area of COP, the SD of the mediolateral and anteroposterior positions of COP were significantly different between EO and EC condition ($p<0.001$, $p=0.02$, and $p<0.001$ respectively), while there was no significant difference for the mean anteroposterior position of COP ($p=0.93$). Twenty-seven (36%) participants had a lateropulsion and 2 (3%) had a contraversive pushing (Table 1).

WBA

Using univariate regressions with a natural cubic spline, there was no significant association between WBA in EO condition and LBA (p=0.12) or SSA (p=0.33), and there was a significant association between WBA in EC condition and LBA (p=0.01, adjusted R^2=0.11) indicating a non-linear relationship. In EC condition, WBA increased as LBA deviated from +0.21 degree both to the right and to the left (Supplementary Fig. 1). There was no significant association between WBA in EC condition and SSA (p=0.27).

After the intermediary stepwise multivariate regression for USN variables, only anosognosia remained significantly associated with WBA in EO condition (p=0.05), and only behavioural neglect remained significantly associated with WBA in EC condition (p=0.01; Table 2).

After the intermediary stepwise multivariate regression for other demographic and clinical variables, we found a model including the time post-stroke as significant variable (p<0.001) and the kinaesthetic sensibility of paretic lower limb as non-significant variable of WBA in EO condition (p=0.17; Table 2), and only the time post-stroke remained significantly associated with WBA in EC condition (p<0.001; Table 2).

Finally, a multivariate regression enabled to design the final model that explained WBA in EO condition (adjusted R^2=0.22) including the time post-stroke as only significant predictor (B=0.06, Standard error [SE]=0.02, p=0.003, η^2=0.22; Supplementary Fig. 2), but also anosognosia (B=0.11, SE=0.17, p=0.52) and kinaesthetic sensibility (B=-0.93, SE=0.56, p=0.10) as non-significant predictors. In EC condition, the multivariate GAM revealed that the time post-stroke (edf=1.61, p<0.001), LBA (edf=0.80, p=0.02), and the interaction between LBA and behavioural neglect (edf=1.65, p=0.04) were significantly associated with WBA while behavioural neglect was not (edf=0.18, p=0.24; Fig. 3 and Supplementary Fig. 3). This model, ti(WBA)=ti(time post-stroke)+ti(CBS)+ti(LBA)+ti(CBS, LBA), explained about 36% of the deviance of WBA in EC condition (adjusted R^2=0.32). Model adequacy plots are available in Supplementary Fig. 4.

Discussion

The main objective of the study presented herein was to determine the independent contribution of misperceptions of spatial reference frames and USN on WBA. In patients with ipsilesional asymmetrical or non-asymmetrical weight bearing after right stroke, neither SSA,

LBA, nor USN were independently associated with WBA in EO condition. In EC condition, LBA, behavioural neglect and the interaction between LBA and behavioural neglect were independently associated with WBA while SSA was not.

Our results confirm previous findings but also bring a novelty: the influence of LBA on WBA may not be uniform according to the severity of behavioural neglect. Indeed, in patients with no behavioural neglect, the influence was important and appeared linear: a contralesional deviation of LBA would contribute to a greater WBA while an ipsilesional deviation would lead to lower WBA. Conversely, in case of behavioural neglect, the influence of LBA on WBA varied and was lower. In patients with a moderate behavioural neglect, the ipsilesional deviation of LBA could lightly contribute to an increase in WBA, while in patients with a severe behavioural neglect, the contralesional deviation of LBA could contribute to an increase in WBA. The influence of LBA on WBA depended on both the magnitude and the direction of the deviation of LBA, in accordance with previous findings,[11] but also on behavioural neglect. Considering the non-significant association between behavioural neglect and WBA and the significant association between LBA and WBA, the significant interaction effect between LBA and behavioural neglect on WBA could be interpreted as a modulating effect of behavioural neglect on the association between LBA and WBA. The results presented herein reinforce the hypothesis that the misperception of this spatial reference frame could partly explain WBA according to the severity of behavioural neglect.[11,32] In a theoretical framework based on the use of internal models to manage spatial representations,[45–49] the presence of behavioural neglect would modulate the contribution of the body egocentric reference that is LBA in body weight distribution. Contrary to the behavioural neglect, other components of USN were not associated with WBA, which could be explained by the lesser sensitiveness of the conventional paper-and-pencil tests, especially in patients suffering from mild USN.[65, 72]

Finding an influence of LBA but not of SSA on WBA is consistent with results reported by Jamal *et al.* in chronic stage of stroke.[32] This could suggest that WBA is a postural behaviour linked to body egocentric spatial reference frame in the frontal plane. Nonetheless, the significant interaction which was found between behavioural neglect and LBA on WBA could also reflect the involvement, abeit weaker, of spatial representations in the horizontal plane. Indeed, the

USN is a spatial cognition deficit mainly expressed in terms of right/left deviation in the horizontal plane. WBA may be resulted from 3-dimensional spatial representations.[33]

The third variable of the model explaining the WBA is the time post-stroke. The study presented herein is a cross-sectional analysis of a clinical trial in which patients were included if they could stand alone on a posturographic platform without help for 30 sec. The time post-stroke reflects therefore the delay from the stroke until when the patient was able to stand alone. This association between the time post-stroke and WBA in both EO and EC conditions suggests that the longer the time after the stroke for the patient to be able to stand alone, the greater the WBA. Therefore, this variable reflects the severity of postural disorders in patients with stroke. Several studies have suggested that a greater WBA would be a compensative way for patients with larger postural instability to be able to stand.[3,16–18] The contribution of other deficits could also be reflected through this variable. Further investigations are needed to clarify this.

It is also to note that in the study presented herein, the association between LBA and WBA was only significant in EC condition and not in EO condition. These findings differ from those reported in a study by Barra *et al.*[11] in which a significant correlation between WBA with EO and LBA has been evidenced in 22 patients with a right or left stroke. These patients were not selected on their WBA or the side of stroke, making it difficult to compare results. Any correlation was not performed for the EC condition. The visual dependence found after stroke [73–75] could explain why LBA was not associated with WBA. In EO condition, patients are likely to have a greater reliance on visual inputs than proprioceptive inputs which contributes to the perception of LBA. The patients included in the present study had visual dependence as shown by the increase in body sway in EC condition than EO condition.[75]

The present study has several limitations. It is a cross-sectional study based on the baseline or pre-intervention assessment from the AVCPOSTIM multicentric RCT whose primary objective was not to investigate the relationship between spatial reference frames and USN, and postural disorders. A longitudinal study with mixed models could be relevant to confirm the findings presented herein and would be more suitable to evaluate the influence of time post-stroke. In addition, the number of participants in this cross-sectional study was not estimated “a priori” in order to take into account the large number of variables to include in multivariate regression models. Another limitation concerns the representativeness of the participants

included in the study with respect to patients likely to suffer from the sequelae of stroke. The 40% ceiling threshold for weight bearing on the paretic lower limb during the inclusion visit led to the recruitment of mainly ipsilesional asymmetric participants. Therefore, the main findings of the present study contribute to improve the understanding of WBA towards the non-paretic side after right stroke. This work should be duplicate with participants comprehensively assessed in routine care.

Conclusion

Our study shows the involvement of the body egocentric spatial reference frame, assessed by LBA, to explain the WBA in EC condition in patients predominantly asymmetric towards the non-paretic limb after subacute right stroke. In addition, the behavioural neglect would modulate the contribution of this body egocentric spatial reference frame to the body weight distribution of these patients. The misperceptions of spatial reference frames, such as SSA and LBA, were not associated with WBA in EO condition. The time post-stroke independently contributes to WBA in EO and EC condition. Further investigations are needed to confirm these findings in a representative sample of all patients after stroke.

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Competing interests

The authors report no competing interest.

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Table 1. Characteristics of participants

	Participants	Missing data (n)
Participants, n	86	NA
General characteristics		
Age in years, mean±sd	59.4±10.4	0
Sex: male/female, n (%)	59 (69%) / 27 (31%)	0
Manual laterality: left/right, n (%)	4 (5%) / 80 (95%)	2
Stroke lesion		
Time post-stroke in days, median [IQR]	78 [74.8]	2
Type of lesion: ischemia/haemorrhage, n (%)	54 (64%) / 30 (36%)	2
Motor and sensorial deficits		
Motor weakness, /100pts, mean±sd	55.3±21.1	3
Spasticity, /12pts, median [IQR]	3 [5]	3
Epicritic sensibility, /6pts, median [IQR]	3 [4]	3
Kinaesthetic sensibility, /6pts, median [IQR]	5 [3]	3
LHH: yes/no, n (%)	32 (45%) / 39 (55%)	15
Postural disorders		
WBA, EO/EC, mean±sd	18.4±10.0 / 17.7±9.7	3 / 3
Sway area of COP, EO/EC in mm^2, median [IQR]	547.5 [1062.3] / 736.7 [1539.1]	3 / 3
SD of ML position of COP, EO/EC, median [IQR]	6.2 [6.7] / 7.4 [7.5]	4 / 4
SD of AP position of COP, EO/EC, median [IQR]	7.2 [4.0] / 8.5 [5.5]	4 / 4
Mean anteroposterior position of COP, EO/EC, in mm, mean±sd	40.5±16.8 / 40.4±16.7	3 / 3
Upright/Lateropulsion/Pushing, n (%)	45 (61%) / 27 (36%) / 2 (3%)	12
Spatial reference frames		
Manual SSA in deg, median [IQR]	-1.8 [8.8]	3

LBA in deg, median [IQR]	-0.08 [3.7]	7
Unilateral spatial neglect		
Exploratory/visuo-motor component, y/n, n (%)	49 (64%) / 28 (36%)	9
Perceptive/visuo-spatial component, y/n, n (%)	27 (34%) / 52 (66%)	7
Personal neglect, y/n, n (%)	23 (30%) / 55 (70%)	8
Behavioural neglect, /30pts, median [IQR]	6.5 [11.8]	12
Anosognosia, /30pts, median [IQR]	2 [7]	12
Balance and gait		
BBS, /56pts, median [IQR]	38 [18.5]	4
PASS, /36pts, median [IQR]	30 [3.75]	4
TUG, in sec, median [IQR]	44 [48]	13

AP, anteroposterior; BBS, Berg balance scale; COP, centre of pressure; Deg, degree; EC, eyes closed; EO, eyes open; IQR, interquartile range; LBA, longitudinal body axis; LHH, lateral homonymous hemianopia; ML, mediolateral; PASS, postural assessment scale for stroke; NA, not applicable; TUG, timed up and go test; sd, standard deviation; SSA, subjective straight-ahead

Table 2. Univariate regressions and intermediary stepwise multivariate regressions with USN and other demographic and clinical variables for WBA

Variable	WBA - EO					WBA - EC				
	Univariate			Multivariate		Univariate			Multivariate	
	B (SE)	adj. R^2	p	B (SE)	P	B (SE)	adj. R^2	P	B (SE)	p
General characteristics										
Age in years	0.0003 (0.11)	-0.01	1			0.03 (0.10)	-0.01	0.78		
Sex (female)	1.66 (2.36)	-0.01	0.48			2.98 (2.28)	0.01	0.19		
Manual laterality (RH)	-5.54 (5.12)	0.002	0.28			-2.72 (4.99)	-0.01	0.59		
Stroke lesion										
Time post-stroke in days	0.08 (0.02)	0.23	<0.001* η^2=0.24	0.08 (0.02)	<0.001* η^2=0.26	0.08 (0.02)	0.23	<0.001* η^2=0.24	0.08 (0.02)	<0.001* η^2=0.27
Type of lesion (hem.)	0.59 (2.31)	-0.01	0.80			-0.70 (2.24)	-0.01	0.76		
Motor and sensorial deficits										
Motor weakness	-0.14 (0.05)	0.08	<0.01* η^2=0.09			-0.12 (0.05)	0.06	0.02* η^2=0.07		
Spasticity	0.77 (0.38)	0.04	0.04* η^2=0.05			0.83 (0.36)	0.05	0.02* η^2=0.06		
Epicritic sensibility	-0.90 (0.50)	0.03	0.07‡ η^2=0.04			-0.89 (0.48)	0.03	0.07‡ η^2=0.04		
Kinaes. sensibility	-1.68 (0.57)	0.09	<0.01* η^2=0.10	-0.78 (0.56)	0.17	-1.13 (0.57)	0.04	0.05* η^2=0.05		
LHH (no LHH)	-3.49 (2.27)	0.02	0.13			Not in EC condition				
Postural disorders										
Sway area of COP in mm^2	-0.0003 (0.001)	-0.01	0.81			-0.0003 (0.0004)	-0.005	0.44		

SD of ML position of COP	-0.02 (0.24)	-0.01	0.98			r=0.21, p=0.06[a]				
SD of AP position of COP	0.51 (0.38)	0.01	0.18			0.01 (0.22)	-0.01	0.96		
AP position of COP in mm	0.02 (0.07)	-0.01	0.77			0.006 (0.07)	-0.01	0.93		
Lateropulsion	-0.31 (1.07)	-0.01	0.78			-0.67 (1.07)	-0.01	0.53		
Unilateral spatial neglect										
Exploratory/visuo-motor component										
Column of the 1st bell	0.14 (0.52)	-0.01	0.78			0.55 (0.50)	0.003	0.28		
Difference L-R	0.28 (0.28)	-0.0002	0.32			0.34 (0.28)	0.007	0.22		
Total omissions	0.25 (0.18)	0.01	0.18			0.17 (0.18)	-0.001	0.34		
Duration in s	0.002 (0.01)	-0.01	0.86			0.01 (0.01)	-0.005	0.42		
Perceptive/visuo-spatial component										
Deviation in mm	-0.02 (0.05)	-0.01	0.74			r=0.10, p=0.37[a]				
Personal neglect										
Omissions	0.16 (0.39)	-0.01	0.68			0.11 (0.38)	-0.01	0.77		
Behavioural neglect										
CBS	0.33 (0.17)	0.04	0.053‡ η^2=0.05			0.41 (0.16)	0.07	0.01* η^2=0.08	0.41 (0.16)	0.01* η^2=0.08
Anosognosia	0.35 (0.18)	0.04	0.05* η^2=0.05	0.35 (0.18)	0.05* η^2=0.05	0.41 (0.18)	0.06	0.02* η^2=0.07		

B is the unstandardised coefficient and SE its standard error. The effect size (η^2) for regressions with p-value≤0.1 was reported.

* p-value≤0.05; ‡ p-value≤0.1; [a] Spearman correlation.

adj, adjusted; AP, anteroposterior; CBS, Catherine Bergego Scale; COP, centre of pressure; EC, eyes closed; EO, eyes opened; hem, haemorrhage; Kinaes, kinaesthetic; L, left; LHH, lateral homonymous hemianopia; ML, mediolateral; NA, not applicable; R, right; reg, regression; RH, right-handed; SE, standard error; WBA, weight bearing asymmetry

Figure 1. Flow diagram of participants in the study

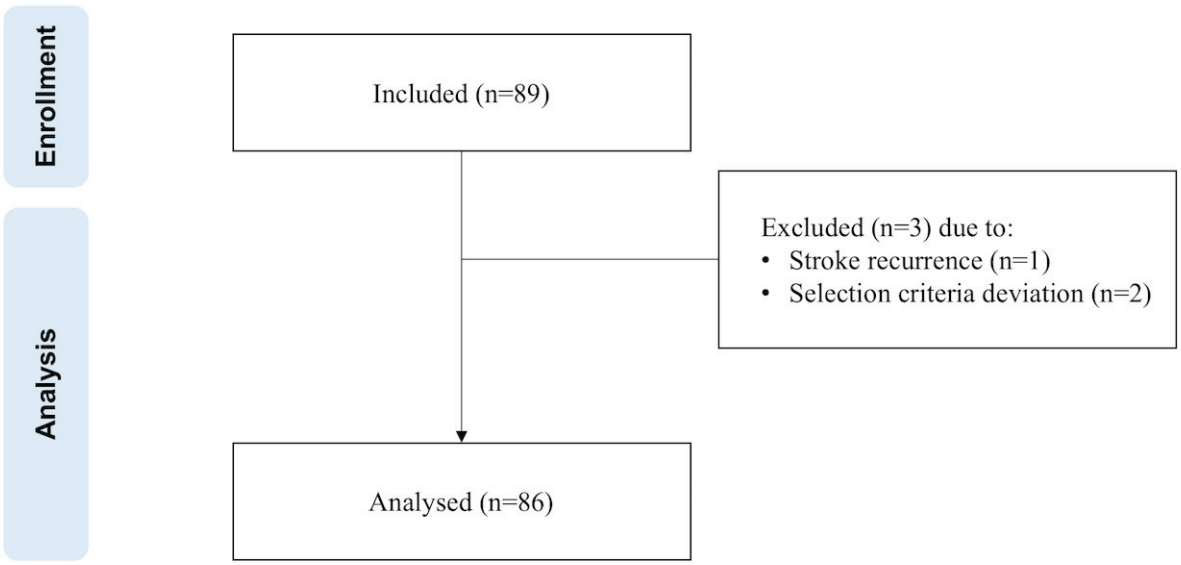
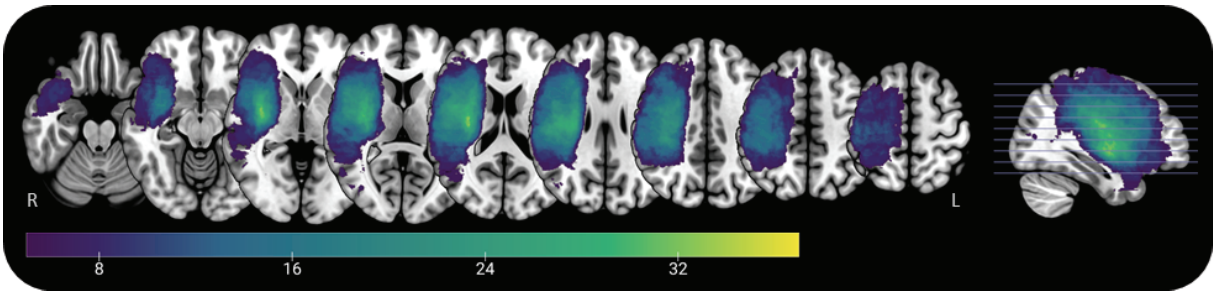
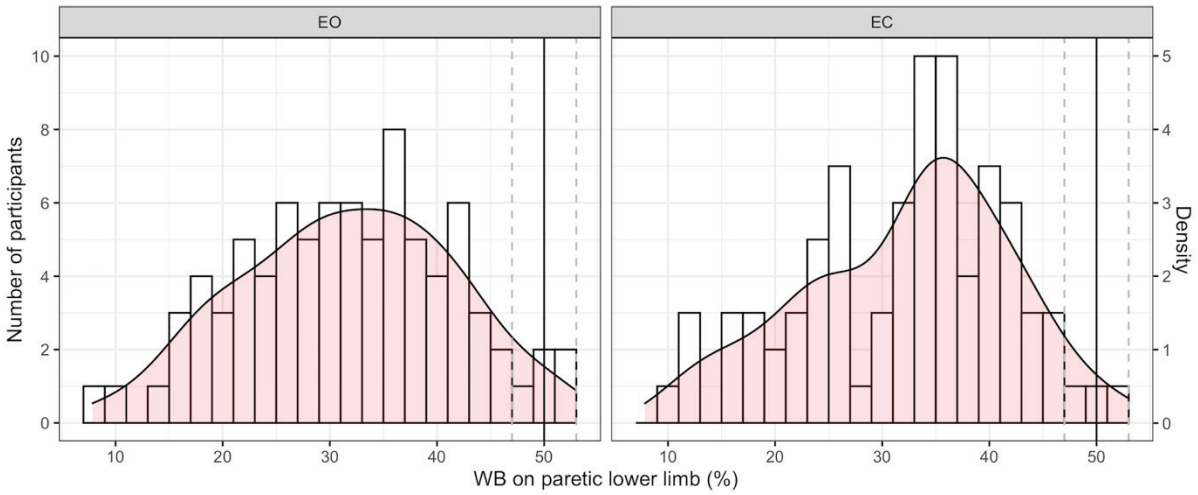


Figure 2. Overlap of individual stroke lesions on a T1-template in the Montreal neurological institute template space



Colour scale indicates the number of patients for which the lesion extended in this voxel. The sections were located in MNI at -22, -12, -2, 8, 18, 28, 38, 48 and 58. This overlap of lesions was done using using “MRIcroGL” software.

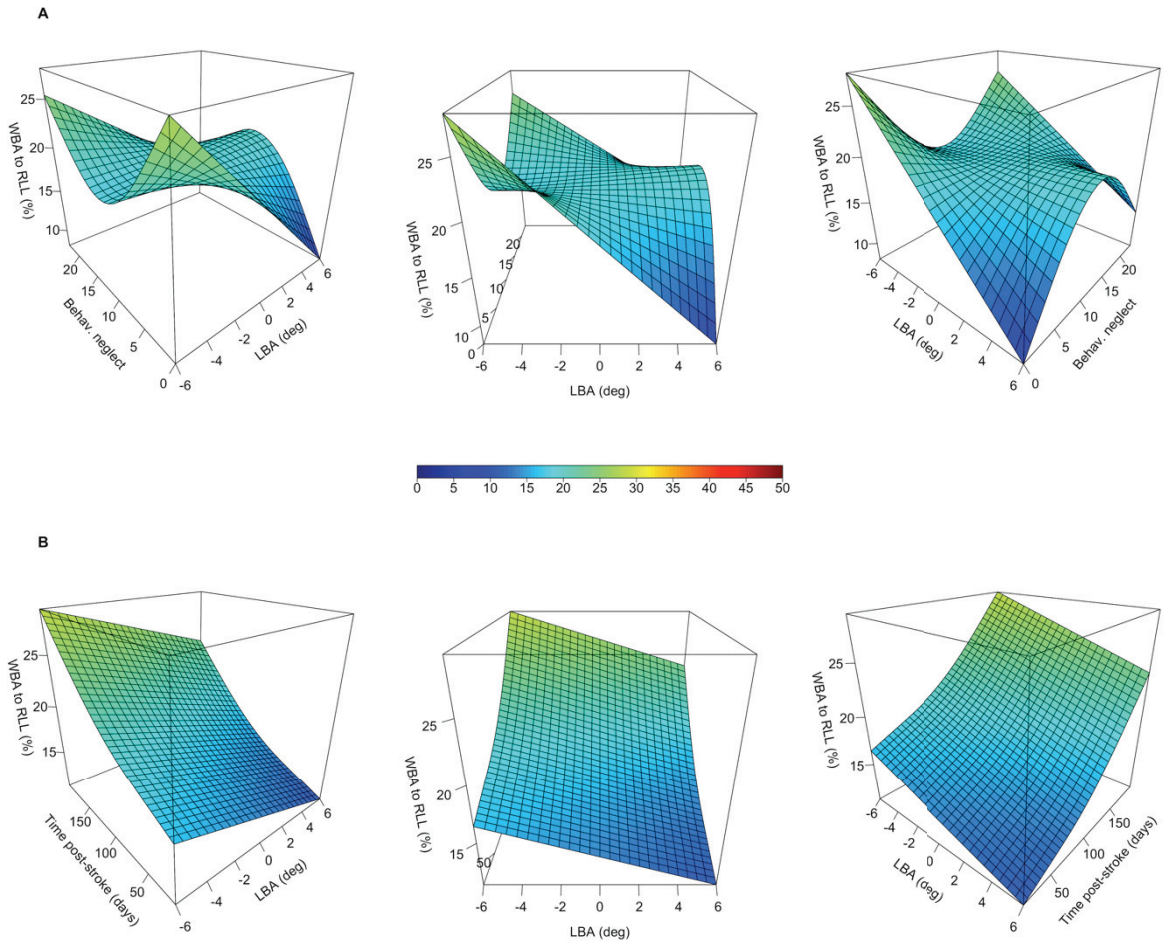
Figure 3. Histograms of weight bearing on paretic lower limb of participants included.



The scale for histograms is on the left axis while the scale for the density curve is on the right axis.

EC, eyes closed; EO eyes open; WB weight bearing

Figure 4. Three dimensional plots of predictive model of effects of LBA, behavioural neglect, and time post-stroke explaining WBA in EC condition in patients with right stroke: for LBA and behavioural neglect (2A) and for time post-stroke and LBA (2B).



For LBA, a negative value means a position on the left side while a positive value means a position on the right side.

Behav, behavioural; EC, eyes closed; LBA longitudinal body axis; RLL, right lower limb; WBA, weight bearing asymmetry

3.2.3. Analyse supplémentaire sur l'instabilité posturale

A l'issue de ces résultats, il semblerait également pertinent de s'interroger sur l'influence que les cadres référentiels spatiaux et la négligence spatiale unilatérale pourraient avoir sur un autre des déficits posturaux consécutif à l'AVC qu'est l'instabilité posturale. Le rationnel sous-tendant cette question est semblable à celui pour l'asymétrie d'appui. Comme présenté dans le sous-chapitre 2.4, l'instabilité posturale après AVC a des conséquences fonctionnelles préjudiciables pour les patients, notamment en terme de risque de chutes.[163] Tout comme l'asymétrie d'appui, les patients après lésion droite présentent une plus grande instabilité posturale que ceux ayant une lésion gauche.[133,141,229] A notre connaissance, aucune étude n'a, à ce jour, investigué une telle problématique.

La méthodologie suivie a été la même que celle pour l'étude transversale présentée précédemment qui portait sur l'asymétrie d'appui. Elle ne sera donc pas re-détaillée. Une analyse en composante principale sur toutes les variables de posturographie a été ajoutée i) afin de s'assurer que les 3 variables que sont la surface d'oscillation, la variabilité médiolatérale et la variabilité antéropostérieure du centre de pression reflètent bien la même composante posturale, à savoir l'instabilité posturale ; et ii) afin de sélectionner la variable à expliquer.

Cette analyse en composante principale (Figure 15) montre qu'environ 95% de la variance était expliquée par trois dimensions. La surface d'oscillation, la variabilité médiolatérale et la variabilité antéropostérieure du centre de pression contribuaient à la première dimension, l'appui du poids du corps sur le membre non-parétique et la position médiolatérale moyenne du centre de pression contribuaient à la seconde, et enfin la position antéropostérieure moyenne du centre de pression à la troisième. Ainsi, la première dimension représente l'instabilité posturale. Très fortement corrélée à cette première dimension tant en condition yeux ouverts ($r=0.96$, $p<0.001$) qu'en condition yeux fermés ($r=0.95$, $p<0.001$), la surface d'oscillation du centre de pression représente bien l'instabilité posturale.

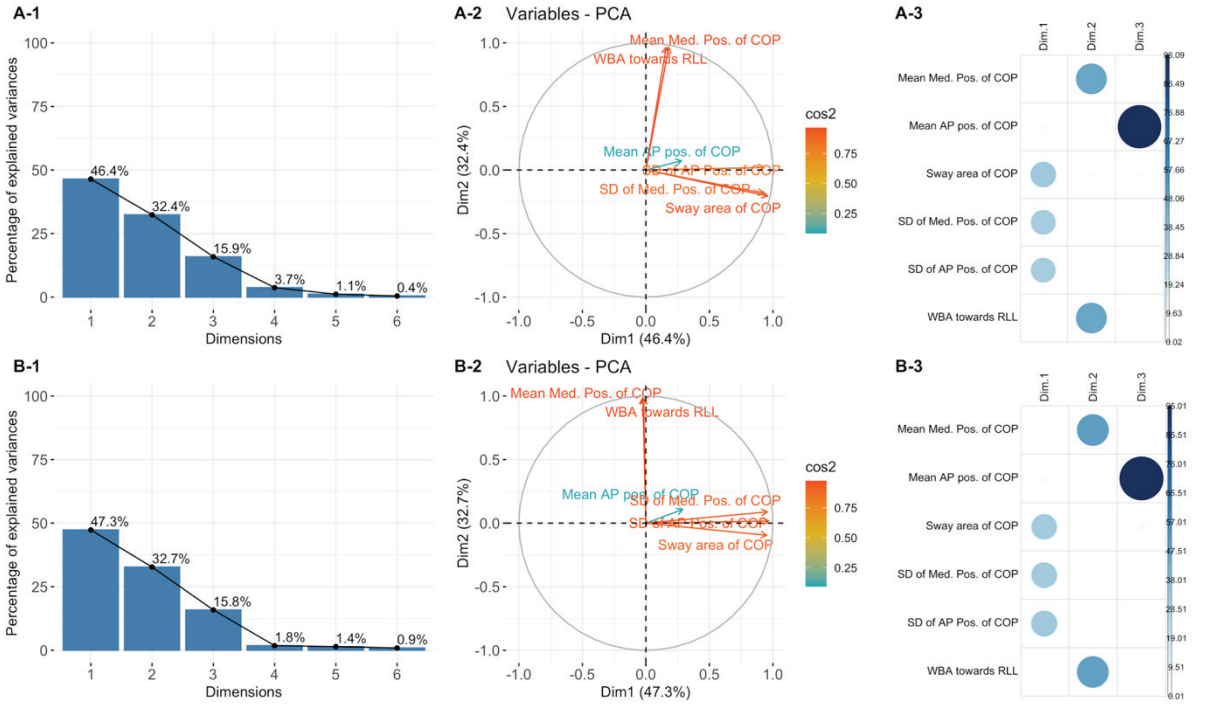


Figure 15. Analyse en composantes principales (quantité de variance expliquée par chaque dimension [1], projection des variables selon les deux dimensions principales [2], et contribution des variables aux dimensions [3]) des variables de posturographie en condition yeux ouverts (A) et yeux fermés (B).

Pour rappel, la surface d'oscillation, la variabilité médiolatérale et la variabilité antéropostérieure du centre de pression étaient significativement différentes entre la condition yeux ouverts et la condition yeux fermés ($p<0.001$, $p=0.02$, et $p<0.001$ respectivement).

Ni le droit devant manuel, ni l'axe corporel longitudinal subjectif n'étaient significativement associés avec la surface d'oscillation du centre de pression lors des régressions univariées avec splines cubiques naturelles en condition yeux ouverts ($p=0.72$ et $p=0.58$, respectivement) et yeux fermés ($p=0.66$ et $p=0.56$, respectivement).

A l'issue de la régression multivariée avec sélection de variables selon une méthode ascendante et descendante sur les variables de la négligence spatiale unilatérale, l'anosognosie restait comme prédicteur significatif de la surface d'oscillation du centre de pression pour la condition yeux ouverts ($p=0.03$). En condition yeux fermés, l'anosognosie restait également comme prédicteur significatif ($p=0.04$) avec la composante visuo-

spatiale/perceptive de la négligence spatiale unilatérale comme prédicteur non significatif de la surface d'oscillation du centre de pression (p=0.07 ; Table 1).

A l'issue de la régression multivariée avec sélection de variables selon une méthode ascendante et descendante sur les autres variables démographiques et cliniques, le déficit moteur (p=0.02), la sensibilité kinesthésique (p=0.01) et l'hémianopsie latérale homonyme (p=0.05) restaient comme prédicteurs significatifs de la surface d'oscillation du centre de pression pour la condition yeux ouverts. En condition yeux fermés, le déficit moteur (p=0.002), la sensibilité kinesthésique (p=0.003) et la position antéropostérieure moyenne du centre de pression (p=0.02) restaient comme prédicteurs significatifs de la surface d'oscillation du centre de pression (Table 1).

In fine, la régression multivariée rapportait que le déficit moteur (B=-0.006, SE=0.002, p=0.01), la sensibilité kinesthésique (B=-0.06, SE=0.02, p=0.01) et l'hémianopsie latérale homonyme (B=-0.22, SE=0.10, p=0.03) étaient des prédicteurs significatifs de la surface d'oscillation du centre de pression en condition yeux ouverts. L'anosognosie n'était pas significative (B=-0.0006, SE=0.008, p=0.94) dans le modèle final de régression (adjusted R^2=0.31; Figure 16). En condition yeux fermés, la régression multivariée montrait que le déficit moteur (B=-0.006, SE=0.002, p=0.009), la sensibilité kinesthésique (B=-0.07, SE=0.02, p=0.005) et la position antéropostérieure moyenne du centre de pression (B=0.006, SE=0.003, p=0.04) étaient des prédicteurs significatifs de la surface d'oscillation du centre de pression, tandis que la composante visuo-spatiale/perceptive de la négligence spatiale unilatérale (B=0.003, SE=0.002, p=0.09) et l'anosognosie (B=0.007, SE=0.008, p=0.35) étaient non significatifs (adjusted R^2=0.34; Figure 16).

Table 1. Résultats des régressions univariées et multivariées intermédiaires pour les variables démographiques et cliniques et les variables de la négligence spatiale unilatérale

Variable	Surface d'oscillation du CdP - YO					Surface d'oscillation du CdP - YF				
	Univarié			Multivarié		Univarié			Multivarié	
	B (SE)	R^2 adj.	p	B (SE)	p	B (SE)	R^2 adj.	p	B (SE)	p
Caractéristiques générales										
Age en années	-0.002 (0.005)	-0.01	0.73			-0.001 (0.005)	-0.01	0.80		
Sexe (femme)	-0.18 (0.10)	0.02	0.08‡			r=-0.29, p=0.008[a]*				
			η^2=0.04							
Latéralité manuelle (drt)	0.11 (0.23)	-0.01	0.64			0.15 (0.23)	-0.007	0.51		
Lésion cérébrale										
Délai post-AVC en jr	0.002 (0.0008)	0.06	0.01*			0.003 (0.0008)	0.10	0.002*		
			η^2=0.04					η^2=0.12		
Type de lésion (hem.)	-0.006 (0.10)	-0.01	0.96			0.02 (0.10)	-0.01	0.83		
Déficits moteur et sensoriel										
Faiblesse motrice	-0.009 (0.002)	0.16	<0.001*	-0.006 (0.002)	0.02*	-0.009 (0.002)	0.17	<0.001*	-0.007 (0.002)	0.002*
			η^2=0.17		η^2=0.19			η^2=0.18		η^2=0.22
Spasticité	0.04 (0.02)	0.05	0.03*			0.02 (0.02)	0.01	0.17		
			η^2=0.06					η^2=0.02		
Sensibilité superficielle	-0.06 (0.02)	0.08	0.008*			-0.06 (0.02)	0.08	0.006*		
			η^2=0.09					η^2=0.09		
Sensibilité kinesthésique	-0.09 (0.02)	0.14	<0.001*	-0.06 (0.02)	0.01*	-0.10 (0.02)	0.17	<0.001*	-0.07 (0.02)	0.003*
			η^2=0.16		η^2=0.10			η^2=0.18		η^2=0.13
HLH (pas HLH)	-0.27 (0.10)	0.09	0.006*	-0.18 (0.09)	0.05*	Pas en condition YF				
			η^2=0.11		η^2=0.06					
Troubles posturaux										
Asymétrie d'appui, en %	r=0.11, p=0.33[a]					0.006 (0.005)	0.006	0.23		
Position AP du CdP en mm	r=0.35, p=0.001[a]*					0.008 (0.003)	0.09	0.004*	0.006 (0.002)	0.02*

								η^2=0.10		η^2=0.07
Latéropulsion	0.06 (0.05)	0.009	0.20			0.06 (0.05)	0.006	0.23		
Négligence spatiale unilatéral										
Composante exploratoire/visuo-motrice										
Colonne 1ere cloche	0.0003 (0.02)	-0.01	0.99			0.004 (0.02)	-0.01	0.87		
Différence G-D	0.009 (0.01)	-0.006	0.47			0.006 (0.01)	-0.01	0.64		
Omissions totale	0.0006 (0.007)	-0.01	0.94			-0.0009 (0.008)	-0.01	0.90		
Durée en sec	0.001 (0.0006)	0.03	0.09‡ η^2=0.04			0.0007 (0.0006)	0.008	0.21		
Composante perceptive/visuo-spatiale										
Déviation en mm	0.004 (0.002)	0.02	0.13			0.004 (0.002)	0.03	0.08‡ η^2=0.04	0.004 (0.002)	0.07‡ η^2=0.05
Négligence personnelle										
Omissions	0.004 (0.02)	-0.01	0.80			0.005 (0.02)	-0.01	0.76		
Négligence comportementale										
CBS	0.02 (0.008)	0.06	0.02* η^2=0.07			0.02 (0.008)	0.06	0.02* η^2=0.07		
Anosognosie	0.02 (0.008)	0.06	0.02* η^2=0.07	0.02 (0.008)	0.03* η^2=0.07	0.02 (0.008)	0.05	0.04* η^2=0.06	0.02 (0.008)	0.04* η^2=0.06

A l'exception des corrélations de Spearman, toutes les régressions ont été réalisées après transformation de la variable dépendante (la surface d'oscillation du CdP) par un logarithme de base 10 en raison de la non-normalité des résidus et de l'asymétrie de distribution vers les valeurs positives. B est le coefficient non standardisé et SE sont erreur type. Pour les régressions avec une valeur du p ≤0.1, la taille de l'effet (η^2) a été reportée.

* p≤0.05 ; ‡ p≤0.1 ; [a] Corrélation de Spearman

adj, adjusté AP, antéroposterieur ; CBS, Échelle de Catherine Bergego ; CdP, centre de pression ; D, droite ; drt, droitier ; G, gauche ; hem, hémorragie ; HLH, hémianopsie latérale homonyme ; jr, jour ; SE erreur type ; YF, yeux fermés ; YO, yeux ouverts

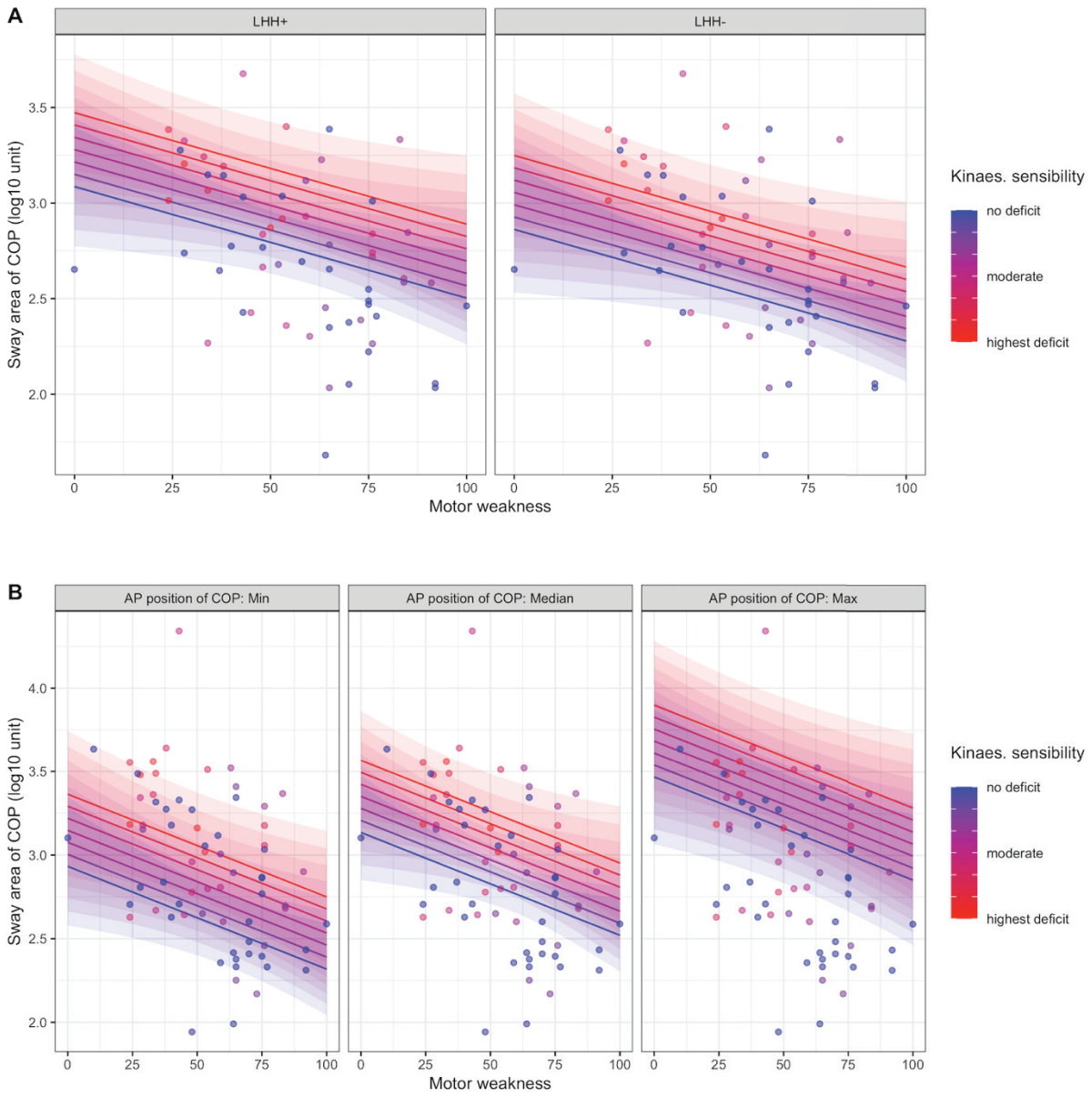


Figure 16. Modèle final explicatif de la surface d'oscillation du centre de pression en condition yeux ouverts (A) et yeux fermés (B) chez des patients après AVC droit.

Ainsi les résultats montrent que la perception des cadres référentiels spatiaux et la négligence spatiale unilatérale n'étaient pas indépendamment associées avec l'instabilité posturale, quelle que soit la condition d'ouverture des yeux. En revanche, le déficit moteur, le déficit de sensibilité kinesthésique et l'hémianopsie latérale homonyme étaient indépendamment associés avec l'instabilité posturale en condition yeux ouverts, tandis que le déficit moteur, le déficit de sensibilité kinesthésique, et la position antéropostérieure moyenne du centre de pression étaient indépendamment associés avec l'instabilité posturale

en condition yeux fermés. A ma connaissance, de tels résultats n'ont jamais été rapportés auparavant.

Ces résultats suggèrent que ce sont les déficits sensori-moteurs qui contribuent à l'instabilité posturale. Plus les déficits moteur et de sensibilité kinesthésique étaient sévères, plus l'instabilité posturale était importante. Ces résultats seraient cohérents avec ceux issus de l'analyse des « patterns » de déplacement du centre de pression sous chaque membre inférieur qui montrait que l'instabilité posturale était liée à une diminution de la participation du membre parétique.[139]

Par ailleurs, plus le centre de pression était projeté antérieurement, plus les patients étaient instables. Alors qu'après un AVC, la position antéropostérieure moyenne n'est pas significativement différente des sujets sains,[133] le fait de se projeter en avant est un facteur d'instabilité qui pourrait être la conséquence de l'altération de la stratégie de répartition des appuis sur l'axe antéropostérieur du pied mis en œuvre par les chevilles, comme montré par Rougier et Pérennou.[155] Il est important de rappeler qu'en station debout, la projection du centre de gravité est en antérieure au centre articulaire de la cheville et tend à nous faire chuter en avant. Le tonus musculaire du triceps sural est donc fondamental pour assurer l'équilibre en position debout.

De plus, ces résultats apportent un éclairage sur l'influence de la vision et des déficits visuels comme l'hémianopsie latérale homonyme, sur la stabilité posturale. En condition yeux ouverts, l'instabilité posturale était significativement plus grande en cas d'hémianopsie latérale homonyme. Ainsi, cela suggèrerait que percevoir seulement un hémi-champ visuel soit un facteur de plus grande instabilité. Pour rappel, les patients oscillaient significativement plus en condition yeux fermés qu'en condition yeux ouverts. Il est important de préciser que cette majoration d'instabilité posturale à la fermeture des yeux (par rapport aux yeux ouverts) était : i) retrouvée tant chez les patients présentant une hémianopsie latérale homonyme ($p<0.001$) que chez ceux n'en présentant pas ($p=0.001$) en condition yeux ouverts ; ii) mais qu'elle était également plus importante chez les patients atteints d'une hémianopsie latérale homonyme que chez ceux qui en étaient préservés ($p=0.04$), en condition yeux ouverts. Ainsi, plus l'entrée visuelle est présente et préservée, plus la stabilité posturale est importante. Ces résultats sont cohérents avec l'existence d'une dépendance visuelle après un AVC.[142–144] Si Yates *et al.* ont bien rapporté que la présence d'un déficit moteur et sensitif augmentait le

risque de chute des patients après AVC (ce qui conforterait nos résultats), en revanche dans leur étude, le risque de chute diminuait s'ils ajoutaient la présence d'une hémianopsie latérale homonyme.[230]

Il semble intéressant de noter que les variables associées avec l'asymétrie d'appui n'étaient pas les mêmes que celles associées avec l'instabilité posturale. Cela irait dans le sens que ce seraient deux dimensions distinctes des troubles posturaux après AVC.

Comme cela a été présenté dans l'étude sur les déterminants de l'asymétrie d'appui, il est important de rappeler que ces analyses ont été conduites sur les données de participants présentant tous un AVC droit, et un certain niveau d'asymétrie d'appui vers le membre inférieur droit lors de leur inclusion. Ces résultats ne peuvent donc pas être généralisés à tous les patients atteints d'AVC. Les participants inclus ne représentent qu'une sous-population dont la répartition du poids du corps sur les membres inférieurs s'étend de la symétrie d'appui à une asymétrie très importante vers le membre non-parétique. Les résultats permettent, cependant, de mieux comprendre l'asymétrie d'appui et l'instabilité posturale dans cette sous-population d'AVC, en identifiant les facteurs qui en sont associés.

4. Perspective therapeutique : l'adaptation prismatique

4.1. Les manipulations sensorielles

Compte tenu des conséquences fonctionnelles des troubles de la posture et de l'équilibre après un AVC (détaillées dans le sous-chapitre 2.3), il est donc essentiel de disposer de rééducations efficaces afin de les limiter au maximum. L'évaluation de l'efficacité des rééducations sur les troubles posturaux et de l'équilibre après AVC présentée dans le sous-chapitre 2.4, révèle que peu de rééducations ont comme cible une modulation des cadres référentiels spatiaux dans la perspective d'améliorer les troubles de la posture et de l'équilibre.

Plusieurs études ont, par exemple, évalué les effets de vibrations appliquées au niveau des muscles cervicaux controlésionnels sur la posture et l'équilibre des patients après AVC.[231,232] De même, Pérénnou *et al.* ont étudié les effets d'une neurostimulation électrique transcutanée (TENS pour « Transcutaneous Electrical Nerve Stimulation ») des muscles cervicaux controlésionnels sur la stabilité posturale.[233] Toutes ces études ont montré, à la suite des interventions, une réduction des troubles posturaux et/ou de l'équilibre. De façon similaire, Rode *et al.*[152] par stimulation calorifique vestibulaire et Bonan *et al.*[234] par stimulations optocinétiques et galvaniques vestibulaires ont amélioré l'asymétrie d'appui. Même si très peu de ces études avaient le design et la qualité méthodologique suffisante pour apporter des preuves fiables, les stimulations sensorielles semblent être une piste prometteuse pour améliorer les troubles posturaux et/ou de l'équilibre post-AVC. Ce potentiel effet postural serait médié par une modification des cadres référentiels spatiaux selon un mécanisme « bottom-up » (ascendant), échappant à la conscience du sujet.[235]

4.2. LE CAS DE L'ADAPTATION PRISMATIQUE

Selon le même raisonnement, l'adaptation prismatique pourrait avoir un effet sur les troubles posturaux et de l'équilibre après un AVC droit. Cette intervention consiste en l'utilisation de lunettes prismatiques déviant l'axe optique durant une tache motrice, la plupart du temps une répétition de mouvements de pointages avec le membre supérieur sain en position assise.

Chez les patients avec une lésion droite, l'adaptation prismatique réalisée avec des lunettes déviant l'axe optique de 10 degrés vers le coté de la lésion entraine des erreurs de pointages lors des premiers mouvements, qui sont compensées après quelques répétitions.[198,236] Cela témoignerait d'une recalibration permettant au sujet de modifier la commande motrice pour atteindre la cible. Cette phase de compensation relèverait d'une stratégie cognitive immédiate.[237,238]

A l'issue d'un certain nombre de répétitions, il est observé, en l'absence de lunettes prismatiques, une erreur dans la direction opposée à la déviation prismatique lors d'un pointage du droit devant manuel.[198,236] Cet « after-effect » sensori-moteur, qui est qualifié d'adaptation vraie, résulterait d'un processus lent et automatique de réalignement spatial pour faire correspondre les cadres référentiels visuo-moteur et visuo-proprioceptif.[237,239] La conséquence de ce réalignement des cadres référentiels spatiaux serait la correction indirecte de la réponse motrice. L'implication du réseau cérébello-pariétal dans les mécanismes de recalibration et de réalignement spatial est fortement suspecté (Figure 17).[240–242]

Plusieurs études ont montré une généralisation de cet « after-effect » sensori-moteur à des fonctions cognitives non exposées comme la cognition spatiale.[228] L'adaptation prismatique agirait par une action « bottom-up » depuis un niveau sensori-moteur vers un niveau cognitif, ce qui expliquerait la généralisation de « l'after-effect » sensori-moteur à la cognition spatiale.[198,228,243] Cette action « bottom-up » serait supportée par l'activation de régions cérébrales temporales et pré-frontales (Figure 17).[240,241,244]

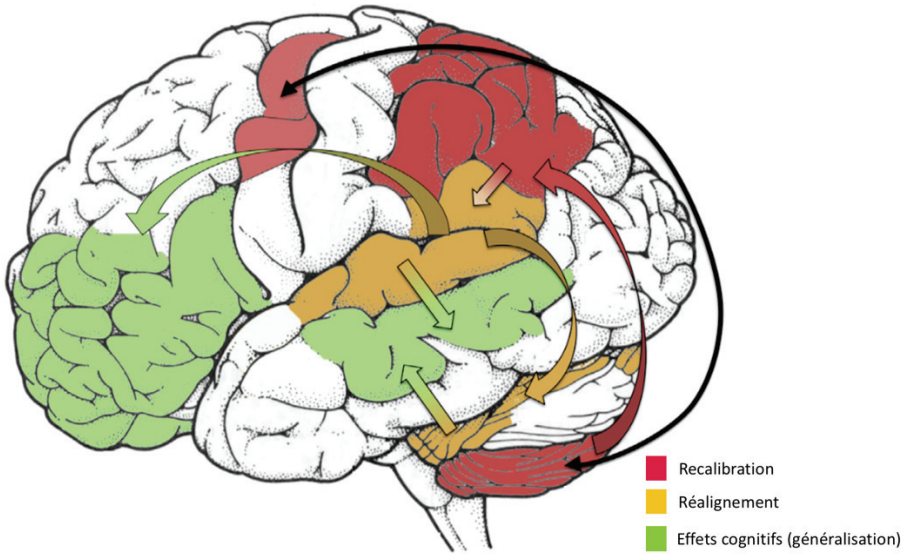


Figure 17. Cadre neuro-anatomique supportant les processus de recalibration (rouge), de réalignement (orange) et d'effets cognitifs (vert) de l'adaptation prismatique (proposé par Panico *et al.*, 2019).

Cependant les effets de l'adaptation prismatique ne semblent pas systématiques. En effet, les manifestations cliniques de le négligence spatiale unilatérale n'ont pas été améliorées chez tous les patients post-AVC après adaptation prismatique.[225,241,244,245] Lunven *et al.*[246] ont montré que les patients atteints d'un AVC chronique droit ayant bénéficié d'une amélioration de la négligence visuo-spatiale étaient ceux avec une plus grande épaisseur des cortex temporo-pariétal, préfrontal et cingulaire gauches mais également avec une meilleure préservation des fibres de la substance blanche au niveau du genou et du tronc du corps calleux. Ces résultats suggèrent le rôle de l'hémisphère sain et des connexions inter-hémisphériques entre les aires sensori-motrices et pré-frontales dans les effets de l'adaptation prismatique.[246]

Quand l'étude pilote (présentée ci-dessous) a débuté, trois essais avaient étudié les effets de l'adaptation prismatique sur les troubles posturaux debout après un AVC.[221,222,224] Les objectifs, les designs, les caractéristiques des participants, les modalités d'application de l'adaptation prismatique ainsi que les critères de jugement différaient : Une seule étude reposait sur une comparaison par rapport à un placebo,[221] comportait plusieurs séances d'adaptation prismatique,[224] comprenait l'évaluation d'un cadre référentiel spatial,[222] ou comprenait une mesure à distance de l'intervention,[224] et aucune d'entre elles n'avait évalué

les effets sur l'équilibre, privilégiant les troubles posturaux. Pour autant, ces trois études suggéraient une amélioration des troubles de la posture après adaptation prismatique.

Ainsi, une étude pilote a été conduite pour compléter ces résultats préliminaires par une évaluation des effets immédiats et persistants d'une série de plusieurs séances d'adaptation prismatique sur l'équilibre (dans un objectif fonctionnel), et sur les cadres référentiels spatiaux égocentrés (dans une démarche explicative). Cette étude a également cherché à évaluer la faisabilité de conduire un essai clinique plus important.

4.3. ÉTUDE EXPERIMENTALE PILOTE

Les résultats de cette étude préliminaire conduite sur des patients atteint d'un AVC droit à un stade chronique ont été publiés dans un journal scientifique international à comité de lecture.

Cogn Process
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SHORT REPORT

Long-lasting reduction in postural asymmetry by prism adaptation after right brain lesion without neglect

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Abstract
Background Right brain damage (RBD) involves postural asymmetry and spatial frame disorders. In acute RBD patients, postural asymmetry is immediately reduced after one single session of prism adaptation (PA), without assessment of effects on spatial frames.
Aim To assess long-term effects of PA on posture and spatial frames in chronic RBD patients, without neglect.
Method Six chronic RBD patients without neglect (mean delay 45 months) were included. Each patient sustained 10 PA sessions of 20 min during 2 weeks. Outcome measures were: (1) posturographic analysis (mediolateral position of centre of pressure (X_{cop}), (2) subjective straight ahead (SSA) and perception of longitudinal body axis (LBA). Each parameter was assessed by three pretests and three post-tests (+2 h, day + 3 and day + 7).
Results In pretests, patients showed a shift of the X_{cop} and SSA. In post-tests, results displayed (1) a significant reduction in mediolateral postural asymmetry at D + 7; (2) a significant left deviation of SSA at D + 3 and enduring at D + 7; and (3) no significant modification of LBA. The mean curves of X_{cop} and SSA between pre- and post-tests were similar.
Conclusions PA involves persistent reduction in postural asymmetry in RBD patients without neglect. These findings were obtained at a chronic stage. This new effect cannot be explained by reduction in spatial attentional shift. Improvement may be explained by a better calibration of extra personal space frames used for posture, without effect on personal space frame. Findings argue in favour of a bottom-up effect of PA on mechanisms underlying spatial cognition.

Keywords Stroke · Spatial representation · Prism adaptation · Posture · Egocentric reference · Subjective straight ahead

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Introduction

Right brain damage (RBD) involves postural asymmetry and spatial frame disorders. This asymmetry is characterized by a larger weight-bearing asymmetry (WBA) on the paretic limb, leading to worse functional recovery (Rode et al. 1997; Perennou et al. 1999; Genthon et al. 2008). That WBA is found in RBD patients with unilateral spatial neglect or not (Genthon et al. 2008; Tilikete et al. 2001). Motor and/or somatosensory deficits and asymmetric muscular tone participate in WBA. In addition, spatial frame disorders, such as displacement of egocentric reference (orientation of the body longitudinal axis), may account for that WBA (Rode et al. 1997; Barra et al. 2009). That WBA can be immediately reduced by prism

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adaptation (PA) in acute and chronic RBD patients with neglect or not (Tilikete et al. 2001; Padula et al. 2009; Nijboer et al. 2014). This improvement was reported after one single session of PA. A long-term reduction was observed after 8 weeks of PA in neglect RBD patients (Shiraishi et al. 2008). No study was carried out with the evaluation of egocentric reference frame. These effects could be explained by an action of PA on spatial frame disorders due to RBD. The aim of study was to test this hypothesis by assessing long-term effects of PA on posture and spatial frames in chronic RBD patients without neglect.

Methods

A pilot and prospective study without control group was carried out in the neurological rehabilitation department of Hospices Civils de Lyon from February to December 2014. The inclusion criteria were : (1) a single RBD, (2) no neglect, (3) an imbalance characterized by a persistent and invaliding WBA on the paretic limb, (4) a post-stroke time $\geq$6 months and (5) the ability to stay during 30 s in standing position with eyes opened (EO) and closed (EC) without help. The exclusion criteria were : (1) bilateral brain lesions, (2) other neurological or psychiatric disease, (3) osteo-articular disease, (4) visual deficit and (5) inability to understand instructions.

Participants

Six right-handed patients (five males, one female) with chronic RBD (mean delay post-onset 44.8 months, SD 32.6) were included. All showed left hemiparesis and incomplete somatosensory deficit of left hemibody. One patient exhibited a left hemianopia. No participant showed a cephalic and ocular deviation. No auditory or visual extinction to double simultaneous stimulation was noted. All showed no neglect. All patients were aware of their motor and somatosensory deficits. No global cognitive disorder was present (mean MMS 25.8, SD 2.4). All showed a postural imbalance characterized by a WBA on paretic limb, involving a functional limitation (posture and walking). Lesions were assessed by clinical MRI and for one patient by CT scan. Four patients had a ischaemic lesion, and two had a haemorrhagic lesion. Lesion masks of patients were first drawn on the native brain images by using the MRIcron software (Rorden et al. 2007). Brain images were normalized to a standard brain template (Montreal Neurological Institute) using rigid and elastic deformation tools (SPM8, http://www.fil.ion.ucl.ac.uk/spm), except for the voxels contained in the lesion mask. Finally, patients' lesions were segmented a second time on the normalized images by ML, who was naïve as to the patients' deficit, and checked by AH and GR. Figure 1 shows the lesions of each patient and the lesions' overlap of the six patients. The maximum overlap was located in the subcortical white matter; moreover, 5 out of 6 patients showed common lesions including the superior temporal cortex, inferior frontal and posterior parietal cortices.

Parameters

Posturographic parameters included the mean mediolateral (X_{cop}) and anteroposterior (Y_{cop}) positions of centre of pressure (COP) (expressed in mm), the mean sway surface of COP (expressed in mm^2), the mean mediolateral and anteroposterior variability of COP (standard deviation of X_{cop} and Y_{cop}) and the mean weight bearing (WB) on the right and left lower limbs (expressed in % of body weight). These parameters were measured on posturographic platform (Techno concept®) with 4 repeated measurements of 30 s each one (2 EO and 2 EC) without help nor support by upper limbs.

Subjective spatial frames of reference were assessed by the subjective straight ahead (SSA) and the perception of longitudinal body axis (LBA). The SSA position was assessed by the right hand in the darkness. The patient was comfortably seated, the trunk and the head in vertical position in front of a graduated table as a protractor (zero position was ahead of belly button). The starting position of the hand was different at each trial according to a sequence (30°, −20°, 10°, −30°, 20°, −10°). The patient was asked to point straight ahead (see Rode et al. 2015). The LBA perception was performed according to the procedure proposed by Barra et al. (2009). The patient was in supine position in the darkness. The patient was asked to indicate when a luminous rod was adjusted in the frontal plane to align with his LBA. The starting position of the rod was different at each trial according to a sequence (30°, 20°, −30°, 10°, −20°, −10°). By convention, a negative value corresponded to a left position and a positive value corresponded to a right position for both tests. Six trials were executed for both tests.

Clinical parameters included the Scale for Controversive Pushing (SCP), the Postural Assessment Scale for Stroke Patients (PASS) and the Berg Balance Scale (BBS).

All parameters were measured before (pretests at day-18, day-16 and day-14) and after intervention (post-tests at +2 h, day + 3 and day + 7), excepted for PASS and BBS (pretest day-18 and post-test day + 7). Day 0 corresponded to the last day of intervention.

Prism adaptation

PA was carried out by wearing a pair of glasses producing a 10° rightward optical deviation of the visual field. During

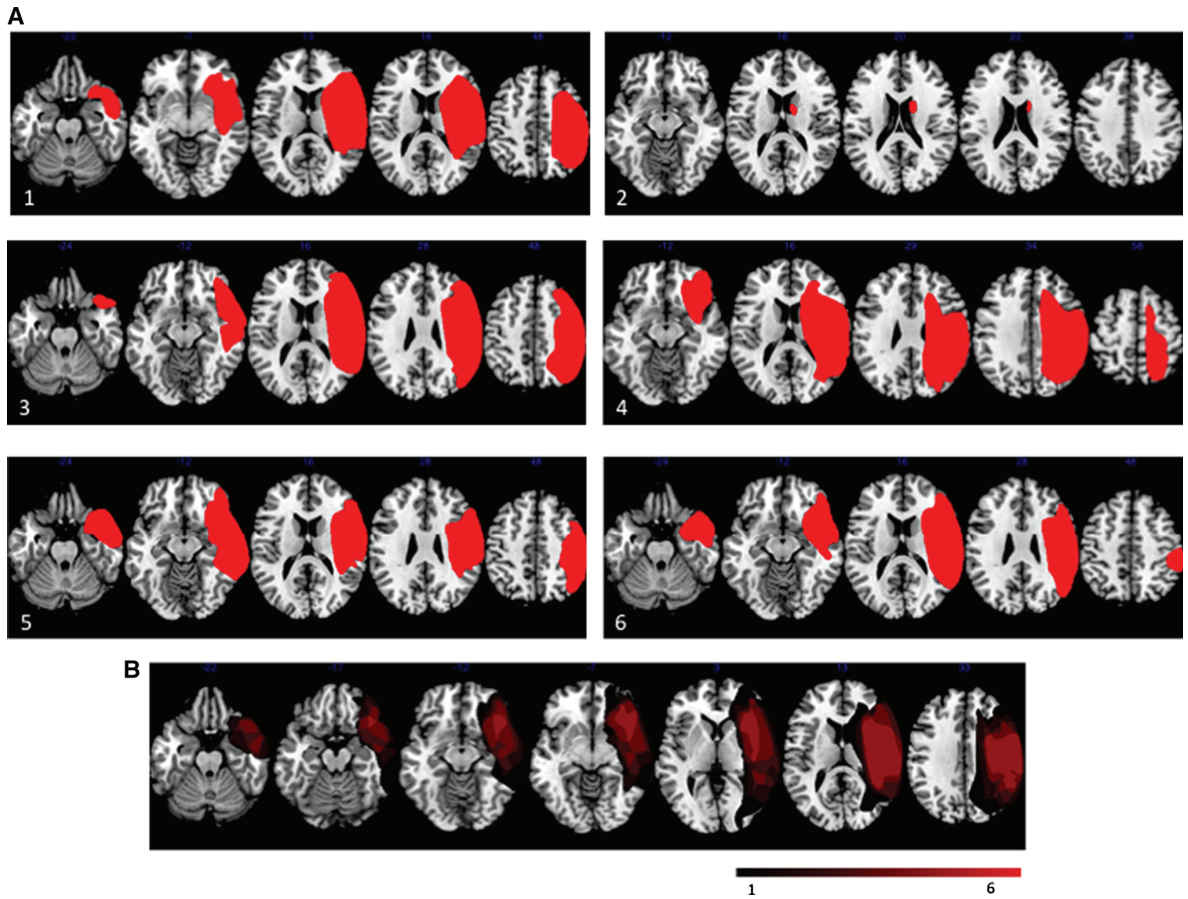

Fig. 1 Patients' lesions description. **a** Reconstruction of the brain lesions for each patient in MNI space. **b** Overlap of the six brain lesions. The colour range indicates the number of patients' lesion for each voxel

prism exposure, the participant had to execute quickly rapid pointing movements towards visual targets without vision of the initial position of the right hand. Targets were located 10° to the left or to the right of the middle of his body, the targets being made to pseudo-randomly alternate. The procedure included one daily PA session of 20 min during 2 weeks. Thus, patients sustained 10 PA sessions (see Rossetti et al. 1998; Rode et al. 2015).

Statistical analysis

Each post-test has been compared with the mean of three pretests (or the single pretest for PASS and BBS). Differences were analysed by a Student test or an analysis of variance with repeated measures (rmANOVA) (normality was checked with Kolmogorov–Smirnov test). RmANOVA was completed by additional planned comparisons by univariate tests. When the distribution was not normal, differences were analysed by an nonparametric Friedman ANOVA and/or by a Wilcoxon matched-pair signed-rank test. As regards posturographic parameters, rmANOVA was performed with four main factors [pre–post; sessions (1–3); eyes opened or closed; trials (1, 2)]. For LBA and SSA, rmANOVA was executed with three main factors [pre–post; sessions (1–3); trials (1–6)].

Results

All mean values and SD of 6 patients in pre- and post-tests in EO condition are described in Table 1. No significant difference between three pretests was found, in EO or EC conditions for all parameters.

In the pretests, patients showed a rightward shift of the mean X_{cop}, with a WBA on the paretic lower limb. In the post-tests, a progressive reduction in mean X_{cop} was shown from +2 h (−1.6 mm) and was significant at D + 7 (−11.3 mm), without significant modification of mean

Table 1 Mean and SD of parameters EO before (pretests D−18, D−16 and D−14) and after PA (post-tests +2 h, D + 3 and D + 7)

	Pretests				Post-tests		
	Pretest 1	Pretest 2	Pretest 3	Mean	+2 h	D + 3	D + 7
Posturographic parameters							
X_{cop}	50.4 (32.8)	55.5 (33.5)	53.0 (28.8)	52.9 (10.7)	51.4 (34.2)	45.6 (42.0)	41.7 (31.2)***
Y_{cop}	52.5 (8.3)	55.2 (11.7)	50.9 (12.3)	52.9 (10.7)	49.4 (9.8)	55.3 (15.0)	59.7 (17.1)
Sway area	809.2 (749)	803.5 (762.2)	682.0 (625.7)	764.9 (696.8)	724.3 (573.1)	499.9 (317.6)	886.7 (1103.8)
X_{cop} variability	7.7 (4.9)	7.0 (4.3)	6.0 (4.5)	6.9 (4.5)	6.5 (3.3)	4.8 (2.0)	7.5 (7.0)
Y_{cop} variability	7.8 (3.8)	7.0 (3.0)	7.5 (3.5)	7.4 (3.4)	7.0 (3.1)	6.7 (2.5)	6.6 (3.5)
WB on right LL (%)	68.4 (11.3)	70.8 (11.7)	69.7 (10.0)	69.6 (10.7)	68.9 (12.2)	66.2 (14.2)	66.5 (11.7)**
WB on left LL (%)	31.6 (11.3)	29.2 (11.7)	30.3 (10.0)	30.4 (10.6)	31.1 (12.2)	33.8 (14.2)	33.5 (11.7)**
Spatial frame parameters							
SSA	−0.5 (16.5)	1.1 (11.7)	−0.4 (10.7)	0.1 (13.1)	−5.0 (16.8)	−6.8 (14.3)*	−12.0 (12.0)*
LBA	−0.9 (6.4)	−1.3 (7.5)	−0.4 (7.5)	−0.9 (7.1)	−0.8 (7.4)	−2.2 (7.2)	−1.2 (8.6)
Clinical parameters							
SCP	2.9 (1.9)	2.6 (1.7)	2.3 (1.3)	2.6 (1.6)	2.4 (1.6)	1.6 (1.1)**	1.6 (1.3)*
PASS	27.8 (5.7)						30.7 (3.9)*
BBS	34 (12.4)						38.8 (11.8)***

LL lower limbs

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

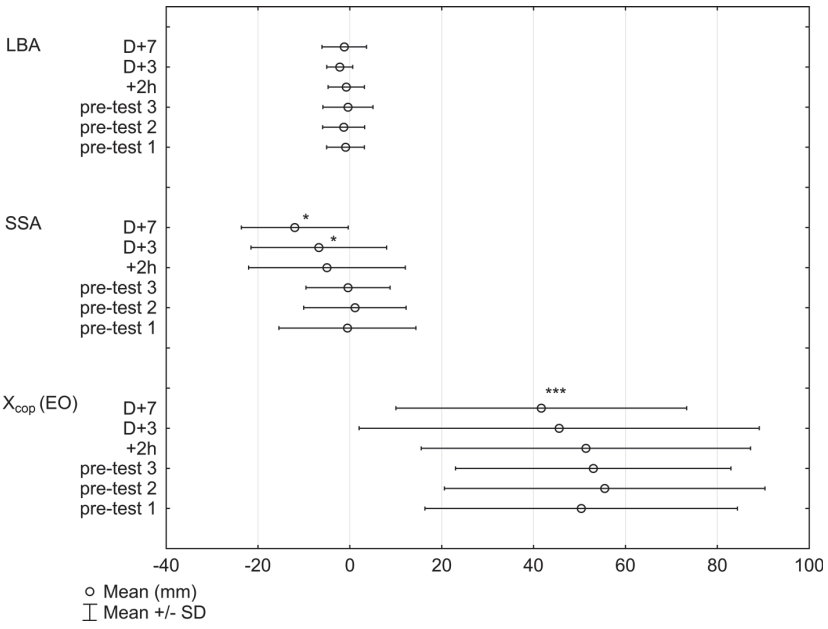

Fig. 2 Mean X_{cop} (EO), SSA and LBA of six chronic RBD patients measured before (pretests D−18, D−16 and D−14) and after PA (post-tests +2 h, D + 3 and D + 7). Linear modelling of X_{cop} (EO) and SSA *curves* shows very close tilts (−2.1 ($R^2 = 0.62$) and −2.4 ($R^2 = 0.85$), respectively)

Y_{cop}, and sway area in EO condition. In the same way, the WB on the non-paretic limb was reduced from +2 h (−0.7) and significantly at D + 7 (−3.2). This significant reduction in WBA after PA was associated with a significant increase in functional scores: SCP ($p < 0.05$), PASS ($p < 0.001$) and BBS ($p < 0.001$). In pretests, the mean SSA was 0.1° (SD 13.1). In post-tests, the mean values were, respectively, –5.0° (SD 16.8) at +2 h, −6.8° (SD 14.3) at D + 3 and –12.0° (SD 12.0) at D + 7, reflecting a significant shift (at D + 3 and D + 7) of SSA towards the left side after PA. For LBA, comparison showed no difference between pre- and post-tests. Lastly, the mean of six patients of SSA was correlated with the mean of six patients of X_{cop} (EO) for the three pretests and the three

post-tests (Rs = 0.94; $p = 0.02$), reflecting the same chronological evolution (see Fig. 2).

In EC condition, patients showed no significant difference in pretests compared to EO condition. They displayed a rightward postural shift (51.1 mm, SD 29.3) and forward (56.7 mm, SD 15.7) with an increased WB on the non-paretic limb (69.1 %, SD 10.2). After PA, the mean values of X_{cop} were 55.7 mm (SD 33.6) at +2 h, 42.7 mm (SD 30.4) at D + 3 and 44.9 mm (SD 31.8) at D + 7, without significant difference compared to pretests.

Discussion

In six chronic RBD patients, PA treatment resulted in a reduction in postural asymmetry. Unlike previous studies, this pilot study also reports long-lasting effects (7 days after the intervention) in RBD patients without spatial neglect. These findings confirm that long-term generalization effects of PA may concern symptoms independent from neglect (Jacquin-Courtois et al. 2013). Consequently, reduction in WBA after PA cannot be explained by reduction in spatial attentional shift, nor by the displacement of neglected space into the dysfunctional work space. The dissociated effects of PA on spatial frame parameters (significant shift of SSA without modification of LBA) suggest reduction in WBA may be explained by an action on extra personal space frame used for posture, without effect on personal space frame. These findings therefore support the hypothesis that egocentric spatial frames of reference perturbations are involved in postural imbalance in RBD patients. This observation further supports the notion of bottom-up effects of PA on spatial cognition, involving a modification of motor (postural) responses as a centrally mediated indirect effect. Double-blind essays will be required to confirm the potential impact of these results for the clinical rehabilitation of postural imbalance on RBD patients.

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4.4. PROTOCOLE D'ESSAI CLINIQUE CONTROLE RANDOMISE MULTICENTRIQUE « PEQUIE »

A la suite des résultats préliminaires de l'étude pilote,[135] mais également de ceux d'une autre étude publiée entre temps qui montraient une réduction de l'asymétrie d'appui en position assise cette fois,[223] il a été proposé un essai clinique contrôlé randomisé multicentrique. Son objectif serait d'évaluer les effets de deux semaines d'adaptation prismatique sur l'équilibre et la posture par rapport à une intervention placebo chez des patients AVC après lésion droite à un stade chronique. Ce projet a obtenu un financement au PHRC-interrégional 2016 et sa réalisation est en cours. Il comprend également une étude neuro-anatomique ancillaire.

Cet essai contrôlé randomisé multicentrique a pour objectif principal d'améliorer l'équilibre des patients avec lésion droite à un stade chronique, et comprend également différents objectifs secondaires, certains pragmatiques comme améliorer les troubles posturaux (asymétrie d'appui, instabilité posturale, latéropulsion), et d'autres explicatifs visant à améliorer la compréhension des effets de l'adaptation prismatique.

Le protocole a été soumis à la revue BMJOpen. L'article soumis est présenté dans la thèse. Les figures et les références bibliographiques mentionnées dans le texte sont répertoriées à la fin. Le matériel supplémentaire est reporté en annexe de la thèse.

Effects of prismatic adaptation on balance and postural disorders in patients with chronic right stroke: protocol for a multicentre double-blind randomised sham-controlled trial.

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Abstract

Introduction**:** Patients with right stroke lesion have postural and balance disorders, including weight bearing asymmetry (WBA), more pronounced than patients with left stroke lesion. Spatial cognition disorders post-stroke, such as misperceptions of subjective straight-ahead (SSA) and subjective longitudinal body axis (LBA), are suspected to be involved in these postural and balance disorders. Prismatic adaptation (PA) has showed beneficial effects to reduce visuo-motor disorders but also an expansion of effects on cognitive functions, including spatial cognition. Preliminary studies with a low level of evidence have suggested positive effects of PA on WBA and balance after stroke. The objective is to investigate the effects of PA on balance but also on postural disorders, SSA, LBA, and autonomy in patients with chronic right-stroke lesion.

Methods and analysis: In this multicentre randomised double-blind sham-controlled trial, we will include 28 patients aged from 18 to 80 years, with a first right supratentorial stroke lesion at chronic stage (≥12 months) and having a WBA≥60% towards the right lower limb. Participants will be randomly assigned to the experimental group (performing pointing tasks while wearing glasses shifting optical axis of 10 degrees towards the right side) or to the control group (performing the same procedure while wearing neutral glasses without optical deviation). All participants will receive a 20-minute daily session for 2 weeks in addition to conventional rehabilitation. The primary outcome will be the balance measured using the Berg Balance Scale. Secondary outcomes will include WBA and parameters of body sway during static posturographic assessments, as well as lateropulsion (measured using the Scale for Contraversive Pushing), SSA, LBA, and autonomy (measured using the Barthel Index).
Ethics and dissemination: The study has been approved by the ethical review board in France. Findings will be submitted to peer-reviewed journals relative to rehabilitation or stroke.
Registration: NCT03154138 (clinicaltrials.gov)

Strengths and limitations of this study:

- Evidence of short and long-term effects of PA on balance and postural disorders in adult patients with right chronic stroke.
- To improve the understanding of effects of PA but also the influence of space reference frames on balance and postural disorders in patients with stroke.
- A high level of evidence provided by a multicentre randomised sham-controlled trial with blinding of assessors and patients and intention-to-treat analyses.
- A cheap intervention, easy to implement, with no adverse event known, and not requiring a high level of active participation from patients.

Introduction

Background

Strokes frequently cause postural disorders, including a weight bearing asymmetry (WBA) towards the non-paretic lower limb [1–7] and a greater body sway [2,6–9] during a standing posturographic assessment, but also an impaired body orientation with respect to gravity (known as lateropulsion).[10–12] Patients also suffer from balance disorders [9,13,14] limiting

their level of activity and participation.[15–18] They experience a greater number of falls.[19–21] Gait and quality of life are both associated with balance,[22–25] which underlines the importance of balance in stroke patients.

After stroke, patients can also experience perturbations of spatial cognition. Between 32.5% and 63% of stroke patients have a bias of subjective verticals [10,26–28] and a meta-analysis reported that the mean estimation of the subjective visual vertical was significantly deviated in stroke patients compared to healthy participants.[29] The longitudinal body axis (LBA) could be perceived with a deviation towards the contra-lesional side after stroke.[30] The estimation of subjective straight-ahead (SSA) could also be shown as deviated and/or uncertain, especially in patients after right stroke lesion with an unilateral spatial neglect (USN) which perceived SSA rotated towards the ipsilesional side.[31–34] These misperceptions of spatial reference frames were found more frequently and/or with higher magnitude after right stroke lesion than left stroke lesion.[10,26,28,30,32,35] This could be the consequence of a predominance of the right hemisphere in spatial cognition, as for USN, which is more frequent, severe, and persistent after a right stroke lesion than a left one in right-handed subjects.[36] Furthermore, patients with right stroke lesion were displaying greater postural (*i.e.* WBA, body sway, lateropulsion) and balance disorders.[2,5,14,37] Taking into account that the misperceptions of space reference frames such as the subjective (visual or postural) vertical and the LBA were found associated with body sway,[26] lateropulsion,[10,12] WBA,[38] and balance,[26] the postural and balance disorders after stroke are strongly suspected to be influenced by spatial cognition disorders. Although considered by some authors as a potential strategy of compensation to ensure a better stability,[39–41] the underlying mechanisms of WBA partly involve egocentric spatial reference frames.[38]

State of the art

The rehabilitation of balance is a common goal for patients with stroke. Nowadays, few rehabilitations are considered as effective.[42] Among these is task-oriented training, which involves practicing functional, specific, and goal-centred tasks based on motor learning principles such as repetition, variability, or feedback.[43,44] Because the awareness and the voluntary participation of patients are required, practising task-oriented training is laborious and involves a high workload from patients with stroke, while they frequently experience

fatigue, deficit of attention, and behavioural disorders.[45,46] The need for complementary effective rehabilitation is therefore relevant, especially techniques which modulate spatial frames, such as prismatic adaptation (PA) the effect of which to spatial neglect is well known.[31,47–49]

PA is an intervention consisting in repetitive pointing tasks while the patient is wearing glasses shifting the optical axis towards the right. Under prism exposure, first pointing movements are deviated toward the right side as patients are not able to point at the target. These errors are compensated for once they are noticed and successive trials are performed. When subjects are asked to point straight-ahead after removal of prisms, a shift opposite to the prism deviation is observed, reflecting a "true" adaptation also called sensory-motor after-effect.[31,50] This individuals' behaviour during PA could be explained by two successive mechanisms: A process of recalibration which is a compensatory response needed to modify the motor commands; then a spatial realignment needed to align conflicting visuo-motor and proprioceptive-motor reference frames.[51–54] Very interestingly, numerous studies in healthy subjects and brain-injured patients showed expansion of the sensory-motor after-effects of PA to unexposed sensory, motor, and cognitive functions, such as spatial cognition.[31,47,55–57] A "bottom-up" processing of information from peripheral sensory-motor inputs to high-level cognitive centres bypassing the patient's awareness may explain the expansion of sensory-motor after-effect to cognitive post-effects.[31,47,58] The involvement of cerebello-parietal network in the sensory-motor after-effect and the "bottom-up" activation of prefrontal and temporal areas for cognitive post-effects are strongly suspected.[54,59–61] PA effects could vary according to neuro-anatomical individual features. Patients with greater PA induced cognitive effects on USN showed a significant contribution of undamaged hemisphere and inter-hemispheric connections.[62]

Regarding postural and balance disorders, five studies [63–67] have found a significant reduction in WBA (in sitting or standing position) after using PA with an optical deviation of 10 degrees towards the right in patients with acute or chronic right stroke lesion. However, only one of them assessed effects of PA on balance. Hugues *et al.* have found an improvement of balance after PA in patients at chronic stage without USN jointly with a significant left shift of SSA, a significant reduction in WBA and lateropulsion.[64] This study did not include a control group and the efficacy of PA on balance disorders after stroke is not yet evidenced. To

our knowledge, one randomised controlled trial investigating the effects of PA on postural disorders in patients with a right stroke lesion is on-going, and results are not yet published. This trial enrols patients with stroke at an acute or subacute stage and compares the effects of neck muscle vibrations, PA, conventional rehabilitation, or both PA and neck muscle vibrations on WBA as primary outcome (register number: NCT01677091). To our knowledge, no study has investigated the effects of PA on balance compared to sham intervention in patients with a chronic right stroke.

Objectives and hypothesis

The aim of the present study is to investigate efficacy of 2 weeks of PA on balance as primary outcome, but also on postural disorders, autonomy, and egocentric spatial reference frames (assessed by SSA and LBA) as secondary outcomes, compared to sham intervention on patients with right stroke at chronic stage. A secondary objective is to investigate the relationship between PA induced changes on misperceptions of spatial reference frames and these on postural and balance disorders. We hypothesize that PA would improve the balance of patients with a right chronic stroke lesion jointly with a reduction in postural disorders, resulting from a "bottom-up" effect of PA on egocentric spatial reference frames.

Additional objectives are to determine brain lesions involved in misperceptions of spatial reference frames, postural and balance disorders; and to assess the relationship between brain lesions and PA induced changes on performances.

Methods

The protocol (6th version from 12/12/2019) was developed using the SPIRIT statement.[68]

Design

This is a prospective multicentre randomised double-blind sham-controlled superiority trial conducted in 3 units of physical and rehabilitation medicine in France (Hospices Civils de Lyon; CHU de Grenoble; CHU de Saint-Etienne). Participants will be randomised in two parallel groups: the experimental group will receive 10 daily sessions of PA while the control group will receive 10 daily sessions of sham intervention. In addition, all participants will receive conventional rehabilitation regardless of the allocation group.

Participants and criteria of inclusion

The inclusion criteria are: (1) being aged from 18 to 80 years; (2) having a first right unilateral sustentorial, ischemic or haemorrhagic, stroke as defined by the World Health Organisation and diagnosed on the basis on both a clinical examination and a CT or RMI scan confirmation; (3) having had a stroke more than a year ago (time post-stroke≥12 months); (4) being able to stand for at least 30 seconds with eyes open and with eyes closed; (5) having a WBA≥60% on the paretic lower limb during a posturographic assessment in quiet static standing position with eyes open; and (6) signing an informed and free consent. The exclusion criteria are: (1) having a brainstem, cerebellum, or bilateral stroke lesion; (2) having any orthopaedic or rheumatism disease, visual deficit due to a retina disease, or any other disease likely to interfere with the assessments of the study according to the judgement of investigators; (3) having any difficulty to speak or understand the language or psychiatric disorders limiting the understanding of the instructions, the procedures, and the consent collection; and (4) being pregnant or breastfeeding, being subject of a guardianship or tutelage measure, or not having social health insurance.

Procedure

A standardised procedure will be conducted in all the participating centres (Fig. 1). Patients with stroke admitted in rehabilitation units or coming for their on-going medical follow-up will be screened. Patients who volunteer to participate will then meet with a medical physician authorised by the study for an inclusion visit in order to formally check the inclusion/exclusion criteria and to collect their informed consent. The study duration for each participant will be of 3 months and 3 weeks (111 days). During the first week, patient characteristics at baseline will be collected and 2 pre-intervention assessments will be performed on 2 different days. Then, the randomisation will take place. A structural brain MRI will also be carried out preferably during the first week. During the second and third weeks, participants will receive PA or sham intervention according to their allocation group, 5 days per week. The day of the last session of PA/sham will be considered as "day 0" (D0). The post-intervention assessments will be performed 2 hours after the last PA/sham session, and 3 and 7 days after D0. Following these 4 weeks in units of physical and rehabilitation medicine, participants will either be

discharged from the hospital, or continue their hospital stay according to their clinical needs. Participants will also be assessed 1 and 3 months after D0.

Randomisation

The randomisation will be stratified according to the centres and the presence of USN (yes/no) determined using the GEREN test battery (see outcome part below).[69] A computer-generated randomisation list with blocks and a 1:1 ratio will be used for group allocation (SAS version 9.3, SAS Institute Inc., Cary, NC, USA). This list will be managed and stored by only two independent investigators (SBD and LV) from outside the units where the study will take place. The list will be not accessible to any other investigators, staff members, or patients. The randomisation will be performed after the completion of baseline and pre-intervention assessments. Because SBD or LV will not be involved in any part of the screening, eligibility, or inclusion of participants, the allocation will be concealed.

Interventions

The therapists in charge of PA/sham intervention will be trained before the opening of the centre. Only these therapists will be informed of the allocation group, neither the participant nor any staff member will be aware of it. The participants are likely to know the allocation group by looking the glasses used if they have a high knowledge of the modalities of PA. The PA or sham interventions will be delivered in a room separated from other rehabilitation settings, and will be the same for the 2 groups. Knowing that patients with stroke often have cognitive deficits, their ability to discover the allocation group appears low and we can therefore consider the patient blinding as sufficient.

Prism adaptation

According to the method previously used [31,48,49,63], the participant will wear prim glasses (OptiquePeter.com) shifting the optical axis of 10 degrees towards the right side (Fig. 2). During 20-minute prism exposure, the therapist will pseudo-randomly ask the patient to make several sets of approximately 50 rapid pointing movements towards 2 different visual targets positioned 10 degrees on the right and left sides of the mid-line body axis of the patient. During the first pointing tasks, the patient's movement is shifted towards the right side of the visual target. Then, the participant will take into account the initial error and will compensate

it in order to reach the target. At the end of the PA session, when a pointing movement is asked of the patient after having removed the glasses, this one will be deviated towards the left side of the target. This constitutes the visuo-motor (sensori-motor) "after-effect" of PA (Fig. 3).[31,48] The PA will be dispensed daily in 20-minute sessions, 5 days per week during 2 weeks. If a session is missed, 2 sessions could be carried out the following day. Thirty minutes per session will be scheduled to take into account the time for installation, explanations, and potential rests. No adverse event has ever been reported before.[31,48,49,63]

Sham intervention

The procedures and the modalities will be identical to those applied in the experimental group except for the glasses used. The device will be fitted out 2 prismatic lenses set up so as not to deviate the optical axis (Fig. 2). The sham glasses will look like prismatic glasses.

Conventional rehabilitation

In addition to PA or sham intervention, the participants will receive a conventional rehabilitation (physical therapy, occupational therapy, or speech therapy) not exceeding 90 minutes on average per day. The content and the duration will be determined by the physician of the unit in charge of the participant according to the clinical needs and before the beginning of the study. Therapists in charge of the conventional rehabilitation should not know the allocation group of participants. Rehabilitations likely to modify spatial cognition such as biofeedback platform, virtual reality, other sensory interventions, or constraint-induced therapy, will be proscribed during the duration of the study.

Outcomes

All assessors will be blinded to the allocation group and they cannot be in charge of conventional rehabilitation. Data extracted from medical records will be: age in years, sex, manual laterality measured using the Edinburg Handedness Inventory, time post-stroke in days, the type (ischemia or haemorrhage) and the location of the stroke lesion based on recent CT or MRI scans, medical history, the presence of an aphasia and lateral homonymous hemianopia, and current medication. In addition, we will assess at baseline motor weakness but also spasticity, and superficial and deep sensibility of left body (supplemental material).

The presence of USN will be determined using GEREN tests.[69] This battery of tests includes (1) a preliminary assessment of awareness, sensorial extinction, and hemianopia, (2) an assessment of gaze orientation and personal neglect, (3) an assessment of extrapersonal neglect using paper and pencil tests (the bells test, figure copying, clock drawing, the line bisection, the overlapping figures test, a reading test, and a writing test), and (4) a behavioural assessment of neglect and anosognosia using the Catherine Bergego Scale. Based on the cut-off defining normality or abnormality for each test, we will consider the presence of USN if at least one test is abnormal. Overall cognitive disorders will be measured using the Mini-Mental State Examination.

The duration and frequency of interventions during the first 4 weeks after inclusion, as well as the observance and compliance of patients to PA/sham sessions will be monitored. The summary of assessments at each time point is reported in Table 1.

Table 1. Summary of baseline, pre-intervention, and post-intervention assessments at each time point

	Inclusion	Pre-intervention assessments (D-18 to D-14)		Intervention (D-11 to D0)	(+2H)	(D+3)	(D+7)	(M+ 1)	(M+3)
					Post-intervention assessments				
Baseline characteristics									
Medical information	X								
Motor weakness	X								
Spasticity	X								
Sensibility	X								
Aphasia and hemianopia	X								
USN (GEREN tests)	X								
Global cognitive disorders	X								
Balance and postural disorders									
Berg Balance Scale		X	X				X	X	X
Posturographic parameters		X	X		X	X	X	X	X
Scale for Contraversive Pushing		X	X		X	X	X	X	X
Spatial reference frames									
Manual straight-ahead		X	X		X	X	X	X	X
Visual straight-ahead		X	X		X	X	X	X	X
Open-loop pointing		X	X		X	X	X	X	X
Longitudinal body axis		X	X		X	X	X	X	X
Autonomy									
Barthel Index			X				X	X	X
Brain imagery									
TDM or MRI scan			X						
Observance/Compliance				X					
Adverse events	X	X	X	X	X	X	X	X	X

Abbreviations: D, day; H, hour; M, month; MRI, magnetic resonance imaging; TDM, tomodensitometry; USN, unilateral spatial neglect.

Primary outcome

Based on published results,[64] the primary outcome will be the balance measured at D+7 using the Berg Balance Scale (BBS). Validated in patients with stroke,[70] this scale comprises 14 items each scored from 0 to 4 and assesses the functional abilities of balance (the higher the score, the better the balance).

Secondary outcomes

The secondary outcomes will be: the balance assessed using the BBS at M+1 and M+3; postural disorders assessed at +2h, D+3, D+7, M+1 and M+3 (the mean mediolateral position of COP [mm], the mean anteroposterior position of COP [mm], the sway area of COP [mm2], the standard deviation [SD] of mediolateral position of COP, the SD of anteroposterior position of COP, and body weight bearing on left and right lower limb [percent of body weight] measured during a posturographic evaluation, but also lateropulsion measured using the Scale for Contraversive Pushing [SCP]); egocentric spatial reference frames measured at +2h, D+3, D+7, M+1 and M+3 using manual SSA, visual SSA, open-loop pointing (OLP), and LBA; and autonomy measured at D+7, M+1 and M+3 using the Barthel Index.

In standing static position, the posturographic assessment measures the spatial and temporal evolution of the COP by means of two separate force platforms, one under each foot, parallel and 14-cm spaced (Freetest 6, Technoconcept®). Two trials will be performed with eyes opened and two others with eyes closed, each trial will be recorded for 30 s. The mean of two tests for each eye condition will be calculated. No human or technical help during measurements will be allowed. As its reliability is considered as acceptable, posturographic assessment is frequently implemented to assess postural disorders after stroke.[71,72]

The SCP is composed of three parts and assesses: the symmetry of the spontaneous posture, the extension of the area of physical contact to the ground by using an arm or leg, and the resistance to passive correction of posture to an upright position. Both standing and sitting positions are assessed and each contributes to 50% of the score of each part (between 0 to 2 points). On a total of six points, a participant with a score ≤0.5 is considered as "upright" while a participant with a score >0.5 is considered as having a lateropulsion. A contraversive pushing is considered if the score reaches at least 1 for each of 3 parts of SCP.[10,73]

The SSA assessment will be performed in accordance with the method used in Rossetti *et al.* [31] and in Rode *et al.* [48] (Fig. 4). The SSA corresponds to the perception of the sagittal axis in the horizontal plan and thus in the egocentric peri-personal space. Seated in front of the device, the patient will indicate his/her subjective "straight-ahead" direction by a pointing task with a finger of the right hand without visual input for manual SSA. For visual SSA, the patient is seating in the dark and will be asked to say when the luminescent diode moving in front of him/her is perceived in a "straight-ahead" position. The manual SSA therefore reflects the proprioceptive modality while the visual SSA reflects the visual modality. For OLP, the patient will be asked to point with a finger of the right hand at the target drip-line as precisely as possible without time constraint. The pre- and post-intervention test difference on OLP indicates the magnitude of the PA total effect. For each test, 10 trials will be performed.

The LBA corresponds to the patient's representation of the egocentric body space. Here, the procedure of LBA assessment is similar to the one used in Barra *et al.*.[30,74] Patients will be lying on an examination table in a total darkness with their head, trunk, and lower limbs aligned by the assessor. The head and the lower limbs will be laterally constrained. Placed at approximately 25-30 cm above the patient, a device containing a fluorescent tube will be moved by the assessor from the extreme left or right position in the patients' visual field towards the opposite extreme position at a slow speed. Each patient will be asked to say stop when the fluorescent tube reaches the position perceived as being overlapping with his/her LBA. Five trials will be performed with a departure position of the fluorescent tube on the right side and 5 others on the left side. Between each trial, patients will have to close their eyes to prevent any visual feedback or cueing.

For SSA and LBA, the average deviation will be determined using the mean of 10 trials and the uncertainty in the estimate using the SD of 10 trials. By convention, a negative value indicates a deviation towards the left side and a positive value towards the right side.

The Barthel Index is a 10-item scale widely used to assess the functional independence in daily-living activities. A maximal score of 100 points indicates total independence. Its metrological properties are considered as good, which makes it relevant and appropriate to assess autonomy in patients with stroke.[75]

All participants will undergo a brain structural MRI scan. Lesions will be manually delineated on native-space T1 weighted images for each patient. T1-weighted images will be normalized

to the template MNI152 using affine and diffeomorphic deformations [76,77] implemented in BCBtoolkit [78] (http://www.toolkit.bcblab.com). Finally, lesions will be manually drawn in the MNI space. Subsequently, lesions will be overlapped to highlight damaged areas using MRICron.[79] A voxel-based lesion-symptom mapping (VLSM) analysis will be performed using the non-parametric rank-order Brunner-Menzel analysis with voxel-based permutation (1,000; http://www.cabiatl.com/mrico/npm/).[79] The VLSM analysis will be run for the dependent continuous variable of interest and controlled for the overall lesion size. Only voxels damaged in at least 10% of patients will be included in the analysis. Results will be projected onto a high-resolution template in standard space. For atlas-based mapping of white matter disconnection, we will map the lesion from each patient onto tractography reconstructions of white matter pathways obtained from a group of healthy controls.[80] We will quantify the severity of the disconnection by measuring the probability of the tract to be disconnected [81] using the Tractotron software as part of the BCBtoolkit.[78] In the resulting disconnectome map, the voxels will show the probability of disconnection from 0 to 100%. Statistical analyses (association with clinical disorders and PA induced changes) will be performed on these maps using the "Randomise" function implemented in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL), with 5,000 random permutation tests and a Threshold-Free Cluster Enhancement option. Results will be adjusted for FEW corrections for multiple comparisons. In accordance with the additional objectives, we will perform regressions between the grey and white matter brain damages and i) misperceptions of space reference frames, postural and balance disorders; and ii) the changes induced by PA on these outcomes.

Statistical analysis

Descriptive statistics will be computed using count (percentage), mean±SD, or median [interquartile range] as appropriate. We will compare baseline characteristics between groups using the Fisher's exact test or the Pearson's Chi-squared test for qualitative variables, and the independent t-test for continuous measures (or Mann-Whitney test if the hypothesis of normal distribution is rejected).

Unadjusted means and standard errors will be estimated for the primary and secondary continuous outcomes at each time point. Then, we will build linear mixed-effect models with

time as within-participant factor, group as between-participant factor, and time by group interaction. The centres and USN will be included as covariates. Group, time, and USN will be considered as fixed factors, while participants and centres as random factors (R package "nlme"). The group by time interaction will be examined as well as models including a random intercept only and a random intercept and slopes. The different models will be compared using Akaike and Bayesion information criterion and analysis of residuals. In case of significant effect, we will perform multiple comparisons adjusted using the Bonferroni-like method according to the objectives previously stated. When 2 pre-intervention assessments will have be done, the mean and the individual values of assessments will be used. Based on previous studies, we expect that the BBS variable will follow a normal distribution or a Poisson distribution, making necessary the use of a mixed generalized linear model. Otherwise, we could implement data transformations or non-parametric tests.

We will carry out intention-to-treat analyses. Missing data will be handled by mixed-effects models. For secondary outcomes, per-protocol analyses will be additionally computed. We will also perform sensitivity analyses using an analysis of covariance controlling for baseline values as fixed factor.[82–84] Additional planned analyses are reported in supplemental material.

The investigator in charge of analyses will be blinded to allocation group. All statistical analyses will be performed using R software (R Foundation for Statistical Computing, Vienna, Austria; available in http://www.R-project.org/) with a p-value≤0.05 considered as statistically significant.

Sample size

According to the pilot study [64], we could postulate a within-group difference at D+7 of 4.83 points on BBS for the experimental group and of 2 points for the control group, with a pooled SD of change of 2. On the basis of these hypotheses, considering alpha risk of 0.05, a statistical power of 95%, and a bilateral test, we have to include 13 participants per group. To take into account potential lost to follow-up or dropping out before the primary outcome, one additional participant by group will be included. We will therefore include 28 participants.

Ethics and dissemination

Promoted by the Hospices Civils de Lyon, this study was approved by an institutional review board ("Comité de protection des personnes Nord Ouest IV"; 2017-A01809-44) and registered on Clinicaltrials.gov (NCT03154138). The procedure will be performed in respect of the Helsinki Declaration. Before inclusion, information relative to the study will be given to eligible participants. The participants agreeing to participate will sign a free and informed consent. Any potential important modification of protocol will be submitted to the institutional review board according to the French law. Procedures to collect and store patient data are in accordance with General Data Protection Regulation of European Union, and have been declared to the Comission nationale de l'informatique et des libertés (CNIL: French committee for data protection) in accordance with existing regulations in France. Patients will not have to support any cost related to their participation in the study. All participants will receive conventional rehabilitation in accordance with current practices. The risk for participants is considered as low: PA is frequently used to treat USN and, to our knowledge no adverse event has ever been reported.

Information relative to data management and monitoring are reported in supplemental material.

Patient and public involvement, and dissemination

The protocol presented herein was developed without patient or public involvement. Neither participants nor the public will not be involved in result analysis and their interpretation, as well as in the writing of the final manuscript. The results will be submitted to peer-reviewed journals relative to rehabilitation or stroke, as well as to international congresses, in order to disseminate findings and discuss the interest of PA in rehabilitation with researchers, healthcare givers, and patients. Authorship eligibility will be based on the criteria of the International Committee of Medical Journal Editors (ICJME). The full protocol (in French), the model consent form (in French), the data that will support the study results, and the statistical code will be available from upon reasonable request to the corresponding author and Prof. Gilles Rode.

Discussion

The interest of the study presented herein is to determine if PA could improve balance and postural disorders in patients with right stroke lesion at a chronic stage. By a bottom-up action from a sensori-motor representation level to a cognitive representation level, PA is likely to modify postural disorders related to misperceptions of spatial reference frames. The present study is a pragmatic trial focusing on balance as the primary outcome. Considered as a level of activity in the model of disability according to International Classification of Functioning, Disability, and Health, balance is an essential concern for patients after stroke. Findings from this trial are likely to have a high level of evidence taking into account the methodology implemented.

PA is thought to have many advantages: it is cheap and easy to implement with only one therapist; its use is safe as no adverse event has been reported although it is used in clinical practice to treat USN; it can be delivered to patients both in acute-subacute or chronic stage, with light or severe impairments, and to inpatients, outpatients, and at home. In addition, as it does not require a high level of participation from patients, PA could be a relevant intervention in patients with severe attention deficits and could complement the range of existing interventions.

This trial also includes secondary explicative objectives to improve the understanding of PA mechanisms, especially how the expansion of sensory-motor after-effects of PA on spatial references frames could improve balance. This could be of high relevance from a theoretical and pragmatic point of view. In addition, the neuro-anatomical study could contribute to identify patients likely to be responders by highlighting neural networks likely to mediate effects of PA.

Authors' contributions: All authors have contributed the conception and the methodology. AH and GR were in charge of writing the original draft. The other authors have contributed the reviewing and editing of the manuscript.

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Competing interest statement: The authors have no conflict interest to declare.

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Figure 1. Procedure from enrolment to the end of study

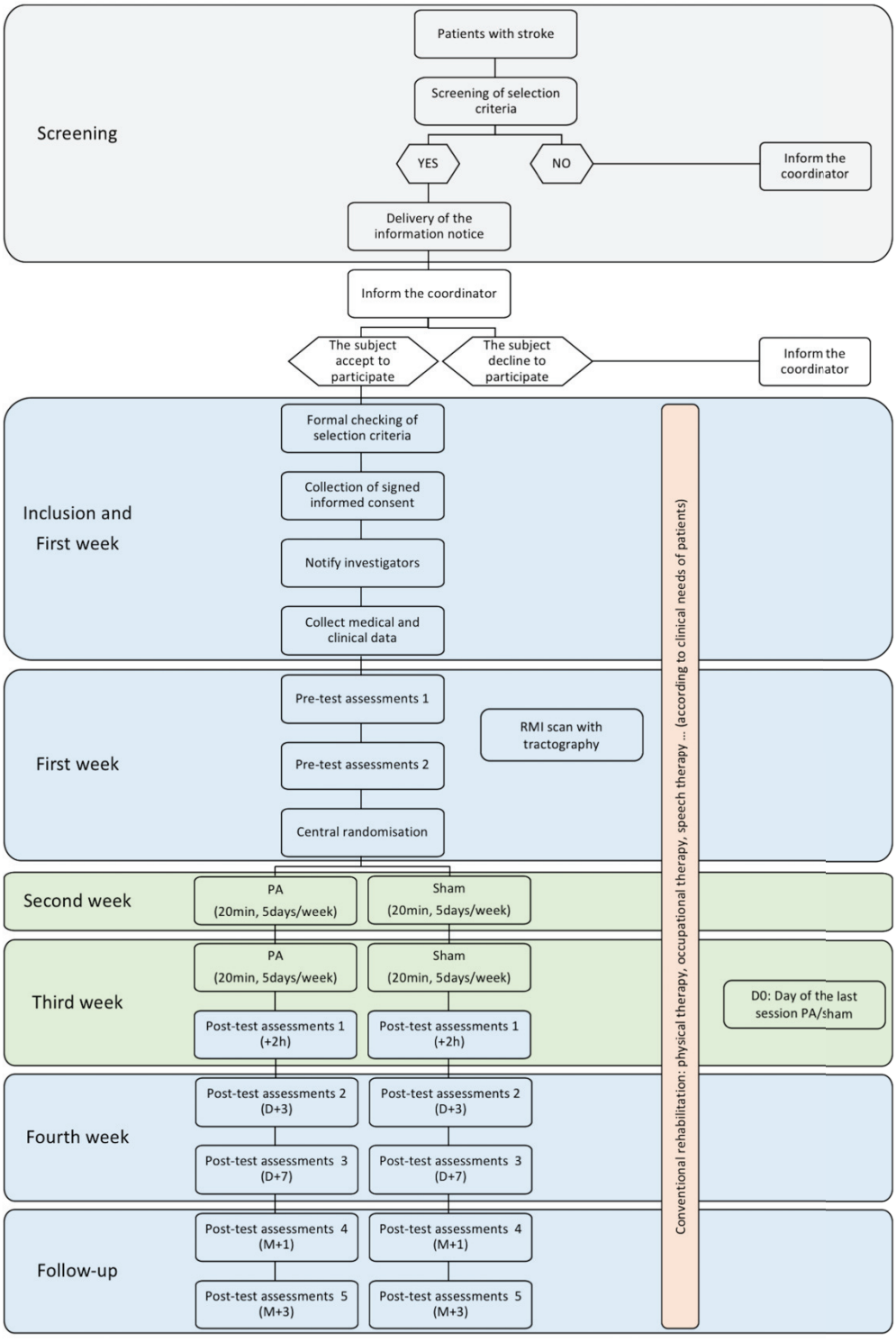
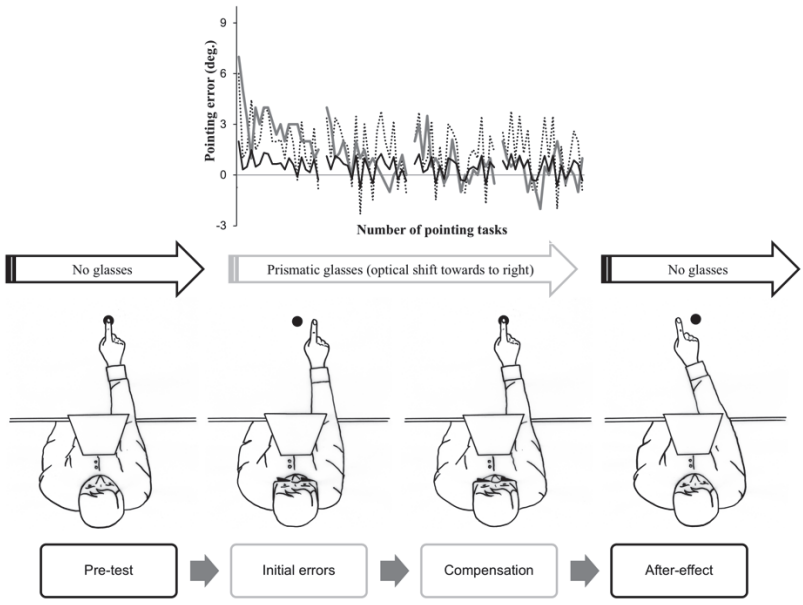


Figure 2. Prismatic glasses (2A) and sham glasses (2B).

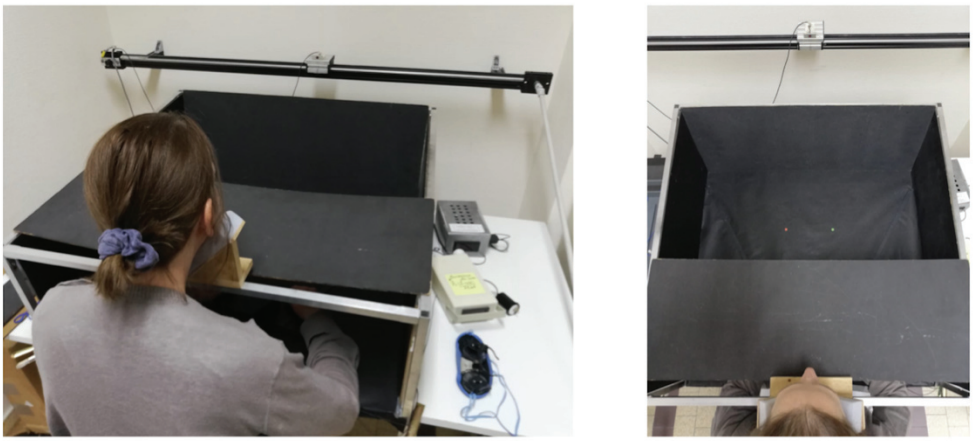
A, a pair of prismatic glasses with an optical deviation of 10 degrees towards to the right side; B, a pair of sham glasses with a neutral optical deviation.

Figure 3. Procedure for prismatic adaptation



The participant will be seated in front of the support set up on a table, with the chin on a part of the support limiting the inclination or rotation of the head and placed in the mid-line body axis. To limit visuo-feedback during pointing tasks with prism exposure, the support hides the initial position of the patient's hand but also at the beginning of the movement course (*i.e.* 20-50%). In addition, the therapist will ensure that the patient perform rapid movements.

Figure 4. Subjective straight-ahead assessment



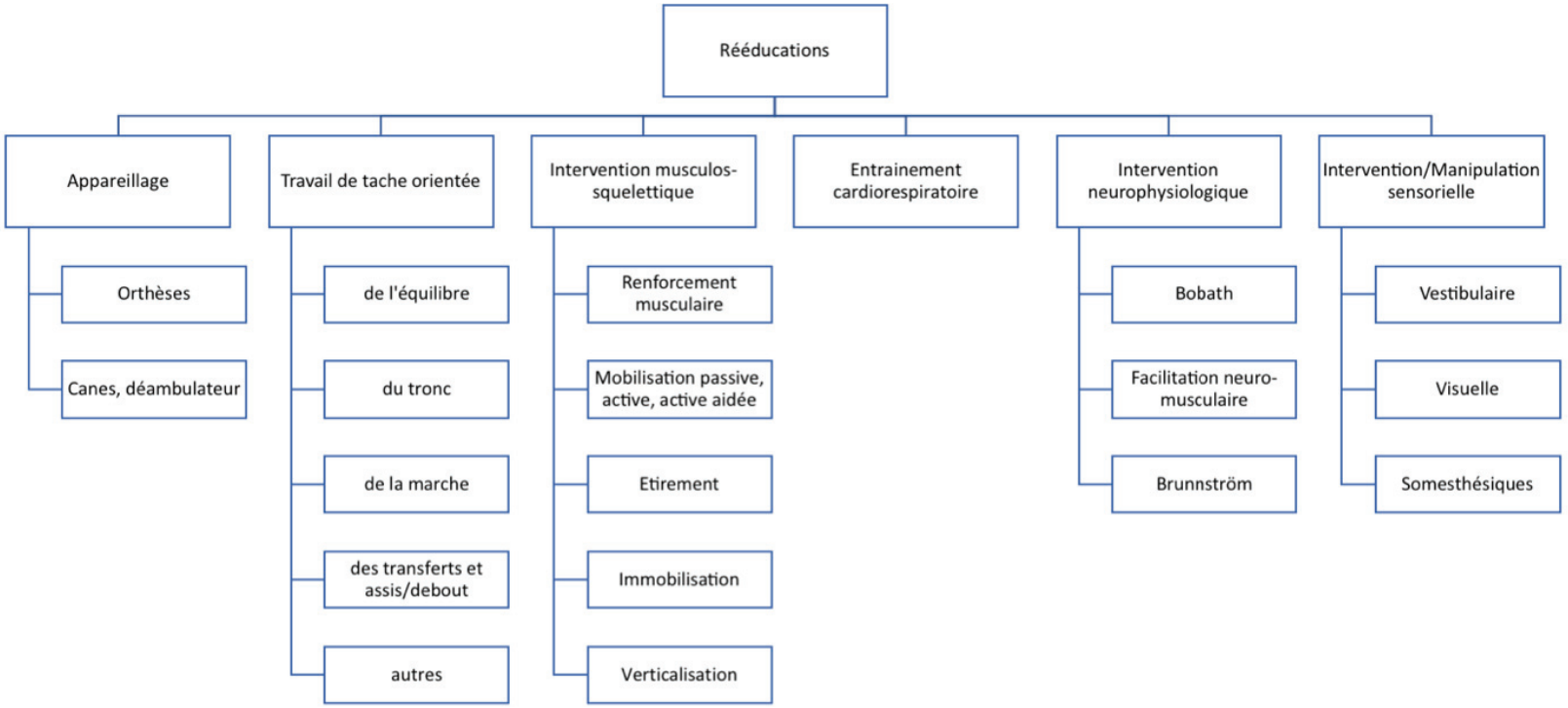
The patient is seated in front of the device set up on a table, with the chin on a part of the device preventing the inclination or rotation of the head. The mid-line device axis will match the patient sagittal axis. For the manual SSA, the assessor asks the patient, placed in the dark, to point on the horizontal plan of the device with the forefinger of the right hand the "straight-ahead" direction. From a departure position of the right hand closer to navel, the patient spreads the arm without restriction, then returns to the initial position. The pointing is measured by means of an electronic system included in the horizontal plan of the device. The angular deviation from the objective sagittal axis is displayed by the device. For the visual SSA, the patient keeps the initial position of manual SSA and the measurement is still performed in a total darkness. A luminescent red diode will move in front of the patient from the extreme left or right position in the visual field towards the opposite extreme position at a slow speed. The diode is at the same height than the gaze of the patient. The head of the patient is still contained in the chin support limiting its inclination and rotation. The investigator asks the patient to say stop when the red diode reaches the position perceived as being "straight-ahead". The angular deviation from the objective sagittal axis is also displayed by the device. For the OLP, the patient is still in total darkness and takes the initial position of manual SSA with his/her hand closer to his/her navel. The red luminescent diode is aligned with the objective sagittal axis of the patient. The investigator asks the patient to point in the direction of the red diode on the horizontal plan of the device with the forefinger of the right hand, and then to return to the initial position. For each test, 10 trials will be performed. For visual SSA, 5 trials will be performed with a departure position of the red diode on the right side of the patient and 5 others on the left side.

5. DISCUSSION GENERALE

5.1. LES PREUVES LIMITEES DES EFFETS DE LA REEDUCATION

Afin d'évaluer l'efficacité des rééducations sur les troubles de l'équilibre et de la posture après AVC, nous avons catégoriser les différents types de rééducations évalués dans les études, en s'appuyant notamment sur une publication de la Cochrane. L'utilisation de classifications participe à améliorer la compréhension des rééducations et de leur usage en pratique clinique. A partir des travaux présentés dans cette thèse, une classification peut être proposée (Figure 18).

Dans la première étude de méta-analyse (Hugues *et al*., 2019), nous avons pu constater que l'effet global de la rééducation était bénéfique immédiatement après intervention sur l'équilibre, l'asymétrie d'appui (en condition yeux ouverts) et l'instabilité posturale (en condition yeux ouverts ou fermés) par rapport à aucune rééducation ; mais aussi sur l'équilibre et l'instabilité posturale (en condition yeux ouverts ou fermés) par rapport à une rééducation placebo ou des soins courants. Ces résultats s'appuient sur un nombre important d'études. Savoir que, dans son ensemble, la rééducation a un effet bénéfique sur les troubles de l'équilibre et de la posture après un AVC est un point positif en termes de santé publique et pour le système de soins. Par ailleurs, l'analyse des effets en fonction des types de rééducations a montré que la rééducation par tache orientée (rééducation motrice fonctionnelle) associée avec une rééducation musculo-squelettique et/ou un entrainement cardio-respiratoire était efficace pour améliorer l'équilibre ; et que les interventions sensorielles amélioraient la stabilité posturale (que ce soit en condition yeux ouverts ou fermés). Ces résultats contribuent à orienter la prise en charge en clinique. Peu d'études avaient auparavant évalué les effets de l'ensemble des rééducations permettant ainsi de dresser une cartographie complète.



Adjuvants thérapeutiques	
Réalité virtuelle	Physiothérapie
Imagerie motrice ou mentale	Biofeedback
Electrostimulation	Indice et stimulation
Thérapie miroir	Double tache cognitivo-motrice
Assistance électromécanique	Milieu aquatique
Support du poids du corps	Observation/Imitation d'une action

Figure 18. Proposition de classification des différentes rééducations utilisées en pratique clinique.

Nous avons pu constater qu'il y avait un nombre important de rééducations différentes : entrainement par tache orientée selon des modalités diverses (avec ou sans réalité virtuelle, imagerie motrice, thérapie miroir …), renforcement musculaire, appareillage, contrainte-induite, technique sensorielle, entrainement cardio-respiratoire, yoga, tai-chi, rééducation du tronc… L'effet traitement était retrouvé non significatif pour plusieurs de ces types de rééducations, probablement en raison d'un nombre trop limité d'études et de participants. Ainsi, il fut impossible de conclure qu'à la direction (en faveur ou non de la rééducation) et à la taille des effets pour un certain nombre de rééducations. Pour celles dont le nombre d'études et de participants était suffisant, la présence d'une hétérogénéité statistique a, parfois, limité l'interprétation des résultats. Dans ces cas, l'utilisation d'un modèle statistique à effet aléatoire a, certes, permis la prise en compte de cette hétérogénéité mais cela ne doit pas faire oublier une possible inclusion dans une même analyse de rééducations aux modalités différentes et de patients aux caractéristiques cliniques hétérogènes… En effet, les modalités d'intervention au sein de chaque type de rééducation étaient souvent variées : la tâche/action à accomplir, les modalités de réalisation et d'application, les adjuvants, la progression, la durée et l'intensité … A ceux-ci, s'est ajoutée la diversité des patients inclus dans les études en termes de lésion cérébrale ou de délai post-AVC. Le recours à l'imagerie cérébrale à l'inclusion des patients dans les études s'est révélé rarement utilisé. Les analyses en sous-groupes selon le stade de l'AVC ou la localisation de la lésion cérébrale n'ont été que peu contributives, soit en en raison du nombre limité d'études rapportant ces informations, soit du fait de l'inclusion dans l'étude d'une population hétérogène sur ces critères. En conséquence, la présence d'une hétérogénéité inexpliquée a pu limiter le niveau de preuve.

Par ailleurs, la qualité méthodologique des études s'est révélée faible. Seuls 2 des 7 types de biais considéré par l'échelle de la Cochrane présentaient un risque de biais faible chez plus de 50% des études. Le risque de biais de sélection en raison d'un défaut dans le secret dans l'allocation, le risque de biais de détection en l'absence d'insu des évaluateurs, le risque de biais d'attrition en raison d'analyses ne prenant pas en compte les données manquantes ou par des méthodes inadaptées, et le risque de biais de publication du fait d'un report sélectif et incomplet des résultats dans les manuscrits étaient particulièrement importants. Ces biais constituent des atteintes à la validité des résultats et sont fréquemment

retrouvés dans les recherches portant sur la personne humaine.[247–251] La rééducation n'échappe pas à cette règle. Plusieurs études méta-épidémiologiques, dont certaines spécifiques de la rééducation, ont montré que ces biais influençaient l'estimation des effets traitements.[247,249,252–258] En effet, le manque d'allocation secrète dans la randomisation, l'absence d'insu des évaluateurs, le traitement inadapté des données manquantes et les biais de publication étaient associés avec une surestimation des effets en faveur du traitement expérimental. Dans ce contexte, les analyses de sensibilité que nous avons conduites selon le niveau de risque de biais pour chacun des critères de jugement (Hugues *et al.* 2019), ont montré, à plusieurs reprises, une modification des résultats de nature à en changer l'interprétation. Cette évaluation de la robustesse des résultats nous a conduits à considérer le niveau de preuve comme limité.

Dans un souci de contrôle du biais de langage, nous avions interrogé les bases de données de la littérature sans exclure d'étude sur la base de leur langue de publication. Afin de contribuer à identifier les facteurs susceptibles d'influencer l'estimation des effets traitements dans le domaine de la rééducation, nous avons évalué l'impact de la langue de publication sur ces derniers. Les résultats ont montré une tendance à une moindre qualité méthodologique et à une surestimation des effets par les études publiées en langue non anglaise. Déjà identifiée dans la littérature en ce qui concernait les études médicales,[247] il apparaît donc une tendance similaire dans le domaine de la rééducation et plus particulièrement en ce qui concerne l'équilibre et la posture après AVC.

Au-delà de ces aspects méthodologiques, la question du « reporting » des résultats dans les publications s'est révélée un problème majeur. Comme rapporté dans Hugues *et al.* en 2019, une part importante des études n'ont pas renseigné, ou de façon incomplète, les caractéristiques des patients relatifs à la lésion cérébrale (localisation, coté, caractère uni ou bilatéral, et nombre d'épisode d'AVC), ou ceux concernant les interventions (modalités, applications, progression, durée, fréquence et nombre de séances). Ces informations manquantes ont eu un impact non négligeable sur l'interprétation des résultats, en réduisant par exemple, la contribution des analyses en sous-groupes selon ces caractéristiques. De plus, nous avons été régulièrement contraints de recourir à des retro-calculs pour estimer l'effet

traitement en raison de la manière inappropriée de rapporter les données relatives aux critères de jugement dans les publications (p-value seulement disponible, résultats par graphique uniquement, valeur des critères de jugement en pré et post-intervention sans estimation des changements intra-groupes ou des différences inter-groupes, non-expression de la dispersion …). Or ces retro-calculs impliquent parfois des choix statistiques sur la base d'hypothèses (imputation de l'écart-type du changement intra-groupe avec un coefficient de corrélation par exemple). L'utilisation d'une approche conservatrice dans ces hypothèses afin d'éviter tout faux positif a pu entrainer une diminution de la précision de mesure (augmentation de la variance), susceptible de rendre non-significatif certaines estimations d'effet traitement. Ce « reporting » insuffisant ou inadapté a probablement limité l'interprétation des résultats et le niveau de preuve.

Plusieurs auteurs ont suggéré l'inadaptation des checklists de pré-soumission des essais cliniques contrôlés randomisés pour les études portant sur la rééducation.[259,260] Un groupe de travail composé de chercheurs internationaux a proposé une méthode et un calendrier pour élaborer une checklist plus adaptée aux études sur la rééducation (« RCTRACK project »), afin d'améliorer la qualité méthodologique et la reproductibilité des résultats. Le rendu de ce travail est attendu pour juin 2021.

Sur la base des méta-analyses présentées dans cette thèse (Hugues *et al.* 2019 et 2020), plusieurs propositions concernant les études investiguant les effets des rééducations après AVC semblent pertinentes :

- Améliorer le « reporting » des caractéristiques des patients relatifs :
    - A la lésion cérébrale : hémisphère atteint, localisation précise, caractère uni ou bilatéral, nombre d'épisode d'AVC et étiologie ischémique ou hémorragique, établis sur la base des données d'imagerie cérébrale et non du seul examen clinique ; mais également du délai post-AVC
    - Aux déficits sensori-moteurs et cognitifs des participants à l'inclusion
- Améliorer la description des rééducations et de leurs modalités d'application :
    - Définition de la nature et des composantes de l'intervention, présentation du rationnel
    - Méthode d'application, progression, intensité, logistique, règle de sécurité …

    - Durée de la rééducation : durée d'une séance, fréquence et nombre total des séance, nombre de semaines du programme.
- Améliorer le contrôle des différents biais méthodologiques lors de la conception et de la réalisation des études, ainsi que la description des moyens utilisés pour y parvenir :
    - Tout particulièrement pour l'allocation secrète, les différents niveaux d'insu, et la gestion des données manquantes et déviations au protocole
- Améliorer le « reporting » des critères de jugement par une publication des résultats :
    - pour tous les critères de jugement, même ceux non-significatifs
    - à tous les temps de mesure collectés,
    - sans se limiter aux valeurs des évaluations pré- et post-intervention mais en rapportant également les changements intra-groupes et différences inter-groupes au moyen d'estimateurs ponctuel (moyenne ou médiane par exemple) et de dispersion clairement précisés
    - basée sur des méthodes statistiques clairement énoncées

5.2. INSUFFISANCE DES MODELES THEORIQUES POUR LA REEDUCATION DE LA POSTURE ET DE L'EQUILIBRE APRES AVC

Les résultats issus de la méta-analyse Hugues *et al.* (2019) montrent que la rééducation par tache orientée (rééducation motrice fonctionnelle) associée avec une rééducation musculo-squelettique et/ou un entrainement cardio-respiratoire était efficace pour améliorer l'équilibre des patients AVC. La rééducation par tache orientée, dont l'objectif est d'améliorer la réalisation d'une tache motrice,[261] ici l'équilibre, se base sur les principes de l'apprentissage moteur,[262,263] comme la répétition d'une tâche fonctionnelle, la variabilité dans et de la tâche à accomplir, le retour d'information implicite et explicite … Une rééducation multimodale ciblant à la fois la commande centrale (travail du geste moteur par tache orientée) et l'effecteur périphérique (réduction de la spasticité, renforcement musculaire, endurance à l'effort, sensibilité) pourrait être un élément essentiel pour améliorer l'équilibre des patients après AVC, conformément au modèle théorique de l'équilibre. Comme développé dans la revue narrative intitulée « Rééducation de l'équilibre du patient cérébro-lésé après AVC » (partie 2.4.5), il semble préférable de privilégier des approches multimodales et diversifiés, en

raison de la nature multifactorielle de l'équilibre, avec une progression selon les principes de l'apprentissage moteur afin de « challenger » le patient.

En ce qui concerne les effets constatés après intervention sensorielle sur la stabilité posturale, il semblerait que ce soit les stimulations sensorielles appliquées localement sur des muscles du membre parétique qui produisent un effet bénéfique. A ce stade, les mécanismes d'action restent méconnus. Dans le cadre des modèles théoriques de la posture, il est possible que la stimulation des récepteurs et voies périphériques (notamment proprioceptives) améliore les fonctions somesthésiques au niveau cortical et/ou leur intégration au niveau central par une réduction du déséquilibre d'afférences sensorielles provenant de l'hémicorps parétique. Dans l'hypothèse d'une forme de négligence somesthésique contribuant aux troubles posturaux,[46] les stimulations sensorielles pourraient agir sur ce déséquilibre d'intégration sensorielle.

De plus, les résultats issus de la méta-analyse Hugues *et al.* (2019) montrent que les effets bénéfiques des rééducations sont, globalement, observés immédiatement après intervention mais qu'ils ne persistent pas à distance. Cet effet transitoire tant que dure la rééducation, sans amélioration durable des troubles posturaux et de l'équilibre, suggérait un effet de compensation plutôt que de récupération vraie. Il est à noter que le nombre d'études évaluant les effets des rééducations à distance était nettement inférieur à celui pour les effets immédiats. Par ailleurs, les effets n'étaient pas statistiquement différents selon le stade de l'AVC, alors même les processus de récupération neurologique ont lieu essentiellement et avec une plus grande intensité aux stades aigu et subaigu.[264]

Quant aux effets positifs de la rééducation constatés au stade chronique de l'AVC, ceux-ci plaident en faveur d'une poursuite de la rééducation dans le temps, que ces effets soient de type compensatoire ou adaptatif. Il faut « tordre le cou » au paradigme du seul entretien d'un état séquellaire au stade chronique et promouvoir également un message de poursuite la stimulation des capacités fonctionnelles.

La question du type d'effet induit par la rééducation reste pleinement ouverte. Si l'effet bénéfique de l'entrainement par tache orientée (seule) observé tant sur l'équilibre (qui relève du domaine des activités selon la classification internationale du fonctionnement et du handicap), que sur la stabilité posturale (qui relève des déficits de fonctions) suggère une

possible récupération de la fonction à l'origine d'une amélioration du niveau d'activité, ces résultats restent cependant limités. Mais plus généralement, la réduction des tailles d'effets dans les analyses contre placebo/soins courants par rapport à celles contre aucun traitement interroge sur la nature des effets spécifiquement induits par la rééducation. De plus, que certaines rééducations aient des effets plus marqués sur l'équilibre, mais moins ou aucun sur l'instabilité posturale et l'asymétrie d'appui, pourrait indiquer un effet de compensation plutôt que de récupération. Cela témoignerait de la difficulté d'agir sur les déficits de fonctions, et qu'en l'absence de processus de récupération vraie implémenté ou soutenu par la rééducation, les améliorations restent transitoires et limitées.

La rééducation des troubles de la posture et de l'équilibre souffrirait de ne pas s'appuyer suffisamment sur des modèles théoriques robustes. Certes la posture et l'équilibre revêtent un caractère multifactoriel, mais la diversité des rééducations évaluées et de leurs modalités d'applications a de quoi surprendre voire interroger quant à la pertinence de certaines études. Le cadre théorique justifiant l'hypothèse de recherche était souvent peu développé. L'hétérogénéité des participants des études notamment en ce qui concerne la lésion cérébrale, le délai post-AVC et les déficits cliniques initiaux semble témoigner d'un manque d'appui sur les cadres théoriques. Inclure des patients ayant des lésions cérébrales à l'origine de tableaux cliniques franchement différents en raison de mécanismes physiopathologiques distincts (comme peuvent l'être les atteintes sus-tensorielles, du tronc cérébral et du cervelet) interroge. Il en est de même pour le délai post-AVC en fonction duquel les processus de récupération neurologique varient. Le recours aux données d'imagerie cérébrale pour l'inclusion des patients dans les études devrait être systématique.

Une conséquence de cette rigueur insuffisante dans la caractérisation des participants est un manque de personnalisation des rééducations par rapport au tableau clinique du patient. Or s'appuyer sur des modèles explicatifs et/ou prédictifs basés sur des critères cliniques robustes permet d'améliorer l'efficience de la rééducation, comme cela a été démontré pour la récupération de la fonction motrice du membre supérieur.[265] Ceci illustre le besoin de modèles théoriques robustes pour appuyer le rationnel des rééducations. Le (trop) grand nombre de paramètres différents mesurés en posturographie (64 dans la méta-analyse Hugues *et al.* 2019, dont certains évalués que par une seule étude !) questionne sur la

pertinence et le rationnel derrière chacun d'entre eux. Enfin, le faible « reporting » évoqué plus haut pourrait aussi s'expliquer par l'insuffisance des modèles sous-tendant les hypothèses de recherche.

Cette nécessité d'un cadre conceptuel et méthodologique a conduit à la création d'un groupe de travail international, intitulé le « *Stroke Recovery and Rehabilitation Roundtable* ». Son objectif est la préconisation de recommandations de consensus sur la manière de concevoir, conduire et rapporter les recherches sur la récupération et la rééducation après AVC.[261,266–271]

C'est dans cette perspective que nous avons analysé les effets des rééducations sur l'équilibre en fonction de leur approche « bottom-up » (ascendante) ou « top-down » (descendante). Ce cadre conceptuel est utilisé pour modéliser le fonctionnement de l'attention. Il conçoit le traitement de l'information selon deux processus, « bottom-up » et « top-down », entre deux niveaux, l'un sensori-moteur (implicite) et l'autre cognitif (explicite). Le processus « top-down » met en jeu la connaissance issue de l'expérience au niveau des centres supérieurs pour agir vers le niveau sensori-moteur, alors que le processus « bottom-up » repose sur le traitement des entrées sensorielles via l'analyse perceptive automatique afin de modifier le comportement moteur sans impliquer des processus conscients (Figure 19).[272] Les rééducations basées sur une approche « bottom-up » ont pour objectif de modifier les déficits sensori-moteurs par des manipulations passives ou adaptation visuo-motrice, sans implication de la conscience du sujet. Les rééducations basées sur une approche « top-down » chercheraient à améliorer les déficits sensori-moteurs en agissant par une mise en jeu des processus conscients et volontaires du sujet. Les approches mixtes combinent les deux types d'approches précédemment citées.[226,243,273]

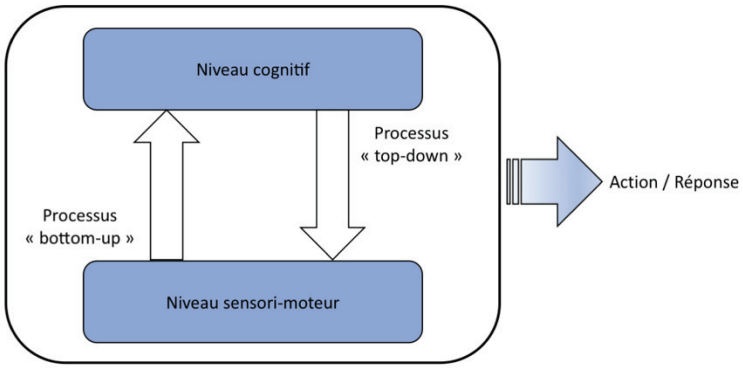


Figure 19. Les processus « bottom-up » et « top-down »

Ce modèle théorique a été utilisé pour évaluer les effets des rééducations sur la négligence spatiale unilatérale après AVC.[226,227,274] Sur la base de la méta-analyse en réseau présentée dans cette thèse, nous avons pu constater que, sur les troubles de l'équilibre, les approches « bottom-up », « top-down » et mixtes avaient des effets bénéfiques, assez proches, immédiatement après l'intervention. Cependant, il semblerait que les approches mixtes aient un effet bénéfique sur l'équilibre également à distance de l'intervention. Le niveau de preuve reste faible, il convient donc d'être prudent mais la combinaison des types d'approches pourrait induire un effet complémentaire relevant probablement plus de l'adaptation que de la compensation.

L'utilisation de cette distinction pour catégoriser les rééducations n'est pas très répandue dans la communauté scientifique de rééducation-réadaptation. Elle est issue notamment des modèles explicatifs des processus attentionnels. Il est indispensable de développer et parfaire les arguments scientifiques permettant de catégoriser les rééducations. Cette classification pourrait fournir un support théorique pertinent aux pratiques cliniques actuelles et futures. En effet, elle distingue les approches rééducatives « top-down » sollicitant les processus attentionnels conscients imposant une contribution active et volontaire du patient dans sa rééducation, des approches rééducatives « bottom-up » impliquant un traitement perceptif automatique sans charge attentionnelle consciente supplémentaire. En rééducation neurologique, les troubles cognitifs sont fréquemment associés. Ils réduisent la capacité attentionnelle des patients, donc leur implication dans la rééducation. Et certainement l'efficacité de celle-ci. Par ailleurs, le patient n'a pas toujours conscience de ses déficits. Cela peut être le cas de certains des troubles posturaux et l'équilibre. En prenant en compte les caractéristiques des déficits, le cadre théorique relatif aux processus « bottom-up » et « top-down » permettrait une plus grande adaptation des rééducations aux troubles du patients.

L'objectif d'efficacité dans les essais cliniques doit s'accompagner d'une recherche des mécanismes d'action des interventions. C'est ainsi qu'a été conçu l'essai clinique « PEQUIE ».

5.3. VERS UN MODELE EXPLICATIF DE L'ASYMETRIE D'APPUI ET DE L'INSTABILITE POSTURALE

Les résultats de l'étude transversale présentée en parties 3.2.2 et 3.2.3 contribuent à la compréhension des déterminants de l'asymétrie d'appui et de l'instabilité posturale après un AVC. L'objectif a été d'étudier les relations entre ces troubles posturaux et les cadres référentiels spatiaux mais également avec les différentes formes de négligence spatiale unilatérale, chez des patients au stade subaigu d'un AVC droit et présentant majoritairement une asymétrie d'appui vers le membre non-parétique.

En ce qui concerne l'asymétrie d'appui, les résultats montrent une contribution différente des deux cadres référentiels spatiaux égocentrés que sont l'axe corporel longitudinal et le droit devant manuel. Le premier représente la direction longitudinale du plan sagittal médian (rotation autour de l'axe antéropostérieur dans le plan frontal) alors que le second représente la direction horizontale de ce même plan médian (rotation autour de l'axe longitudinal dans le plan horizontal). Alors que la déviation de l'axe corporel longitudinal était associée avec l'asymétrie d'appui en condition yeux fermés, il n'y avait pas d'association statistique avec le droit devant quel que soit la condition visuelle. L'asymétrie d'appui ne serait donc influencée que par un seul deux cadres référentiels spatiaux égocentrés, l'axe corporel longitudinal. Seule la dimension de l'espace définie par l'orientation de l'axe longitudinal dans le plan frontal apparaît contributive pour expliquer l'asymétrie d'appui ipsilésionnel après AVC droit.

L'autre résultat de ce travail réside dans la démonstration d'une interaction entre la négligence comportementale et l'orientation de l'axe corporel longitudinal sur l'asymétrie d'appui, en condition yeux fermés. L'influence de ce cadre référentiel spatial égocentré sur l'asymétrie d'appui apparaît modulée par l'intensité de la négligence comportementale. Cette dernière concernent à la fois l'espace personnel et extra-personnel. Dans le cadre de l'intégration multi-sensorielle pour construire une représentation spatiale, il semblerait qu'une forme de concurrence ou d'influence conjointe entre plusieurs déficits de la cognition spatiale s'opère et détermine l'asymétrie d'appui.

Ces résultats s'inscrivent dans les hypothèses développées dans la revue narrative de la littérature sur la relation entre la négligence spatiale unilatérale et les troubles posturaux et de l'équilibre après AVC (partie 3.2.1) : Expression conjointe des déficits de la cognition spatiale ou dépendance de l'un sur l'autre.[46] La proximité des structures cérébrales impliquées dans les perturbations des cadres référentiels spatiaux et la négligence spatiale unilatérale, mais aussi leurs connexions fonctionnelles suggèrent qu'une atteinte simultanée de ces aires cérébrales puisse contribuer aux troubles posturaux et de l'équilibre.[194,275–277] Le caractère plus polymorphe de la négligence spatiale unilatérale (définie comme un biais comportemental ipsilésionnel et un défaut de conscience de l'hémi-espace controlésionnel, résultant d'un déficit d'orientation de l'attention dans l'espace opposé à la lésion et d'une altération de l'exploration et/ou de la construction de l'espace de représentation mentale) touchant différents espaces (personnel, extra-personnel et représenté) plaide en faveur d'une dépendance des perturbations des cadres référentiels spatiaux à celle-ci, qui les engloberait.[14,278]

Cette interaction entre la déviation de l'axe corporel longitudinal dans le plan frontal et la négligence spatiale unilatérale s'exprimant plutôt dans le plan horizontal, renforce l'hypothèse d'une représentation tridimensionnelle de l'espace nécessaire à l'action et au contrôle postural.[279,280]

L'autre apport de l'étude présentée en parties 3.2.2 et 3.2.3 a été de mettre en évidence que les perturbations des cadres référentiels spatiaux égocentrés et la négligence spatiale unilatérale ne semblent pas contribuer à l'instabilité posturale, quel que soit la condition d'ouverture des yeux. Ces résultats contrastent avec Genthon *et al.* (voir la revue narrative de la littérature en partie 3.2.1), retrouvant une association entre la négligence comportementale et l'instabilité posturale.[139] A l'inverse, les déficits sensori-moteurs contribueraient à ce trouble postural. De nos résultats, il apparaît ainsi que l'instabilité posturale relèverait plutôt de déficits sensori-moteurs et que l'asymétrie d'appui relèverait en partie de déficits représentationnels.

Il est important de garder à l'esprit que les résultats de l'étude transversale présentée en parties 3.2.2 et 3.2.3 concernaient un sous-groupe de patients présentant un AVC droit

(n=86) et une asymétrie d'appui moyenne prononcée (68.4% du poids du corps sur le membre inférieur non-parétique) avec un retentissement fonctionnel (score médian sur la « Berg Balance Scale » de 38/56). Cette étude contribue à la compréhension des mécanismes d'asymétrie d'appui et d'instabilité posturale dans une sous-population de patients AVC droit. Cependant, le fait que les modèles multivariés ne parviennent pas à expliquer la totalité de la variance de l'asymétrie d'appui ou de l'instabilité posturale pourrait être du à la relative homogénéité des participants, notamment en ce qui concerne le latéralité de la lésion et la distribution de l'appui. La conduite d'une étude observationnelle longitudinale avec l'inclusion de tous les patients après AVC sus-tensoriels quel que soit leur caractéristique posturaux paraît pertinente. Elle pourrait comprendre une évaluation plus poussée et précise des déficits moteurs et sensitifs afin d'évaluer plus finement leur contribution dans les troubles posturaux, à l'image de ce qui a été fait pour la négligence spatiale unilatérale.

Sur la base du cadre théorique « bottom-up » « top-down » proposé précédemment et des résultats présentés ici, il paraît légitime et pertinent de recourir à des rééducations basées sur une approche « bottom-up » pour réduire l'asymétrie d'appui. Ces approches seraient plus à même d'agir sur les déficits représentationnels peu ou pas accessibles à la conscience du patient. Tel est l'objectif du protocole d'essai clinique contrôlé randomisé « PEQUIE », actuellement en cours de recrutement. Afin d'améliorer l'instabilité posturale, les deux types d'approches « bottom-up » et « top-down » sembleraient pertinentes sur le plan théorique en agissant sur les déficits sensori-moteurs impliqués dans ce trouble postural (sous réserve que ces derniers soient bien la cible des rééducations).

Sur la base de la littérature scientifique (détaillée dans le sous-chapitre 2.2) et des résultats présentés dans cette thèse, il peut être proposé le schéma simplifié suivant afin d'expliquer l'instabilité posturale et l'asymétrie d'appui consécutives à un AVC :

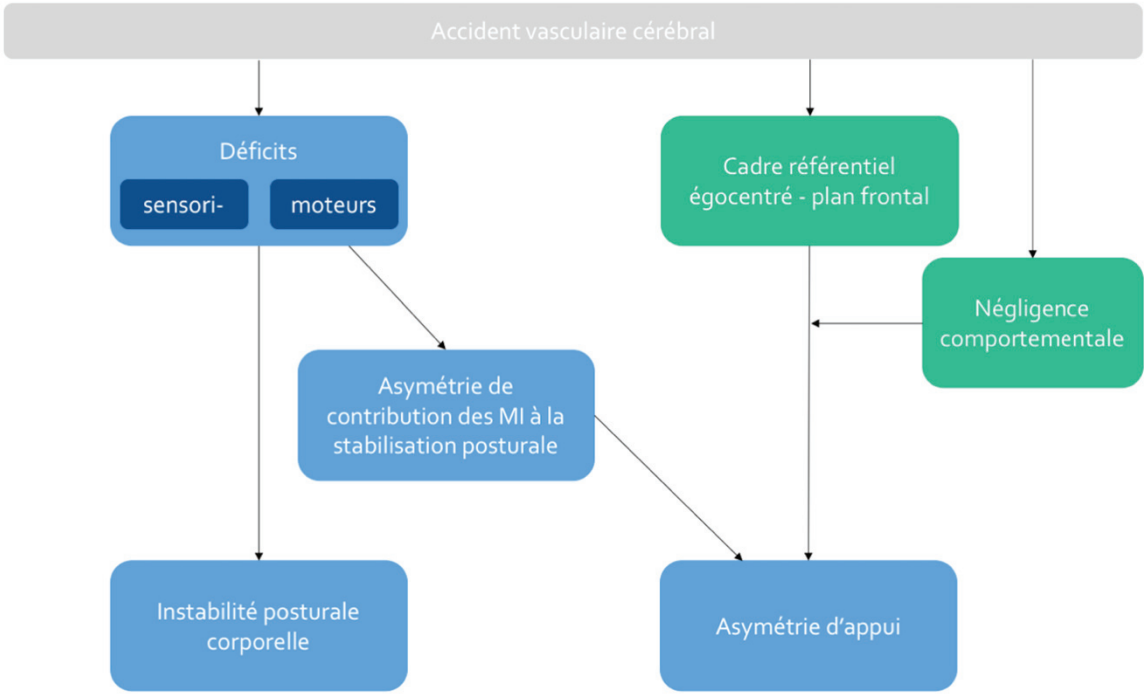


Figure 20. Proposition de schéma simplifié pour expliquer l'instabilité posturale et l'asymétrie d'appui après AVC

5.4. L'ADAPTATION PRISMATIQUE

Dans l'essai clinique contrôlé randomisé « PEQUIE », l'hypothèse est que l'adaptation prismatique améliorerait les troubles de l'équilibre et de la posture des patients, résultant d'un effet « bottom-up » de l'adaptation prismatique sur les cadres référentiels spatiaux égocentrés. Celle-ci s'appuie sur les résultats de l'étude pilote qui a montré une amélioration de l'équilibre et une réduction de l'asymétrie d'appui en parallèle d'un décalage du droit devant manuel vers la gauche 7 jours après 10 séances consécutives d'adaptation prismatique déviant l'axe optique de 10 degrés vers la droite, chez 6 patients avec lésion droite au stade chronique.

Le choix de l'équilibre comme objectif principal s'inscrit dans une démarche d'amélioration fonctionnelle des patients après AVC. Par ailleurs, l'intrication complexe de différents facteurs de l'asymétrie d'appui, dont certains sont peu ou mal connus, justifie que ce dernier soit considéré comme un critère de jugement secondaire. Plus largement, l'amélioration des troubles posturaux est considérée comme un des objectifs secondaires de l'essai clinique. De plus, ils constituent des déficits de fonctions contrairement à l'équilibre qui

est une limitation d'activité sur la classification internationale du fonctionnement et du handicap, et de pertinence clinique plus importante.

En cas de résultats favorables, l'adaptation prismatique viendrait s'ajouter à la rééducation par tache orientée associée avec une rééducation musculo-squelettique et/ou un entrainement cardio-respiratoire comme rééducation efficace pour améliorer l'équilibre des patients après AVC. Ce serait une rééducation complémentaire de l'entrainement par tache orientée. Alors que cette dernière est basée, en autre, sur des approches « top-down » requérant la participation active et volontaire du patient, l'adaptation prismatique ne nécessite pas un niveau de conscience et de participation élevé. La charge attentionnelle réduite rend ce type de rééducation moins laborieux pour le patient.[235] L'adaptation prismatique, au même titre que les autres manipulations sensorielles (vibrations cervicales par exemple) serait une approche complémentaire diversifiant la palette des rééducations dans un objectif de personnalisation de la rééducation des patients.

Outre le bénéfique clinique que pourrait apporter l'adaptation prismatique aux patients, l'intérêt de son utilisation dans un essai clinique sur la posture réside dans la relative solidité du cadre théorique supportant cette intervention. Alors que les effets cliniques de l'adaptation prismatique sont variables en intensité sur les manifestations cliniques de la négligence spatiale unilatérale, son cadre théorique relativement bien étayé contribue à une meilleure compréhension des mécanismes physiopathologiques sous-tendant les déficits et limitations d'activité. Contrairement à d'autres rééducations au cadre théorique moins connu.

Il sera intéressant de comparer les effets éventuels de l'adaptation prismatique sur l'équilibre et sur chacun des troubles posturaux (asymétrie d'appui, instabilité posturale et latéropulsion) mais aussi sur les cadres référentiels spatiaux égocentrés. Ces résultats futurs pourraient améliorer la compréhension des relations entre les troubles de l'équilibre et les troubles posturaux, mais également l'influence des cadres référentiels spatiaux sur ces derniers, dans cette population de patients AVC droits chroniques asymétriques. L'étude neuro-anatomique ancillaire aura pour but d'identifier les réseaux et régions cérébrales susceptibles d'expliquer les potentiels effets de l'adaptation prismatique sur les troubles posturaux et de l'équilibre.

6. CONCLUSION

La première partie de ce travail de recherche a eu pour objectif de déterminer les effets des rééducations sur les troubles de la posture et de l'équilibre et leur niveau de preuve, mais également de contribuer à améliorer la compréhension des mécanismes d'action des rééducations.

Une évaluation de l'ensemble des rééducations a mis en évidence l'efficacité (globale) de celles-ci, mais aussi l'efficacité de certaines approches comme l'entrainement par tache orientée combiné à un travail musculo-squelettique et/ou cardio-respiratoire sur l'équilibre. Une rééducation multimodale et diversifiée ciblant à la fois la commande centrale et l'effecteur périphérique, avec une progression selon les principes de l'apprentissage moteur, améliorerait l'équilibre des patients après un AVC, conformément au modèle théorique du contrôle postural.

Pour autant, il apparaît que les effets sont limités en raison notamment de la faiblesse méthodologique des études et de l'hétérogénéité statistique. La diversité des interventions, de leurs modalités d'application, ainsi que l'hétérogénéité des caractéristiques cliniques des participants ont conduit à limiter l'interprétation des effets et à réduire le niveau de preuve considéré.

Par ailleurs, la nature des effets susceptibles d'être mis en œuvre par les rééducations reste incertaine. Ainsi, l'effet bénéfique généralement observé immédiatement après la rééducation mais sans effet à long-terme sur les troubles posturaux et de l'équilibre, pourrait suggérer un effet de compensation plutôt que de récupération vraie.

La rééducation des troubles de la posture et de l'équilibre souffrirait de ne pas s'appuyer suffisamment sur des modèles théoriques robustes. C'est dans cette optique qu'une méta-analyse des effets des rééducations selon leur approche « bottom-up » ou « top-down » sur les troubles de l'équilibre après AVC a été réalisée. Les résultats suggèrent un possible effet cumulatif des approches mixtes, susceptible de relever de mécanismes adaptatifs plutôt que compensatoires.

La seconde partie de ce travail de thèse a eu pour objectif de mieux comprendre les liens entre, d'une part, l'asymétrie d'appui et l'instabilité posturale, et, d'autre part, les déficits de la cognition spatiale après un AVC. Une étude transversale a ainsi été réalisée au moyen d'analyses multivariées reposant sur des modèles additifs généralisés chez des patients atteints d'un AVC droit subaigu.

La dimension de l'espace définie par l'orientation de l'axe corporel longitudinal dans le plan frontal (référence égocentrée) apparaît contributive pour expliquer l'asymétrie d'appui ipsilésionnel, selon une relation statistique non linéaire. Cette influence apparaît modulée par l'intensité de la négligence comportementale. Ces résultats peuvent être interprétés comme une forme de concurrence ou d'influence conjointe sur le comportement postural. Par ailleurs, il n'y avait pas d'association statistique avec le droit devant manuel, autre cadre référentiel égocentré selon la direction antéropostérieure dans le plan horizontal. Les déficits représentationnels semblent contribuer à l'asymétrie d'appui après AVC, en plus d'être une possible stratégie de compensation pour améliorer la stabilité.

En ce qui concerne l'instabilité posturale après AVC, les perturbations des cadres référentiels spatiaux égocentrés et la négligence spatiale unilatérale ne semblent pas y contribuer. A l'inverse, l'instabilité posturale semblerait déterminée par les déficits sensori-moteurs, comme la faiblesse motrice, la sensibilité profonde ou le déficit visuel.

Dans une démarche de recherche de rééducations efficaces et d'amélioration du cadre théorique, ce travail de thèse s'est intéressé aux effets induits par l'adaptation prismatique. Une étude interventionnelle préliminaire a montré une amélioration de l'équilibre, une réduction de l'asymétrie d'appui et de la latéropulsion conjointement à un décalage du droit devant manuel vers la gauche après adaptation prismatique chez des patients AVC droit chroniques. Ces résultats suggèrent un potentiel effet « bottom-up » de l'adaptation prismatique sur les déficits de la cognition spatiale à l'origine d'une amélioration secondaire des troubles posturaux, conformément au modèle théorique du contrôle postural. Sur la base de ces résultats favorables mais préliminaires, un essai clinique contrôlé randomisé est conduit actuellement, et visera à répondre à un objectif d'efficacité clinique mais également de compréhension des mécanismes d'action de la technique et des déficits posturaux et représentationnels.

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ANNEXES

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TRAVAUX ISSUS DE LA THESE

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Hugues A, Di Marco J, Lunven M, Jacquin-Courtois S, Rossetti Y, Bonan I, Rode G. Long-lasting reduction in postural asymmetry by prism adaptation after right brain lesion without neglect. Cogn Process. 2015 Sep;16 Suppl 1:371-5.

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Chapitres d'ouvrage

Hugues A, Ferreux T, Yelnik A. « Rééducation de l'équilibre du patient cérébrolésé après AVC » dans Yelnik A et Herman P (dir.), L'équilibre en tous sens, Paris, Elsevier Masson, 2021. (sous presse)

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Hugues A. La rééducation par adaptation prismatique des troubles posturaux consécutifs à un AVC. Présentation de la technique et de ses effets. 5ieme Congrès Internationale Francophone des Etudiants en Physiothérapie et Kinésithérapie, France (Nancy), 19-20 Février 2016.

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Hugues A, Di Marco J, Janiaud P, Xue Y, Zhu J, Pires J, Khademi H, Rubio L, Hernandez Bernal P, Bahar Y, Charvat H, Szulc P, Ciumas C, Cucherat M, Bonan I, Gueyffier F, Rode G. Effects of physical therapies aiming directly or indirectly at the recovery of balance after stroke. A meta-analysis. 12th International Society of Physical and Rehabilitation Medicine world congress, Paris (France), 8-12 juillet 2018

Hugues A, Di Marco J, Janiaud P, Xue Y, Zhu J, Pires J, Khademi H, Rubio L, Hernandez Bernal P, Bahar Y, Charvat H, Szulc P, Ciumas C, Cucherat M, Bonan I, Gueyffier F, Rode G. Efficacité de la rééducation par thérapie physique sur la récupération de l'équilibre selon l'ancienneté de l'accident vasculaire cérébral : revue de la littérature et méta-analyse. 7ièmes Journées Francophones de Kinésithérapie, Montpellier (France), 14-16 février 2019

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Hugues A, Di Marco J, Cucherat M, Bonan I, Gueyffier F, Rode G. Limited evidence of physical therapy on balance after stroke: A systematic review and meta-analysis. 14th International Society of Physical and Rehabilitation Medicine world congress, Orlando (USA), 4-9 mars 2020

Hugues A, Di Marco J, Cucherat M, Bonan I, Gueyffier F, Rode G. Publication language and the estimate of effects of physical therapy on balance and postural control after stroke in meta-analyse of randomised controlled trials. 14th International Society of Physical and Rehabilitation Medicine world congress, Orlando (USA), 4-9 mars 2020

Hugues A, Di Marco J, Ribault S, Cucherat M, Gueyffier F, Bonan I, Rode G. Effects of physical therapy on balance and postural control after stroke based on top-down and bottom-up approaches: a subgroup meta-analysis and a network meta-analysis. 11th world congress for neurorehabilitation, Lyon (France), 7-11 octobre 2020

Hugues A, Di Marco J, Cucherat M, Gueyffier F, Bonan I, Rode G. Limited evidence of physical therapy on balance after stroke: A systematic review and meta-analysis. 11th world congress for neurorehabilitation, Lyon (France), 7-11 octobre 2020

Hugues A, Garrone C, Giannesini M, Fernandes Guerra Z, Nivesse N, Girard MO, Jacquin-Courtois S, Rode G, Mateo S. Virtual reality is effective in improving balance but not gait after stroke – an up-dated meta-analysis. 11th world congress for neurorehabilitation, Lyon (France), 7-11 octobre 2020

Pflieger A, Luauté J, **Hugues A**. Effects of rehabilitation on the prevention of respiratory complications such as atelectasis, lung infection and lung congestion in patients with cervical and thoracic spinal cord injury. 11th world congress for neurorehabilitation, Lyon (France), 7-11 octobre 2020

Hugues A, Di Marco J, Ribault S, Cucherat M, Gueyffier F, Bonan I, Rode G. Effets de la rééducation sur l'équilibre et la posture après un AVC en fonction des approches neurophysiologiques « top-down » et « bottom-up » : méta-analyse en sous-groupe et méta-analyse en réseau. 8iemes Journées Francophones de Kinésithérapie, Rennes (France), 26-29 mai 2021

MATERIEL SUPPLEMENTAIRE DE L'ARTICLE 2 – HUGUES *ET AL.*, 2019

S1 Table. Search strategy in databases

S1A Table. Search strategy in Pubmed – October 31, 2015

1	exercise movement techniques OR physical therapy modalities OR learning OR pract* OR train* OR rehabilitation* OR therapeutic* OR therapy OR therapies OR exercise* OR physiotherap* OR neurorehabilitation OR neurophysiological OR orthopaed* OR treatment OR approach* OR concept OR home rehabilitation OR self-guided program* OR fitness OR stretching OR sport OR program* OR movement OR protocol* OR intervention OR activit* OR regim* OR recovery
2	(occupational OR physical OR manual) AND (therapy OR therapies OR therapist OR therapeutic OR therapeutics)
3	#1 OR #2
4	posture OR equilibrium OR balance OR postural balance OR weight bearing OR weight shift OR lateropulsion OR pusher OR pushing OR postural imbalance OR postural asymmetry OR postural control OR postural stability OR postural instability OR postural perturbation OR postural disorders OR postural deficit OR postural trouble OR postural sway OR postural tilt OR postural shift OR body sway OR upright stance OR (weight AND (distribut* OR transfer*))
5	(cerebrovascular OR cerebro-vascular OR cerebral OR intracran* OR hemispheric) AND (accident OR hemorrhag* OR haemorrhag* OR infarct* OR ischemi* OR thrombotic OR thrombosis OR emboli* OR hematoma OR haematoma OR bleed OR damage OR lesion OR occlus*)
6	stroke OR poststroke OR post-stroke OR hemipleg* OR hemipar* OR paretic OR paresis OR CVA
7	(right OR left) AND brain AND (lesion OR damage)
8	#5 OR #6 OR #7
9	meta-analysis OR review* OR animal* OR child* OR cerebral pals* OR case-report OR traumatic brain injury
10	#3 AND #4 AND #8 NOT #9

S1B Table. Search strategy in Embase – October 31, 2015

1	'cerebrovascular accident'/exp OR 'brain ischemia'/exp OR 'hemiplegia'/exp OR 'hemiparesis'/exp OR 'brain infarction'/de OR 'brain hemorrhage'/de OR 'stroke' OR 'poststroke' OR 'post-stroke' OR cerebrovascular OR 'cerebro vascular' OR cerebral OR intracran* OR hemispheric AND (accident OR hemorrhag* OR haemorrhag* OR infarct* OR ischemi* OR thrombotic OR thrombosis OR emboli* OR hematoma OR haematoma OR bleed OR damage OR lesion OR occlus*) OR paretic OR paresis OR cva OR (right OR left AND brain AND (lesion OR damage))
2	'body equilibrium'/exp OR 'balance impairment'/exp OR 'weight bearing'/de OR 'weight shift' OR 'lateropulsion' OR 'pusher' OR 'pushing' OR 'abnormal posture'/exp OR 'postural asymmetry' OR 'postural control' OR 'postural stability' OR 'postural instability'OR 'postural perturbation' OR 'postural deficit' OR 'postural trouble' OR 'postural sway' OR 'postural tilt or postural shift' OR 'body posture'/exp OR 'body sway' OR 'upright stance' OR 'weight distribution' OR 'weight transfert'
3	'training'/exp OR 'rehabilitation medicine'/exp OR 'occupational therapy'/exp OR 'home rehabilitation'/exp OR 'home physiotherapy'/exp OR 'exercise' OR 'neurorehabilitation' OR 'neurophysiological' OR 'orthopaedic' OR 'therapy' OR 'treatment' OR 'approach' OR 'concept' OR 'physical medicine'/exp OR 'physical medicine' OR 'learning'/exp OR 'learning' OR pract* OR therapeutic* OR 'fitness' OR 'stretching' OR program* OR 'movement' OR protocol* OR 'intervention' OR activit* OR regim* OR 'recovery'
4	'meta-analysis' OR 'review' OR 'animal' OR 'children' OR 'cerebral palsy'
5	#1 AND #2 AND #3 NOT #4

S1C Table. Search strategy in Pubmed – January 14, 2019

1	exercise movement techniques OR physical therapy modalities OR learning OR pract* OR train* OR rehabilitation* OR therapeutic* OR therapy OR therapies OR exercise* OR physiotherap* OR neurorehabilitation OR neurophysiological OR orthopaed* OR treatment OR approach* OR concept OR home rehabilitation OR self-guided program* OR fitness OR stretching OR sport OR program* OR movement OR protocol* OR intervention OR activit* OR regim* OR recovery
2	(occupational OR physical OR manual) AND (therapy OR therapies OR therapist OR therapeutic OR therapeutics)
3	#1 OR #2
4	posture OR equilibrium OR balance OR postural balance OR weight bearing OR weight shift OR lateropulsion OR pusher OR pushing OR postural imbalance OR postural asymmetry OR postural control OR postural stability OR postural instability OR postural perturbation OR postural disorders OR postural deficit OR postural trouble OR postural sway OR postural tilt OR postural shift OR body sway OR upright stance OR (weight AND (distribut* OR transfer*))
5	(cerebrovascular OR cerebro-vascular OR cerebral OR intracran* OR hemispheric) AND (accident OR hemorrhag* OR haemorrhag* OR infarct* OR ischemi* OR thrombotic OR thrombosis OR emboli* OR hematoma OR haematoma OR bleed OR damage OR lesion OR occlus*)
6	stroke OR poststroke OR post-stroke OR hemipleg* OR hemipar* OR paretic OR paresis OR CVA
7	(right OR left) AND brain AND (lesion OR damage)
8	#5 OR #6 OR #7
9	Randomized Controlled Trial[Publication Type] OR randomized controlled trial[Publication Type] OR Randomised Controlled Trial[Publication Type] OR randomised controlled trial[Publication Type] OR randomized controlled trials as topic[MeSH Terms] OR randomized controlled trial OR randomised controlled trial OR RCT
10	meta-analysis OR review* OR animal* OR child* OR cerebral pals* OR case-report OR traumatic brain injury
11	#3 AND #4 AND #8 AND #9 NOT #10

S2 Table. Identification of studies included in the systematic review and meta-analysis

Author	Title	Publication	Year of publication	Issue	Volume	Pages
Allison, R; Dennett, R	Pilot randomized controlled trial to assess the impact of additional supported standing practice on functional ability post stroke	Clinical Rehabilitation	2007	7	21	614-619
Arabzadeh, S; Goljaryan, S; Salahzadeh, Z; et al.	Effects of a Task-Oriented Exercise Program on Balance in Patients with Hemiplegia Following Stroke	Iranian Red Crescent Medical Journal	2016	1	20	NA
Askim, T; Morkved, S; Engen, A; et al.	Effects of a community-based intensive motor training program combined with early supported discharge after treatment in a comprehensive stroke unit: a randomized, controlled trial	Stroke	2010	8	41	1697-1703
Au-Yeung, S; Hui-Chan, C; Tang, J	Short-form Tai Chi Improves Standing Balance of People With Chronic Stroke	Neurorehabilitation and Neural Repair	2009	5	23	515-522
Bae, YH; Kim, HG; Min, KS; et al.	Effects of Lower-Leg Kinesiology Taping on Balance Ability in Stroke Patients with Foot Drop	Evidence-Based Complementary and Alternative Medicine	2015	NA	NA	NA
Barcala, L; Colella, F; Araujo, MC; et al.	Análise do equilíbrio em pacientes hemiparéticos após o treino com o programa Wii Fit	Fisioterapia em Movimento	2011	2	24	337-343
Brogardh, C; Flansbjer, UB; Lexell, J	No specific effect of whole-body vibration training in chronic stroke: a double-blind randomized controlled study	Archives of Physical Medicine and Rehabilitation	2012	2	93	253-258
Bunketorp-Käll, L; Lundgren-Nilsson, Å; Samuelsson, H; et al.	Long-Term Improvements After Multimodal Rehabilitation in Late Phase After Stroke: A Randomized Controlled Trial	Stroke	2017	7	48	1916-1924
Büyükavcı, R	The impact of additional trunk balance exercises on balance, functional condition and ambulation in early stroke patients: Randomized controlled trial	Türkiye Fiziksel Tıp ve Rehabilitasyon Dergisi	2016	3	62	248-256
Büyükvural SS, Özbudak DS, Ekiz T, Özgirgin N.	Effects of the bilateral isokinetic strengthening training on functional parameters, gait, and the quality of life in patients with stroke	International Journal of Clinical and Experimental Medicine	2015	9	8	16871-16879
Cabanas-Valdés, R; Bagur-Calafat, C; Girabent-Farrés, M; et al.	The effect of additional core stability exercises on improving dynamic sitting balance and trunk control for subacute stroke patients: a randomized controlled trial	Clinical Rehabilitation	2016	10	30	1024-1033
Chan, KS; Liu, CW; Chen, TW; et al.	Effects of a single session of whole body vibration on ankle plantarflexion spasticity and gait performance in patients with chronic stroke: a randomized controlled trial	Clinical Rehabilitation	2012	12	26	1087-1095

Chen, CH; Lin, KH; Lu, TW; et al.	Immediate effect of lateral-wedged insole on stance and ambulation after stroke:	American Journal of Physical Medicine & Rehabilitation	2010	1	89	48-55
Chen, CL; Chen, FF; Lin, CH; et al.	Effect of anterior ankle-foot orthoses on weight shift in persons with stroke	Archives of Physical Medicine and Rehabilitation	2015	10	96	1795-1801
Chen, D; Yan, T; Li, G; et al.	Functional electrical stimulation based on a working pattern influences function of lower extremity in subjects with early stroke and effects on diffusion tensor imaging: a randomized controlled trial	Zhonghua Yi Xue Za Zhi	2014	37	94	2886-2892
Chen, IC; Cheng, PT; Chen, CL; et al.	Effects of balance training on hemiplegic stroke patients	Chang Gung Medical Journal	2002	9	25	583-590
Chen, JC; Lin, CH; Wei, YC; et al.	Facilitation of motor and balance recovery by thermal intervention for the paretic lower limb of acute stroke: a single-blind randomized clinical trial	Clinical Rehabilitation	2011	9	25	823-832
Chen, T	Effects of Martial Arts on Recovery of Motor Function and Nerve Excitability of Stroke Patients	NeuroQuantology	2018	6	16	894-898
Chern, JS; Chang, HS; Lung, CW; et al.	Static ankle-foot orthosis improves static balance and gait functions in hemiplegic patients after stroke	35th Annual International Conference of the IEEE EMBS	2013	NA	NA	5009-5012
Cho, HY; In, TS; Cho, KH; Song, CH	A single trial of transcutaneous electrical nerve stimulation (TENS) improves spasticity and balance in patients with chronic stroke	The Tohoku Journal of Experimental Medicine	2013	3	229	187-193
Cho, KH; Lee, KJ; Song, CH	Virtual-reality balance training with a video-game system improves dynamic balance in chronic stroke patients	The Tohoku Journal of Experimental Medicine	2012	1	228	69-74
Cho, MK; Kim, JH; Chung, Y; Hwang, S	Treadmill gait training combined with functional electrical stimulation on hip abductor and ankle dorsiflexor muscles for chronic hemiparesis	Gait & Posture	2015	1	42	73-78
Choi, HS; Shin, WS; Bang, DH; et al.	Effects of Game-Based Constraint-Induced Movement Therapy on Balance in Patients with Stroke: A Single-Blind Randomized Controlled Trial	American Journal of Physical Medicine & Rehabilitation	2017	3	96	184-190
Chu, JM; Bao, YH; Zhu, M	[Effects of Acupuncture Intervention Combined with Rehabilitation on Standing-balance-walking Ability in Stroke Patients]	Zhen Ci Yan Jiu (Acupuncture Research)	2015	6	40	474-478
Chung, Y; Kim, JH; Cha, Y; Hwang, S	Therapeutic effect of functional electrical stimulation-triggered gait training corresponding gait cycle for stroke	Gait & Posture	2014	3	40	471-475
Dault, MC; de Haart, M; Geurts, ACH; Arts, IMP; Nienhuis, B	Effects of visual center of pressure feedback on postural control in young and elderly healthy adults and in stroke patients	Human Movement Science	2003	3	22	221-236

Dujović, SD; Malešević, J; Malešević, N; et al.	Novel multi-pad functional electrical stimulation in stroke patients: A single-blind randomized study	NeuroRehabilitation	2017	4	41	791-800
Duncan, P; Richards, L; Wallace, D; et al.	A randomized, controlled pilot study of a home-based exercise program for individuals with mild and moderate stroke	Stroke	1998	10	29	2055-2060
Duncan, P; Studenski, S; Richards, L; et al.	Randomized clinical trial of therapeutic exercise in subacute stroke	Stroke	2003	9	34	2173-2180
Erbil, D; Tugba, G; Murat, TH; et al.	Effects of robot-assisted gait training in chronic stroke patients treated by botulinum toxin-a: A pivotal study	Physiotherapy Research International	2018	3	23	e1718
Fernandez-Gonzalo, R; Fernandez-Gonzalo, S; Turon, M; et al.	Muscle, functional and cognitive adaptations after flywheel resistance training in stroke patients: a pilot randomized controlled trial	Journal of NeuroEngineering and Rehabilitation	2016	1	13	13-37
Ferreira, LAB; Galli, M; Lazzari, RD; et al.	Stabilometric analysis of the effect of postural insoles on static balance in patients with hemiparesis: A randomized, controlled, clinical trial	Journal of Bodywork and Movement Therapies	2017	2	21	290-296
Fritz, SL; Peters, DM; Merlo, AM; Donley, J	Active video-Gaming effects on balance and mobility in individuals with chronic stroke: a randomized controlled trial	Topics in Stroke Rehabilitation	2013	3	20	218-225
Furnari, A; Calabrò, RS; Gervasi, G; et al.	Is hydrokinesitherapy effective on gait and balance in patients with stroke? A clinical and baropodometric investigation	Brain Injury	2014	8	28	1109-1114
Geiger, RA; Allen, JB; O'Keefe, J; et al.	Balance and Mobility Following Stroke: Effects of Physical Therapy Interventions With and Without Biofeedback/Forceplate Training	Physical Therapy	2001	4	81	995-1005
Ghanjal, A; Torkaman, G; Ghabaee, M; Ebrahimi,l; Motoqhey, M	Effect of action observation and imitation on improving the functional activities indices in hemiplegic patients based on mirror neurons theory	J Mazandaran Univ Med Sci	2014	118	24	136-150
Globas, C; Becker, C; Cerny, J; et al.	Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial	Neurorehabilitation and Neural Repair	2012	1	26	85-95
Goliwąs, M; Kocur, P; Wiernicka, M; et al.	Effect of sensorimotor foot stimulation on the body postural, function and load of the lower limb in patients in the late phase after stroke	Fizjoterapia Polska	2017	2	17	24-35
Han,Y; Im, SH; Kim, BR; et al.	Robot-assisted gait training improves brachial–ankle pulse wave velocity and peak aerobic capacity in subacute stroke patients with totally dependent ambulation: Randomized controlled trial	Medicine	2016	41	95	NA
Hart, J; Kanner, H; Gilboa-Mayo, R; et al.	Tai Chi Chuan practice in community-dwelling persons after stroke	International Journal of Rehabilitation Research.	2004	4	27	303-304
Heller, F; Beuret-Blanquart, F; Weber, J	Barobiofeedback et rééducation de la marche de l'hémiplégique	Annales de Réadaptation et de Médecine Physique	2005	4	48	187-195

Hollands, KL; Pelton, TA; Wimperis, A; et al.	Feasibility and Preliminary Efficacy of Visual Cue Training to Improve Adaptability of Walking after Stroke: Multi-Centre, Single-Blind Randomised Control Pilot Trial	PLOS ONE	2015	10	10	e0139261
Holmgren, E; Lindström, B; Gosman-Hedström, G; et al.	What is the benefit of a high intensive exercise program? A randomized controlled trial	Advances in Physiotherapy	2010	3	12	115-124
Hosseini, SA; Fallahpour, M; Sayadi, M; et al.	The impact of mental practice on stroke patients' postural balance	Journal of the Neurological Sciences	2012	1-2	322	263-267
Howe, TE; Taylor, I; Finn, P; Jones, H	Lateral weight transference exercises following acute stroke: a preliminary study of clinical effectiveness	Clinical Rehabilitation	2005	1	19	45-53
Hsieh, HC	Training by Using an Adaptive Foot Switch and Video Games to Improve Balance and Mobility Following Stroke: A Randomised Controlled Trial	Brain Impairment	2019	1	20	16-23
Hsu, HW; Lee, CL; Hsu, MJ; et al.	Effects of noxious versus innocuous thermal stimulation on lower extremity motor recovery 3 months after stroke	Archives of Physical Medicine and Rehabilitation	2013	4	94	633-641
Huh, JS; Lee, YS; Kim, CH; et al.	Effects of Balance Control Training on Functional Outcomes in Subacute Hemiparetic Stroke Patients	Annals of Rehabilitation Medicine	2015	6	39	995
Hung, JW; Yu, MY; Chang, KC; et al.	Feasibility of Using Tetrax Biofeedback Video Games for Balance Training in Patients With Chronic Hemiplegic Stroke	PM&R	2016	10	8	962-970
Hwang, DY; Lee, HJ; Lee, GC; Lee, SM	Treadmill training with tilt sensor functional electrical stimulation for improving balance, gait, and muscle architecture of tibialis anterior of survivors with chronic stroke: A randomized controlled trial	Technology and Health Care	2015	4	23	443-452
Immink, MA; Hillier, S; Petkov, J	Randomized controlled trial of yoga for chronic poststroke hemiparesis: motor function, mental health, and quality of life outcomes	Topics in Stroke Rehabilitation	2014	3	21	256-271
In, T; Lee, K; Song, C	Virtual Reality Reflection Therapy Improves Balance and Gait in Patients with Chronic Stroke: Randomized Controlled Trials	Medical Science Monitor	2016	NA	22	4046-4053
Janssen, TW; Beltman, JM; Elich, P; et al.	Effects of electric stimulation, assisted cycling training in people with chronic stroke	Archives of Physical Medicine and Rehabilitation	2008	3	89	463-469
Jung, J; Choi, W; Lee, S	Trunk stabilization training using visual feedback on an unstable surface improves balance and trunk stability of chronic stroke patients	Medical Science and Technology	2015	NA	56	37-42
Jung, KS; In, TS; Cho, HY	Effects of sit-to-stand training combined with transcutaneous electrical stimulation on spasticity, muscle strength and balance ability in patients with stroke: A randomized controlled study	Gait & Posture	2017	NA	54	183-187

Kamps, A; Schule, K	Cyclic movement training of the lower limb in stroke rehabilitation	Neurologie & Rehabilitation	2005	3	11	S1-S12
Karasu, A; Batur, E; Karataş, G	Effectiveness of Wii-based rehabilitation in stroke: A randomized controlled study	Journal of Rehabilitation Medicine	2018	5	50	406-412
Katz-Leurer, M; Sender, I; Keren, O; Dvir, Z	The influence of early cycling training on balance in stroke patients at the subacute stage. Results of a preliminary trial	Clinical Rehabilitation	2006	5	20	398-405
Khumsapsiri, N; Siriphorn, A; Pooranawatthanakul, K; et al.	Training using a new multidirectional reach tool improves balance in individuals with stroke	Physiotherapy Research International	2018	2	23	NA
Kim, DH; Yi, TI; Kim, JS; et al.	The effects of isokinetic strengthening of trunk muscles on balance in hemiplegic patients	J Korean Acad Rehab Med	2008	3	32	280-284
Kim, JC; Lee, HM	The Effect of Action Observation Training on Balance and Sit to Walk in Chronic Stroke: A Crossover Randomized Controlled Trial	Journal of Motor Behavior	2018	4	50	373-380
Kim, JH; Jang, SH; Kim, CS; et al.	Use of virtual reality to enhance balance and ambulation in chronic stroke: A double-blind, randomized controlled Study:	American Journal of Physical Medicine & Rehabilitation	2009	9	88	693-701
Kim, JY; Kim, DY; Chun, MH; et al.	Effects of robot-(Morning Walk®) assisted gait training for patients after stroke: a randomized controlled trial	Clinical Rehabilitation	2019	3	33	516-523
Kim, SL; Lee, BH	The effects of posterior talar glide and dorsiflexion of the ankle plus mobilization with movement on balance and gait function in patient with chronic stroke: A randomized controlled trial	Journal of Neurosciences in Rural Practice	2018	1	9	61
Kim, YH; Shin, JE; Kim, DH; et al.	Effect of dynamic balance training using visual biofeedback of center of pressure in patients with stroke	J Korean Acad Rehabil Med.	2004	6	28	515-522
Kim, YM; Chun, MH; Kang, SH; Ahn, WH	The effect of neuromuscular electrical stimulation on trunk control in hemiparetic stroke patients	J Korean Acad Rehabil Med.	2009	3	33	265-270
Kılınç, M; Avcu, F; Onursal, O; et al.	The effects of Bobath-based trunk exercises on trunk control, functional capacity, balance, and gait: a pilot randomized controlled trial	Topics in Stroke Rehabilitation	2016	1	23	50-58
Knox, M; Stewart, A; Richards, CL	Six hours of task-oriented training optimizes walking competency post stroke: a randomized controlled trial in the public health-care system of South Africa	Clinical Rehabilitation	2018	8	32	1057-1068
Kunkel, D; Pickering, RM; Burnett, M; et al.	Functional electrical stimulation with exercises for standing balance and weight transfer in acute stroke patients: a Feasibility randomized controlled trial	Neuromodulation: Technology at the Neural Interface	2013	2	16	168-177
Kwong, PWH; Ng, GYF; Chung, RCK; et al.	Bilateral Transcutaneous Electrical Nerve Stimulation Improves Lower-Limb Motor Function in Subjects With Chronic Stroke: A Randomized Controlled Trial	Journal of the American Heart Association	2018	4	7	NA

Langhammer, B; Stanghelle, JK; Lindmark, B	An evaluation of two different exercise regimes during the first year following stroke: A randomised controlled trial	Physiotherapy Theory and Practice	2009	2	25	55-68
Lau, RWK; Yip, SP; Pang, MYC	Whole-body vibration has no effect on neuromotor function and falls in chronic stroke:	Medicine & Science in Sports & Exercise	2012	8	44	1409-1418
Laufer, Y	The effect of walking aids on balance and weight-bearing patterns of patients with hemiparesis in various stance positions	Physical Therapy	2003	2	83	112-122
Lee, CH; Kim, Y; Lee, BH	Augmented reality-based postural control training improves gait function in patients with stroke: Randomized controlled trial	Hong Kong Physiotherapy Journal	2014	2	32	51-57
Lee, DG; Lee, GC; Jeong, JS	Mirror Therapy with Neuromuscular Electrical Stimulation for improving motor function of stroke survivors: A pilot randomized clinical study	Technology and Health Care	2016	4	24	503-511
Lee, HJ; Kang, TW; Kim, BR	Effects of diaphragm and deep abdominal muscle exercise on walking and balance ability in patients with hemiplegia due to stroke	Journal of Exercise Rehabilitation	2018	4	14	648-653
Lee, MM; Lee, KJ; Song, CH	Game-Based Virtual Reality Canoe Paddling Training to Improve Postural Balance and Upper Extremity Function: A Preliminary Randomized Controlled Study of 30 Patients with Subacute Stroke	Medical Science Monitor	2018	NA	24	2590-2598
Lee, NK; Kwon, WJ; Son, SM; et al.	The effects of closed and open kinetic chain exercises on lower limb muscle activity and balance in stroke survivors	NeuroRehabilitation	2013	1	NA	177-183
Lee, SH; Byun, SD; Kim, CH; et al.	Feasibility and effects of newly developed balance control trainer for mobility and balance in chronic stroke patients: a randomized controlled trial	Annals of Rehabilitation Medicine	2012	4	36	521
Lee, SW; Cho, KH; Lee, WH	Effect of a local vibration stimulus training programme on postural sway and gait in chronic stroke patients: a randomized controlled trial	Clinical Rehabilitation	2013	10	27	921-931
Liang, CC; Hsieh, TC; Lin, CH; et al.	Effectiveness of thermal stimulation for the moderately to severely paretic leg after stroke: serial changes at one-year follow-up	Archives of Physical Medicine and Rehabilitation	2012	11	93	1903-1910
Lin, Q; Chen, A; Cheng, K	Effects of acupuncture on motor function, balance function and activities of daily living of patients with Stroke	Chinese Journal of Rehabilitation Medicine	2015	9	30	898-901 and 906
Lindvall, MA; Forsberg, A	Body awareness therapy in persons with stroke: a pilot randomized controlled trial	Clinical Rehabilitation	2014	12	28	1180-1188
Lisinski, P; Huber, J; Gajewska, E; et al.	The body balance training effect on improvement of motor functions in paretic extremities in patients after stroke. A randomized, single blinded trial	Clinical Neurology and Neurosurgery	2012	1	114	31-36

Liu-Ambrose, T; Eng, JJ	Exercise Training and Recreational Activities to Promote Executive Functions in Chronic Stroke: A Proof-of-concept Study	Journal of Stroke and Cerebrovascular Diseases	2015	1	24	130-137
Lu, CL; Yu, B; Basford, JR; et al.	Influences of cane length on the stability of stroke patients	Journal of Rehabilitation Research and Development	1997	1	34	91-100
Lynch, EA; Hillier, SL; Stiller, K; et al.	Sensory retraining of the lower limb after acute stroke: a randomized controlled pilot trial	Archives of Physical Medicine and Rehabilitation	2007	9	88	1101-1107
Marin, PJ; Ferrero, CM; Menéndez, H; et al.	Effects of whole-body vibration on muscle architecture, muscle strength, and balance in stroke patients: a randomized controlled trial	American Journal of Physical Medicine & Rehabilitation	2013	10	92	881-888
Merkert, J; Butz, S; Nieczaj, R; et al.	Combined whole body vibration and balance training using Vibrosphere: Improvement of trunk stability, muscle tone, and postural control in stroke patients during early geriatric rehabilitation	Zeitschrift fur Gerontologie und Geriatrie	2011	4	44	256-261
Milczarek, JJ; Kirby, RL; Harrison, ER; MacLeod, DA	Standard and four-footed canes: their effect on the standing balance of patients with hemiparesis	Archives of Physical Medicine and Rehabilitation	1993	3	74	281-285
Mojica, JA; Nakamura, R; Kobayashi, T; et al..	Effect of ankle-foot orthosis (AFO) on body sway and walking capacity of hemiparetic stroke patients	The Tohoku Journal of Experimental Medicine	1988	4	156	395-401
Moore, JL; Roth, EJ; Killian, C; Hornby, TG	Locomotor Training Improves Daily Stepping Activity and Gait Efficiency in Individuals Poststroke Who Have Reached a “Plateau" in Recovery	Stroke	2010	1	41	129-135
Morioka, S; Yagi, F	Effects of perceptual learning exercises on standing balance using a hardness discrimination task in hemiplegic patients following stroke: a randomized controlled pilot trial	Clinical Rehabilitation	2003	6	17	600-607
Mudie, MH; Winzeler-Mercay, U; Radwan, S; Lee, L	Training symmetry of weight distribution after stroke: a randomized controlled pilot study comparing task-related reach, Bobath and feedback training approaches	Clinical Rehabilitation	2002	6	16	582-592
Nadeau, SE; Wu, SS; Dobkin, Bruce H; et al.	Effects of task-specific and impairment-based training compared with usual care on functional walking ability after inpatient stroke rehabilitation: LEAPS trial	Neurorehabilitation and Neural Repair	2013	4	27	370-380
Ng, SSM; Lai, CWK; Tang, MWS; et al.	Cutaneous electrical stimulation to improve balance performance in patients with sub-acute stroke: a randomised controlled trial	Hong Kong medical journal	2016	Suppl 2	22	S33-6
Nikamp, CDM; Buurke, JH; van der Palen, J; et al.	Early or delayed provision of an ankle-foot orthosis in patients with acute and subacute stroke: a randomized controlled trial	Clinical Rehabilitation	2017	6	31	798-808

Noh, DK; Lim, JY; Shin, HI; et al.	The effect of aquatic therapy on postural balance and muscle strength in stroke survivors - a randomized controlled pilot trial	Clinical Rehabilitation	2008	10-11	22	966-976
Ordahan, B; Karahan, AY; Basaran, A; et al.	Impact of exercises administered to stroke patients with balance trainer on rehabilitation results: a randomized controlled study	Hippokratia	2015	2	19	125-130
Page, SJ; Levine, P; Teepen, J; et al.	Resistance-based, reciprocal upper and lower limb locomotor training in chronic stroke: a randomized, controlled crossover study	Clinical Rehabilitation	2008	7	22	610-617
Park, D; Lee, JH; Kang, TW; et al.	Immediate effects of talus-stabilizing taping on balance and gait parameters in patients with chronic stroke: a cross-sectional study	Topics in Stroke Rehabilitation	2018	6	25	417-423
Park, DS; Lee, DG; Lee, K; et al.	Effects of Virtual Reality Training using Xbox Kinect on Motor Function in Stroke Survivors: A Preliminary Study	Journal of Stroke and Cerebrovascular Diseases	2017	10	26	2313-2319
Park, HK; Lee, HJ; Lee, SJ; et al.	Land-based and acquatic trunk exercise program improve trunk control, balance and activities of daily living ability in stroke: a randomized clinical trial	European Journal of Physical and Rehabilitation Medicine	2018	NA	NA	NA
Park, J; Gong, J; Yim, J	Effects of a sitting boxing program on upper limb function, balance, gait, and quality of life in stroke patients	NeuroRehabilitation	2017	1	40	77-86
Park, J; Seo, D; Choi, W; Lee, S	The effects of exercise with TENS on spasticity, balance, and gait in patients with chronic stroke: a randomized controlled trial	Medical Science Monitor	2014	NA	20	1890-1896
Pollock, AS; Durward, BR; Rowe, PJ; Paul, JP	The effect of independent practice of motor tasks by stroke patients: a pilot randomized controlled trial	Clinical Rehabilitation	2002	5	16	473-480
Pomeroy, V M; Evans, B; Falconer, M; Jones, D; Hill, E; Giakas, G	An exploration of the effects of weighted garments on balance and gait of stroke patients with residual disability	Clinical Rehabilitation	2001	4	15	390-397
Rajaratnam, BS; Gui KJ; Lee JK; et al.	Does the inclusion of virtual reality games within conventional rehabilitation enhance balance retraining after a recent episode of stroke?	Rehabilitation Research and Practice	2013	NA	2013	
Robertson, JA; Eng, JJ; Hung, C	The effect of functional electrical Stimulation on balance function and balance confidence in community-dwelling individuals with stroke	Physiotherapy Canada	2010	2	62	114-119
Rougier, P; Boudrahem, S	Effects of visual feedback of center-of-pressure displacements on undisturbed upright postural control of hemiparetic stroke patients	Restorative Neurology and Neuroscience	2010	6	NA	749-759
Salgueiro, C; Marquez, J	Influencia del entrenamiento visual en el control postural de pacientes con accidente cerebrovascular crónico: estudio piloto aleatorizado controlado	Fisioterapia	2018	6	40	284-290

Sánchez-Mila, Z; Salom-Moreno, J; Fernández-de-las-Peñas, C	Effects of Dry Needling on Post-Stroke Spasticity, Motor Function and Stability Limits: A Randomised Clinical Trial	Acupuncture in Medicine	2018	6	36	358-366
Schmid, AA; Van Puymbroeck, M; Altenburger, PA.; et al.	Poststroke balance improves with yoga: a pilot study	Stroke	2012	9	43	2402-2407
Schuster, C; Butler, J; Andrews, B; et al.	Comparison of embedded and added motor imagery training in patients after stroke: results of a randomised controlled pilot trial	Trials	2012	1	13	
Shatil, S; Ivanova, TD; Mochizuki, G; Garland, SJ	Effects of therapeutic golf rehabilitation on golf performance, balance, and quality of life in individuals following stroke: pilot study	Physiotherapy Canada	2005	2	57	101
Shin, DC; Song, CH	Smartphone-Based Visual Feedback Trunk Control Training Using a Gyroscope and Mirroring Technology for Stroke Patients: Single-blinded, Randomized Clinical Trial of Efficacy and Feasibility	American Journal of Physical Medicine & Rehabilitation	2016	5	95	319-29
Simons, CDM; van Asseldonk, EHF; Kooij, H; et al.	Ankle-foot orthoses in stroke: Effects on functional balance, weight-bearing asymmetry and the contribution of each lower limb to balance control	Clinical Biomechanics	2009	9	24	769-775
Sohn, MK; Jee, SJ; Hwang, P; et al.	The Effects of Shoulder Slings on Balance in Patients With Hemiplegic Stroke	Annals of Rehabilitation Medicine	2015	6	39	986
Song, YB; Chun, MH; Kim, W; et al.	The effect of virtual reality and tetra-ataxiometric posturography programs on stroke patients with impaired standing balance	Annals of Rehabilitation Medicine	2014	2	38	160
Stein, J; Bishop, L; Stein, DJ; et al.	Gait Training with a Robotic Leg Brace After Stroke: A Randomized Controlled Pilot Study	American Journal of Physical Medicine & Rehabilitation	2014	11	93	987-994
Suh, HR; Han, HC; Cho, HY	Immediate therapeutic effect of interferential current therapy on spasticity, balance, and gait function in chronic stroke patients: a randomized control trial	Clinical Rehabilitation	2014	9	28	885-891
Tan, Z; Liu, H; Yan, T; et al.	The effectiveness of functional electrical stimulation based on a normal gait pattern on subjects with early stroke: a randomized controlled trial	BioMed Research International	2014	NA	2014	
Tan, ZM; Jiang, WW; Yan, TB ; et al.	[Effects of functional electrical stimulation based on normal gait pattern on walking function in subjects with recovery of stroke]	Zhonghua Yi Xue Za Zhi (Chinese medical journal)	2016	29	96	2342-2346
Tian, FL; Li, Q; Liu, GR; et al.	Impacts of yin-yang meridians acupuncture with respiratory reinforcing and reducing manipulation on lower limbs balance function in stroke patients	Chinese Acupuncture & Moxibustion	2014	11	34	1047-1050

Tilikete, C; Rode, G; Rossetti, Y; et al.	Prism adaptation to rightward optical deviation improves postural imbalance in left-hemiparetic patients	Current biology	2001	7	11	524-528
Tripp, F; Krakow, K	Effects of an aquatic therapy approach (Halliwick-Therapy) on functional mobility in subacute stroke patients: a randomized controlled trial	Clinical Rehabilitation	2014	5	28	432-439
Tung, FL; Yang, YR; Lee, CC; Wang, RY	Balance outcomes after additional sit-to-stand training in subjects with stroke: a randomized controlled trial	Clinical Rehabilitation	2010	6	24	533-542
Vahlberg, B; Cederholm, T; Lindmark, B; et al.	Short-term and long-term effects of a progressive resistance and balance exercise program in individuals with chronic stroke: a randomized controlled trial	Disability and Rehabilitation	2017	16	39	1615-1622
Van Nes, IJW; Latour, H; Schils, F; et al.	Long-term effects of 6-week whole-body vibration on balance recovery and activities of daily living in the postacute phase of stroke: a randomized, controlled trial	Stroke	2006	9	37	2331-2335
Waldron, RM; Bohannon, RW	Weight distribution when standing: The influence of a single point cane in patients with stroke	Physiotherapy Practice	1989	4	5	171-175
Wang, H; Zhao, Z; Jiang, P; et al.	Effect and mechanism of mirror therapy on rehabilitation of lower limb motor function in patients with stroke hemiplegia	Biomed Research	2017	22	28	6
Wang, RY; Lin, PY; Lee, CC; Yang, YR	Gait and balance performance improvements attributable to ankle-foot orthosis in subjects with hemiparesis:	American Journal of Physical Medicine & Rehabilitation	2007	7	86	556-562
Wang, RY; Yen, LL; Lee, CC; et al.	Effects of an ankle-foot orthosis on balance performance in patients with hemiparesis of different durations	Clinical Rehabilitation	2005	1	19	37-44
Wang, TC; Tsai, AC; Wang, JY; et al.	Caregiver-mediated intervention can improve physical functional recovery of patients with chronic stroke: a randomized controlled trial	Neurorehabilitation and Neural Repair	2015	1	29	3-12
Xie, G; Rao, T; Lin, L; et al.	Effects of Tai Chi Yunshou exercise on community-based stroke patients: a cluster randomized controlled trial	European Review of Aging and Physical Activity	2018	1	15	NA
Xing, J; Wang, YJ; Li, YR	Clinical study on acupuncture combined with hyperbaric oxygenation for improving balance function of cerebral infarction	Chinese Acupuncture & Moxibustion	2007	1	27	12-14
Yadav, R; Walia, S; Vats, M; et al.	Comparison of Effectiveness of Specific Balance Strategy Training Programme with General Balance Training Programme on Balance Performance in Chronic Stroke	Fiziksel Tip ve Rehabilitasyon Bilimleri Dergisi [Journal of Physical Medicine and Rehabilitation Sciences]	2016	1	19	1-6
Yeung, LF; Ockenfeld, C; Pang, MK; et al.	Randomized controlled trial of robot-assisted gait training with dorsiflexion assistance on chronic stroke patients wearing ankle-foot-orthosis	Journal of NeuroEngineering and Rehabilitation	2018	1	15	NA

Yoo, HJ; Pyun, SB	Efficacy of Bedside Respiratory Muscle Training in Patients With Stroke: A Randomized Controlled Trial	American Journal of Physical Medicine & Rehabilitation	2018	10	97	691-697
Yoo, SD; Jeong, YS; Kim, DH; et al.	The efficacy of core strengthening on the trunk balance in patients with subacute stroke	Annals of Rehabilitation Medicine	2010	6	34	677-682
You, G; Liang, H; Yan, T	Functional electrical stimulation early after stroke improves lower limb motor function and ability in activities of daily living	NeuroRehabilitation	2014	3	NA	381-389
Yu, JH; Cho, KH	Effectiveness of Virtual Reality Game on Functional Movement and Activities of Daily Living in Hemiparetic Stroke Patients	Journal of Nanoelectronics and Optoelectronics	2016	1	11	98-102
Yun, N; Joo, MC; Kim, SC; et al.	Robot-assisted gait training effectively improved lateropulsion in subacute stroke patients: a single-blinded randomized controlled trial	European Journal of Physical and Rehabilitation Medicine	2019	6	54	827-836
Zhang, WM; Yang, S; Wang, YJ; et al.	Effect of modified constraint-induced movement therapy on the activities of daily living of patients with acute stroke	Chinese Journal of Contemporary Neurology and Neurosurgery	2015	4	15	280-204

S3 Table. Characteristics of studies and participants

S3A Table. Summary of characteristics of studies and participants

	Both comparisons (PT versus NT and ST/UC)	PT versus NT	PT versus ST/UC
Trials / comparisons	145 / 172	76 / 91	70 / 81
Date of publication	From 1988 to 2019	From 1988 to 2019	From 1998 to 2018
Crossover / parallel group	18 / 127	18 / 58	0 / 70
Trials with 2, 3 or 4 groups	121 / 21 / 3	63 / 10 / 3	58 / 12 / 0
Participants (sum, mean +/- sd, min-max)	5912 / 40.8 +/- 42.9 / 7-408	3049 / 40.1 +/- 48.3 / 8-408	2899 / 41.4 +/- 36.3 / 7-244
Age of participants (years) (wtd mean +/- wtd sd, min-max)	60.8 +/- 44.3 / 46.9-78.5 (on 136 trials, 5730 subjects)	61.3 +/- 46.7 / 50.0-78.54 (on 70 trials, 2916 subjects)	60.1 +/- 41.8 / 46.9-73.9 (on 67 trials, 2850 subjects)
Men / Women (percent)	61% / 39%	59% / 41%	63% / 37%
Time post-stroke (days) (wtd mean +/- wtd sd, min-max)	193.7 +/- 322.4 / 4.5-1985.6 (on 122 trials, 5258 subjects)	152.5 +/- 282.1 / 4.5-1716.7 (on 60 trials, 2653 subjects)	282.0 +/- 461.7 / 11-1985.6 (on 62 trials, 2695 subjects)
Location of stroke lesion			
Only supratentorial stroke (trials/participants)	18 / 656	10 / 297	9 / 395
Only brainstem stroke (trials/participants)	0 / 0	0 / 0	0 / 0
Only cerebellum stroke (trials/participants)	0 / 0	0 / 0	0 / 0
Only other stroke (trials/participants)	0 / 0	0 / 0	0 / 0
Mixed different location of stroke or not determined (trials/participants)	127 / 5256	66 / 823	61 / 2504
Episode of stroke			
Only first episode (trials/participants)	68 / 3133	34 / 1612	35 / 1557
Only multiple episodes (trials/participants)	1/ 30	0 / 0	1 / 30
First or multiple episodes (trials/participants)	12 / 604	8 / 406	4 / 198
Not determined (trials/participants)	64 / 2145	34 / 1031	30 / 1114
Side of stroke lesion			
Only unilateral stroke (trials/participants)	117 / 4683	61 / 2416	57 / 2303
Only bilateral stroke (trials/participants)	0 / 0	0 / 0	0 / 0
Unilateral or bilateral stroke (trials/participants)	6 / 455	2 / 87	4 / 368
Not determined (trials/participants)	22 / 774	13 / 546	9 / 228
Etiology of stroke			
Only ischemic stroke (trials/participants)	12 / 379	6 / 224	7 / 191
Only hemorrhagic stroke (trials/participants)	0 / 0	0 / 0	0 / 0
Only ischemic or hemorrhagic stroke (trials/participants)	90 / 3589	43 / 1597	47 / 1992
Other stroke or not determined (trials/participants)	43 / 1944	27 / 1228	16 / 716

Stage of stroke for eligibility or inclusion of participants in trials			
Only acute stroke (trials/participants)	11 / 389	7 / 240	4 / 149
Only subacute stroke (trials/participants)	8 / 759	6 / 647	3 / 148
Only chronic stroke (trials/participants)	57 / 1910	24 / 686	33 / 1224
Mixed stages or not determined (trials/participants)	69 / 2854	39 / 1476	30 / 1378
Description of stroke lesion using brain imagery			
No imagery used (trials/participants)	90 / 3193	46 / 1526	44 / 1667
Use of imagery reported but without description of lesion (trials/participants)	44 / 2421	24 / 1381	21 / 1076
Imagery used with description of lesion in text (trials/participants)	11 / 298	6 / 142	5 / 156
Ethic			
Consultation of ethic committee (trials/participants)	115 / 4807	57 / 2245	59 / 2598
Respect of Helsinki declaration (trials/participants)	24 / 1407	10 / 840	14 / 567

Abbreviations: min, minimum; max, maximum; NA, not applicable; NT, no treatment; PT, physical therapy; ST, sham treatment; sd, standard deviation; UC, usual care; wtd, weighted.

S3B Table. Characteristics of studies and participants for each study included

Study	Date	Age of participant		Participants	Man		Woman		Size of group (Num)				Type of RCT
		Mean (y)	SD (y)	Num	Num	Percent	Num	Percent	A	B	C	D	
Allison et Dennett, 2007	2007	75.69	12.78	17	nd	nd	nd	nd	7	NA	10	NA	PG
Arabzadeh et al., 2018	2018	59.25	19.10	20	15	75.00	5	25.00	10	NA	10	NA	CO
Askim et al., 2010	2010	76.54	8.82	62	29	47	33	53	30	NA	32	NA	PG
Au-Yeung et al., 2009	2009	64.51	10.74	136	79	58.09	57	41.91	74	NA	62	NA	PG
Bae et al., 2015	2015	64.29	7.71	30	nd	nd	nd	nd	15	NA	15	NA	CO
Barcala et al., 2011	2011	58.00	12.57	12	5	42	7	58	6	NA	6	NA	PG
Brogardh et al., 2012	2012	62.00	7.00	31	25	81	6	19	16	NA	15	NA	PG
Bunketorp-Kall et al., 2017	2017	63.00	6.60	123	69	56.10	54	43.90	41	41	41	NA	CO
Buyukavci et al., 2016	2016	63.09	10.38	65	33	50.77	32	49.23	33	NA	32	NA	PG
Büyükvural Şen et al., 2015	2015	53.35	11.35	50	33	66	17	34	25	NA	25	NA	PG
Cabanas-Valdés et al., 2015	2015	75.31	10.01	80	40	50	40	50	40	NA	40	NA	PG
Chan KS et al., 2012	2012	55.50	9.27	30	21	70	9	30	15	NA	15	NA	PG
Chen CH et al., 2010	2010	57.50	10.44	10	10	100	0	0	10	10	10	NA	CO
Chen CL et al., 2015	2015	57.10	12.70	24	13	54	11	46	24	NA	24	NA	CO
Chen D et al., 2014	2014	59.31	9.6	48	27	56	21	44	18	15	15	NA	PG
Chen IC et al., 2002	2002	57.22	10.91	41	13	32	28	68	23	NA	18	NA	PG
Chen JC et al., 2011	2011	60.08	11.43	33	22	67	11	33	17	NA	16	NA	PG
Chen, 2018	2018	nd	nd	16	nd	nd	nd	nd	8	NA	8	NA	CO
Chern et al., 2013	2013	nd	nd	15	11	73	4	27	15	15	15	15	CO
Cho HY et al., 2013	2013	55.41	10.10	42	27	64	15	36	22	NA	20	NA	PG
Cho KH et al., 2012	2012	64.20	7.54	22	14	64	8	36	11	NA	11	NA	PG
Cho MK et al., 2015	2015	56.00	8.69	31	19	61	12	39	10	10	11	NA	PG
Choi HS et al., 2017	2017	61.92	5.59	36	21	58.33	15	41.67	12	12	12	NA	CO
Chu et al., 2015	2015	67.03	10.99	145	89	61.38	56	38.62	48	49	48	NA	PG
Chung et al., 2014	2014	58.30	7.53	18	14	78	4	22	9	NA	9	NA	PG
Dault et al., 2003	2003	57.80	10.80	10	5	50	5	50	10	NA	10	NA	CO
Dujovic et al., 2017	2017	nd	nd	16	10	62.50	6	37.50	8	NA	8	NA	CO
Duncan et al., 1998	1998	67.55	8.26	20	nd	nd	nd	nd	10	NA	10	NA	PG
Duncan et al., 2003	2003	69.39	10.30	92	50	54	42	46	44	NA	48	NA	PG
Erbil et al., 2018	2018	49.64	11.26	43	27	62.79	16	37.21	29	NA	14	NA	PG
Fernandez-Gonzalo et al., 2016	2016	63.53	11.42	29	22	75.86	7	24.14	14	NA	15	NA	PG
Ferreira et al., 2017	2017	59.20	10.40	20	14	70.00	6	30.00	12	NA	8	NA	PG
Fritz et al., 2013	2013	66.16	9.63	28	nd	nd	nd	nd	15	NA	13	NA	PG
Furnari et al., 2014	2014	70.00	6.00	40	20	50.00	20	50.00	20	NA	20	NA	PG
Geiger et al., 2001	2001	60.38	15.39	13	9	69.23	4	30.77	7	NA	6	NA	PG

Ghanjal et al., 2014	2014	54.43	7.39	36	26	72	10	28	12	12	12	NA	PG
Globas et al., 2012	2012	68.70	6.30	36	29	81	7	19	18	NA	18	NA	PG
Goliwas et al., 2017	2017	63.42	8.74	37	21	56.76	16	43.24	20	NA	17	NA	PG
Han et al., 2016	2016	65.71	13.22	56	32	57.14	24	42.86	30	NA	26	NA	PG
Hart et al., 2004	2004	54.77	nd	18	16	89	2	11	9	NA	9	NA	PG
Heller et al., 2005	2005	60.42	12.80	26	15	58	11	42	13	NA	13	NA	PG
Hollands et al., 2015	2015	58.36	14.57	56	33	58.93	23	41.07	18	19	19	NA	PG
Holmgren et al., 2010	2010	78.54	7.47	34	21	61.76	13	38.24	15	NA	19	NA	PG
Hosseini et al., 2012	2012	48.10	10.50	30	16	53.33	14	46.67	15	NA	15	NA	PG
Howe et al., 2005	2005	71.09	9.22	35	18	51	17	49	17	NA	18	NA	PG
Hsieh, 2019	2019	58.80	12.00	56	33	58.93	23	41.07	28	NA	28	NA	CO
Hsu et al., 2013	2013	51.88	13.35	23	14	61	9	39	11	NA	12	NA	PG
Huh et al., 2015	2015	65.84	5.88	40	26	65.00	14	35.00	23	NA	17	NA	PG
Hung et al., 2016	2016	53.92	13.24	23	16	69.57	7	30.43	12	NA	11	NA	PG
Hwang et al., 2015	2015	49.74	6.30	30	17	57	13	43	15	NA	15	NA	PG
Immink et al., 2014	2014	59.60	15.70	22	9	41	13	59	11	NA	11	NA	PG
In et al., 2016	2016	55.92	10.85	25	15	60.00	10	40.00	13	NA	12	NA	PG
Janssen et al., 2008	2008	54.75	10.08	12	6	50	6	50	6	NA	6	NA	PG
Jung et al., 2015	2015	53.59	13.14	22	11	50	11	50	11	NA	11	NA	PG
Jung et al., 2017	2017	56.25	10.17	40	23	57.50	17	42.50	20	NA	20	NA	CO
Kamps et Schule, 2005	2005	64.41	9.39	31	22	71	9	29	16	NA	15	NA	PG
Karasu et al., 2018	2018	63.20	11.70	23	10	43.48	13	56.52	12	NA	11	NA	PG
Katz-Leurer et al., 2006	2006	62.50	8.94	24	13	54	11	46	10	NA	14	NA	PG
Khumsapsiri et al., 2018	2018	59.25	10.02	16	7	43.75	9	56.25	8	NA	8	NA	CO
Kilinc et al., 2015	2015	55.08	10.62	22	9	40.91	13	59.09	12	NA	10	NA	PG
Kim DH et al., 2008	2008	52.44	10.20	16	7	88	1	13	8	NA	8	NA	PG
Kim JC et Lee, 2018	2018	55.10	7.84	21	19	90.48	2	9.52	11	NA	10	NA	PG
Kim JH et al., 2009	2009	51.96	8.40	24	13	54	11	46	12	NA	12	NA	PG
Kim JY et al., 2018	2018	58.99	12.98	48	33	68.75	15	31.25	25	NA	23	NA	PG
Kim SL et Lee, 2018	2018	46.94	12.90	30	18	60.00	12	40.00	15	NA	15	NA	CO
Kim YH et al., 2004	2004	58.85	25.32	38	24	63	14	37	13	13	12	NA	PG
Kim YM et al., 2009	2009	64.80	12.74	32	17	53	15	47	16	NA	16	NA	PG
Knox et al., 2018	2018	50.00	13.76	144	72	50.00	72	50.00	51	45	48	NA	PG
Kunkel et al., 2013	2013	68.37	14.90	21	12	57	9	43	7	7	7	NA	PG
Kwong et al., 2018	2018	62.00	5.40	80	50	62.50	30	37.50	40	NA	40	NA	CO
Langhammer et al., 2009	2009	73.87	13.25	67	43	57	32	43	32	NA	35	NA	PG
Lau RWK et al., 2012	2012	57.35	11.13	82	58	71	24	29	41	NA	41	NA	PG
Laufer, 2003	2003	71.20	7.00	30	18	60	12	40	30	30	30	NA	CO
Lee CH et al., 2014	2014	51.10	12.06	21	14	67	7	33	10	NA	11	NA	PG

Lee D et al., 2016	2016	54.70	6.47	27	14	51.85	13	48.15	14	NA	13	NA	PG
Lee HJ et al., 2018	2018	60.00	7.41	20	10	50.00	10	50.00	10	NA	10	NA	CO
Lee MM et al., 2018	2018	61.57	7.53	30	18	60.00	12	40.00	15	NA	15	NA	CO
Lee NK et al., 2013	2013	59.40	7.40	33	20	61	13	39	11	11	11	NA	PG
Lee SH et al., 2012	2012	53.93	11.07	40	25	63	15	38	20	NA	20	NA	PG
Lee SW et al., 2013	2013	54.48	8.27	31	24	77	7	23	16	NA	15	NA	PG
Liang et al., 2012	2012	57.92	11.69	30	19	63	11	37	15	NA	15	NA	PG
Lin Q et al., 2015	2015	60.95	7.53	64	41	64.06	23	35.94	32	NA	32	NA	PG
Lindvall et Forsberg, 2014	2014	63.77	10.44	46	27	59	19	41	24	NA	22	NA	PG
Lisinski et al., 2012	2012	64.00	16.40	26	10	38	16	62	13	NA	13	NA	PG
Liu-Ambrose et Eng, 2015	2015	65.20	10.40	25	15	60	10	40	11	NA	14	NA	PG
Lu et al., 1997	1997	58.90	6.90	10	10	100	0	0	10	10	10	NA	CO
Lynch et al., 2007	2007	61.52	13.72	21	16	76	5	24	10	NA	11	NA	PG
Marin et al., 2013	2013	63.25	9.20	20	11	55	9	45	11	NA	9	NA	PG
Merkert et al., 2011	2011	74.50	8.39	66	22	33	44	67	33	NA	33	NA	PG
Milczarek et al., 1993	1993	59.93	13.18	14	8	57	6	43	14	NA	14	NA	CO
Mojica et al., 1988	1988	nd	nd	8	5	63	3	38	8	NA	8	NA	CO
Moore JL et al., 2010	2010	50.00	15.00	20	14	70	6	30	nd	NA	nd	NA	CO
Morioka et Yagi, 2003	2003	61.90	11.88	26	17	65	9	35	12	NA	14	NA	PG
Mudie et al., 2002	2002	72.40	9.01	40	21	53	19	48	10	10	10	10	PG
Nadeau et al., 2013	2013	61.99	12.73	408	224	55	184	45	139	126	143	NA	PG
Ng et al., 2016	2016	70.10	9.90	76	48	63.16	28	36.84	37	NA	39	NA	PG
Nikamp et al., 2017	2017	57.20	9.20	33	20	60.61	13	39.39	16	NA	17	NA	PG
Noh et al., 2008	2008	63.87	10.72	25	11	44.00	14	56.00	13	NA	12	NA	PG
Ordahan et al., 2015	2015	57.10	9.20	50	31	62.00	19	38.00	25	NA	25	NA	CO
Page et al., 2008	2008	61.29	12.30	7	5	71.43	2	28.57	4	NA	3	NA	PG
Park D et al., 2018	2018	58.50	10.07	20	12	60.00	8	40.00	20	20	20	NA	CO
Park DS et al., 2017	2017	63.65	13.94	20	10	50.00	10	50.00	10	NA	10	NA	CO
Park et al., 2014	2014	71.17	3.57	29	20	69	9	31	15	NA	14	NA	PG
Park HK et al., 2018	2018	56.70	12.52	29	22	75.86	7	24.14	14	NA	15	NA	PG
Park J et al., 2017	2017	nd	nd	30	nd	nd	nd	nd	15	NA	15	NA	CO
Pollock et al., 2002	2002	69.91	12.50	28	12	43	16	57	9	NA	19	NA	PG
Pomeroy et al., 2001	2001	nd	nd	24	18	75	6	25	12	NA	12	NA	PG
Rajaratnam et al., 2013	2013	61.60	7.80	19	7	37	12	63	9	NA	10	NA	PG
Robertson et al., 2010	2010	54.40	10.40	15	12	80	3	20	15	NA	15	NA	CO
Rougier et Boudrahem, 2010	2010	61.79	11.42	39	24	62	15	38	39	NA	39	NA	CO
Salgueiro et Marquez, 2018	2018	57.30	8.54	12	9	75.00	3	25.00	6	NA	6	NA	PG
Sanchez-Mila et al., 2018	2018	57.00	12.00	26	13	50.00	13	50.00	14	NA	12	NA	PG
Schmid et al., 2012	2012	63.10	8.80	47	38	81	9	19	37	NA	10	NA	PG

Schuster et al., 2012	2012	63.42	10.21	39	27	69	12	31	13	14	12	NA	PG
Shatil et al., 2005	2005	63.8	15.8	18	11	61	7	39	10	NA	8	NA	PG
Shin et al., 2016	2016	58.50	11.84	24	nd	nd	nd	nd	12	NA	12	NA	CO
Simons et al., 2009	2009	57.20	10.23	20	14	70	6	30	20	NA	20	NA	CO
Sohn et al., 2015	2015	57.00	12.00	27	17	62.96	10	37.04	27	NA	27	NA	CO
Song et al., 2014	2014	62.47	14.95	30	16	53	14	47	10	10	10	NA	PG
Stein et al., 2014	2014	57.10	8.21	24	16.92	70.50	7.08	29.50	12	NA	12	NA	PG
Suh et al., 2014	2014	54.13	12.10	42	29	69	13	31	21	NA	21	NA	PG
Tan et al., 2014	2014	64.97	9.32	45	24	51	23	49	16	15	14	NA	PG
Tan et al., 2016	2016	58.26	12.59	58	32	55.17	26	44.83	29	15	14	NA	PG
Tian et al., 2014	2014	56.5	14.72	100	54	54	46	46	50	NA	50	NA	PG
Tilikete et al., 2001	2001	54.67	nd	15	6	40	9	60	5	5	5	NA	PG
Tripp and Krakow, 2014	2014	64.91	14.79	30	19	63	11	37	14	NA	16	NA	PG
Tung et al., 2010	2010	51.85	12.95	32	20	63	12	38	16	NA	16	NA	PG
Vahlberg et al., 2017	2017	73.14	5.39	67	51	76.12	16	23.88	34	NA	33	NA	PG
VanNes et al., 2006	2006	61.12	10.27	53	30	57	23	43	27	NA	26	NA	PG
Waldron et Bohannon, 1989	1989	63.20	10.10	20	nd	nd	nd	nd	20	20	20	20	CO
Wang et al., 2017	2017	52.73	2.82	36	26	72.22	10	27.78	18	NA	18	NA	CO
Wang RY, Lin PY et al., 2007	2007	60.36	13.95	58	44	76	14	24	58	NA	58	NA	CO
Wang RY, Yen LL et al., 2005 part 1	2005	59.90	13.00	42	23	55	19	45	42	NA	42	NA	CO
Wang RY, Yen LL et al., 2005 part 2	2005	62.30	11.80	61	51	84	10	16	61	NA	61	NA	CO
Wang TC et al., 2015	2015	63.73	10.12	51	30	59	21	41	25	NA	26	NA	PG
Xie et al., 2018	2018	60.49	8.64	244	182	74.59	62	25.41	120	NA	124	NA	PG
Xing et al., 2007	2007	50.87	11.66	72	52	72	20	28	36	NA	36	NA	PG
Yadav et al., 2015	2015	55.29	10.06	24	19	79.17	5	20.83	12	NA	12	NA	CO
Yeung et al., 2018	2018	57.90	12.00	19	13	68.42	6	31.58	9	NA	10	NA	PG
Yoo et al., 2010	2010	60.74	15.38	59	30	51	29	49	28	NA	31	NA	PG
Yoo et al., 2018	2018	61.00	nd	40	26	65.00	14	35.00	20	NA	20	NA	CO
You et al., 2014	2014	62.41	10.27	37	21	57	16	43	19	NA	18	NA	PG
Yu et Cho, 2016	2016	63.75	5.36	20	12	60.00	8	40.00	10	NA	10	NA	CO
Yun et al., 2018	2018	63.90	8.20	36	19	52.78	17	47.22	18	NA	18	NA	CO
Zhang et al., 2015	2015	59.22	5.19	60	33	55	27	45	30	NA	30	NA	PG

Abbreviations: CO, crossover; NA, not applicable; nd, not documented; Num, number; PG, parallel group.

S3C Table. Characteristics of participants for each study included

Study	Supratentorial stroke		Right supratentorial stroke		Left supratentorial stroke		Brainstem stroke		Cerebellum stroke		Other location of stroke	
	Trial	Participant	Trial	Participant	Trial	Participant	Trial	Participant	Trial	Participant	Trial	Participant
Allison et Dennett, 2007	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Arabzadeh et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Askim et al., 2010	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Au-Yeung et al., 2009	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Bae et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Barcala et al., 2011	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Brogardh et al., 2012	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Bunketorp-Kall et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Buyukavci et al., 2016	nd	nd	nd	nd	nd	nd	nd	nd	No	0	nd	nd
Büyükvural Şen et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Cabanas-Valdés et al., 2015	Yes	67	Yes	40	Yes	27	Yes	10	Yes	3	No	0
Chan KS et al., 2012	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Chen CH et al., 2010	Yes	9	Yes	4	Yes	5	Yes	1	No	0	No	0
Chen CL et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Chen D et al., 2014	Yes	nd	nd	nd	nd	nd	nd	nd	nd	nd	No	0
Chen IC et al., 2002	Yes	41	Yes	21	Yes	20	No	0	No	0	No	0
Chen JC et al., 2011	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Chen, 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Chern et al., 2013	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Cho HY et al., 2013	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Cho KH et al., 2012	Yes	nd	nd	nd	nd	nd	Yes	nd	No	0	No	0
Cho MK et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Choi HS et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Chu et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Chung et al., 2014	Yes	nd	nd	nd	nd	nd	Yes	nd	No	0	No	0
Dault et al., 2003	Yes	9	Yes	8	Yes	1	Yes	1	No	0	No	0
Dujovic et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Duncan et al., 1998	Yes	nd	nd	nd	nd	nd	Yes	1	nd	nd	No	0
Duncan et al., 2003	Yes	84	Yes	44	Yes	40	Yes	nd	nd	nd	Yes	nd
Erbil et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Fernandez-Gonzalo et al., 2016	Yes	29	Yes	15	Yes	14	nd	nd	No	0	No	0
Ferreira et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd

Fritz et al., 2013	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Furnari et al., 2014	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Geiger et al., 2001	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Ghanjal et al., 2014	Yes	36	Yes	14	Yes	22	No	0	No	0	No	0
Globas et al., 2012	Yes	36	Yes	13	Yes	23	No	0	No	0	No	0
Goliwas et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Han et al., 2016	Yes	56	Yes	22	Yes	34	No	0	No	0	No	0
Hart et al., 2004	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Heller et al., 2005	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Hollands et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Holmgren et al., 2010	Yes	28	nd	nd	nd	nd	nd	nd	nd	nd	No	0
Hosseini et al., 2012	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Howe et al., 2005	Yes	26	nd	nd	nd	nd	nd	nd	nd	nd	Yes	5
Hsieh, 2019	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Hsu et al., 2013	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Huh et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Hung et al., 2016	nd	nd	nd	nd	nd	nd	nd	nd	No	0	nd	nd
Hwang et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Immink et al., 2014	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
In et al., 2016	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Janssen et al., 2008	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Jung et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Jung et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Kamps et Schule, 2005	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Karasu et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	No	0	nd	nd
Katz-Leurer et al., 2006	Yes	nd	nd	nd	nd	nd	No	0	nd	nd	No	0
Khumsapsiri et al., 2018	Yes	16	nd	nd	nd	nd	No	0	No	0	No	0
Kilinc et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Kim DH et al., 2008	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Kim JC et Lee, 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Kim JH et al., 2009	Yes	23	Yes	13	Yes	10	Yes	1	No	0	No	0
Kim JY et al., 2018	Yes	42	nd	nd	nd	nd	Yes	5	No	0	Yes	2
Kim SL et Lee, 2018	Yes	29	Yes	nd	Yes	nd	Yes	1	No	0	No	0
Kim YH et al., 2004	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Kim YM et al., 2009	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Knox et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Kunkel et al., 2013	Yes	14	nd	nd	nd	nd	nd	nd	nd	nd	No	0
Kwong et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Langhammer et al., 2009	Yes	67	Yes	nd	Yes	nd	No	0	No	0	No	0

Lau RWK et al., 2012	Yes	nd	nd	nd	nd	nd	nd	nd	nd	nd	No	0
Laufer, 2003	Yes	30	Yes	12	Yes	18	No	0	No	0	No	0
Lee CH et al., 2014	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lee D et al., 2016	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lee HJ et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lee MM et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	No	0	No	0
Lee NK et al., 2013	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lee SH et al., 2012	Yes	40	Yes	24	Yes	16	No	0	No	0	No	0
Lee SW et al., 2013	Yes	nd	nd	nd	nd	nd	Yes	nd	No	0	No	0
Liang et al., 2012	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lin Q et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lindvall et Forsberg, 2014	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lisinski et al., 2012	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Liu-Ambrose et Eng, 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lu et al., 1997	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lynch et al., 2007	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Marin et al., 2013	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Merkert et al., 2011	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Milczarek et al., 1993	Yes	11	Yes	4	Yes	9	Yes	1	No	0	No	0
Mojica et al., 1988	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Moore JL et al., 2010	Yes	20	Yes	16	Yes	4	No	0	No	0	No	0
Morioka et Yagi, 2003	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Mudie et al., 2002	Yes	22	nd	nd	nd	nd	nd	nd	Yes	3	nd	nd
Nadeau et al., 2013	Yes	300	Yes	nd	Yes	nd	Yes	59	Yes	1	Yes	48
Ng et al., 2016	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Nikamp et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Noh et al., 2008	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Ordahan et al., 2015	Yes	50	Yes	29	Yes	21	No	0	No	0	No	0
Page et al., 2008	Yes	nd	Yes	3	nd	nd	nd	nd	nd	nd	nd	nd
Park D et al., 2018	Yes	20	Yes	7	Yes	13	No	0	No	0	No	0
Park DS et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Park et al., 2014	Yes	nd	nd	nd	nd	nd	Yes	nd	No	0	No	0
Park HK et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Park J et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Pollock et al., 2002	Yes	23	nd	nd	nd	nd	nd	nd	nd	nd	No	0
Pomeroy et al., 2001	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Rajaratnam et al., 2013	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Robertson et al., 2010	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Rougier et Boudrahem, 2010	Yes	37	Yes	20	Yes	17	Yes	2	No	0	No	0

Salgueiro et Marquez, 2018	nd	nd	nd	nd	nd	nd	nd	nd	No	0	No	0
Sanchez-Mila et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Schmid et al., 2012	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Schuster et al., 2012	Yes	27	Yes	13	Yes	14	Yes	7	Yes	2	Yes	3
Shatil et al., 2005	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Shin et al., 2016	Yes	24	Yes	9	Yes	15	No	0	No	0	No	0
Simons et al., 2009	Yes	20	Yes	10	Yes	10	No	0	No	0	No	0
Sohn et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Song et al., 2014	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Stein et al., 2014	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Suh et al., 2014	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Tan et al., 2014	Yes	45	nd	nd	nd	nd	No	0	No	0	No	0
Tan et al., 2016	Yes	nd	nd	nd	nd	nd	nd	nd	nd	nd	No	0
Tian et al., 2014	Yes	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Tilikete et al., 2001	Yes	15	Yes	15	No	0	No	0	No	0	No	0
Tripp and Krakow, 2014	Yes	20	Yes	11	Yes	9	Yes	4	Yes	1	Yes	5
Tung et al., 2010	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Vahlberg et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
VanNes et al., 2006	Yes	53	Yes	28	Yes	25	No	0	No	0	No	0
Waldron et Bohannon, 1989	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Wang et al., 2017	Yes	36	Yes	19	Yes	17	No	0	No	0	No	0
Wang RY, Lin PY et al., 2007	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Wang RY, Yen LL et al., 2005 part 1	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Wang RY, Yen LL et al., 2005 part 2	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Wang TC et al., 2015	Yes	51	Yes	27	Yes	24	No	0	No	0	No	0
Xie et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Xing et al., 2007	Yes	64	nd	nd	nd	nd	Yes	5	Yes	3	No	0
Yadav et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Yeung et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Yoo et al., 2010	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Yoo et al., 2018	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
You et al., 2014	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Yu et Cho, 2016	nd	nd	nd	nd	nd	nd	nd	nd	No	0	No	0
Yun et al., 2018	Yes	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Zhang et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd

Abbreviations: nd, not documented.

S3D Table. Characteristics of participants for each study included

Study	Episode of stroke	First stroke (Participant)	Multiple stroke (Participant)	Unilateral / bilateral stroke	Unilateral stroke (Participant)	Bilateral stroke (Participant)	Ischemic stroke		Hemorrhagic stroke		Other etiology of stroke	
							Trial	Participant	Trial	Participant	Trial	Participant
Allison et Dennett, 2007	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Arabzadeh et al., 2018	nd	nd	nd	U	20	0	1	20	0	0	0	0
Askim et al., 2010	F & M	55	7	nd	nd	nd	nd	nd	Yes	3	nd	nd
Au-Yeung et al., 2009	nd	nd	nd	U	136	0	nd	nd	nd	nd	nd	nd
Bae et al., 2015	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Barcala et al., 2011	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Brogardh et al., 2012	nd	nd	nd	U	31	0	Yes	27	Yes	4	No	0
Bunketorp-Kall et al., 2017	F & M	nd	nd	U	123	0	1	87	1	36	0	0
Buyukavci et al., 2016	F	65	0	nd	nd	nd	1	52	1	12	0	0
Büyükvural Şen et al., 2015	nd	nd	nd	U	50	0	Yes	44	Yes	6	No	0
Cabanas-Valdés et al., 2015	F	80	0	U	80	0	Yes	65	Yes	15	No	0
Chan KS et al., 2012	F	30	0	U	30	0	Yes	15	Yes	15	No	0
Chen CH et al., 2010	F	10	0	U	10	0	Yes	3	Yes	7	No	0
Chen CL et al., 2015	nd	nd	nd	U	24	0	Yes	16	Yes	7	Yes	1
Chen D et al., 2014	nd	nd	nd	U	48	0	Yes	37	Yes	11	No	0
Chen IC et al., 2002	F	41	0	U	41	0	nd	nd	nd	nd	nd	nd
Chen JC et al., 2011	F	33	0	U	33	0	Yes	11	Yes	22	No	0

Chen, 2018	F & M	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Chern et al., 2013	nd	nd	nd	U	15	0	nd	nd	nd	nd	nd	nd
Cho HY et al., 2013	F	42	0	nd	nd	nd	Yes	29	Yes	13	No	0
Cho KH et al., 2012	F	22	0	U	22	0	Yes	13	Yes	9	No	0
Cho MK et al., 2015	F	31	0	U	31	0	Yes	14	Yes	17	No	0
Choi HS et al., 2017	nd	nd	nd	U	36	0	nd	nd	nd	nd	nd	nd
Chu et al., 2015	F	145	0	U	145	0	1	113	1	32	0	0
Chung et al., 2014	F	18	0	U	18	0	Yes	9	Yes	9	No	0
Dault et al., 2003	F	10	0	U	10	0	Yes	10	No	0	No	0
Dujovic et al., 2017	F	16	0	U	16	0	1	13	1	3	0	0
Duncan et al., 1998	nd	nd	nd	U	19	nd	Yes	18	Yes	2	No	0
Duncan et al., 2003	nd	nd	nd	U	84	nd	Yes	83	nd	nd	nd	nd
Erbil et al., 2018	nd	nd	nd	U	43	0	1	28	1	15	0	0
Fernandez-Gonzalo et al., 2016	F & M	28	1	U	29	0	1	20	1	9	0	0
Ferreira et al., 2017	nd	nd	nd	U	20	0	1	16	1	4	0	0
Fritz et al., 2013	nd	nd	nd	U	28	0	nd	nd	nd	nd	nd	nd
Furnari et al., 2014	F	40	0	U	40	0	nd	nd	nd	nd	nd	nd
Geiger et al., 2001	nd	nd	nd	U	13	0	nd	nd	nd	nd	nd	nd
Ghanjal et al., 2014	F	36	0	U	36	0	Yes	36	No	0	No	0

Globas et al., 2012	nd	nd	nd	U	36	0	nd	nd	nd	nd	nd	nd
Goliwas et al., 2017	nd	nd	nd	U	37	0	1	37	0	0	0	0
Han et al., 2016	F	56	0	U	56	0	1	33	1	23	0	0
Hart et al., 2004	F	18	0	U	18	0	nd	nd	nd	nd	nd	nd
Heller et al., 2005	F	26	0	U	26	0	Yes	15	Yes	11	No	0
Hollands et al., 2015	nd	nd	nd	U & B	51	5	1	49	1	7	0	0
Holmgren et al., 2010	F & M	19	15	nd	nd	nd	1	23	1	1	1	10
Hosseini et al., 2012	M	0	30	nd	nd	nd	nd	nd	nd	nd	nd	nd
Howe et al., 2005	F & M	28	7	U	35	0	Yes	nd	Yes	nd	No	nd
Hsieh, 2019	nd	nd	nd	U	56	0	1	56	0	0	0	0
Hsu et al., 2013	F	23	0	U	23	0	Yes	11	Yes	12	No	0
Huh et al., 2015	nd	nd	nd	U	40	0	1	22	1	18	0	0
Hung et al., 2016	nd	nd	nd	U	23	0	1	17	1	6	0	0
Hwang et al., 2015	F & M	nd	nd	U	30	0	Yes	14	Yes	16	No	0
Immink et al., 2014	nd	nd	nd	U	22	0	nd	nd	nd	nd	nd	nd
In et al., 2016	nd	nd	nd	U	25	0	1	16	1	9	0	0
Janssen et al., 2008	nd	nd	nd	U	12	0	Yes	11	Yes	1	No	0
Jung et al., 2015	nd	nd	nd	U	22	0	nd	nd	nd	nd	nd	nd
Jung et al., 2017	F	40	0	U	40	0	1	23	1	17	0	0
Kamps et Schule, 2005	nd	nd	nd	U	31	0	Yes	31	No	0	No	0

Karasu et al., 2018	F	23	0	U	23	0	1	18	1	5	0	0
Katz-Leurer et al., 2006	F	24	0	U	24	0	Yes	24	No	0	No	0
Khumsapsiri et al., 2018	F	16	0	U	16	0	1	11	1	5	0	0
Kilinc et al., 2015	F	22	0	U	22	0	1	11	1	11	0	0
Kim DH et al., 2008	nd	nd	nd	U	16	0	nd	nd	nd	nd	nd	nd
Kim JC et Lee, 2018	nd	nd	nd	U	21	0	1	14	1	7	0	0
Kim JH et al., 2009	F	24	0	U	24	0	Yes	11	Yes	13	No	0
Kim JY et al., 2018	F	48	0	U	48	0	1	32	1	16	0	0
Kim SL et Lee, 2018	F	30	0	U	30	0	1	12	1	18	0	0
Kim YH et al., 2004	nd	nd	nd	U	38	0	Yes	28	Yes	10	No	0
Kim YM et al., 2009	nd	nd	nd	U	32	0	Yes	23	Yes	9	No	0
Knox et al., 2018	F	144	0	U	144	0	1	nd	1	nd	0	0
Kunkel et al., 2013	F	21	0	U & B	18	3	Yes	20	Yes	1	No	0
Kwong et al., 2018	nd	nd	nd	U	80	0	1	49	1	30	1	1
Langhammer et al., 2009	F	67	0	U	67	0	Yes	nd	Yes	nd	No	0
Lau RWK et al., 2012	nd	nd	nd	U	82	0	Yes	41	nd	nd	nd	nd
Laufer, 2003	F	30	0	U	30	0	Yes	29	Yes	1	No	0
Lee CH et al., 2014	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lee D et al., 2016	nd	nd	nd	U	27	0	1	8	1	20	0	0
Lee HJ et al., 2018	nd	nd	nd	U	20	0	1	18	1	2	0	0

Lee MM et al., 2018	nd	nd	nd	U	30	0	1	19	1	11	0	0
Lee NK et al., 2013	F	33	0	U	33	0	Yes	20	Yes	13	No	0
Lee SH et al., 2012	F	40	0	U	40	0	Yes	27	Yes	13	No	0
Lee SW et al., 2013	F	31	0	U	31	0	Yes	19	Yes	12	No	0
Liang et al., 2012	F	30	0	U	30	0	Yes	18	Yes	12	No	0
Lin Q et al., 2015	nd	nd	nd	nd	nd	nd	1	42	1	22	0	0
Lindvall et Forsberg, 2014	F & M	38	8	U	46	0	Yes	34	Yes	12	No	0
Lisinski et al., 2012	nd	nd	nd	U	26	0	Yes	26	No	0	No	0
Liu-Ambrose et Eng, 2015	F	25	0	nd	nd	nd	Yes	14	Yes	10	No	0
Lu et al., 1997	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lynch et al., 2007	F	21	0	U	21	0	Yes	18	Yes	3	No	0
Marin et al., 2013	nd	nd	nd	U	39	0	Yes	17	Yes	3	No	0
Merkert et al., 2011	F & M	46	20	U & B	54	12	Yes	53	Yes	7	Yes	6
Milczarek et al., 1993	nd	nd	nd	U	14	0	Yes	11	Yes	3	No	0
Mojica et al., 1988	nd	nd	nd	U	8	0	nd	nd	nd	nd	nd	nd
Moore JL et al., 2010	nd	nd	nd	U	20	0	Yes	10	Yes	10	No	0
Morioka et Yagi, 2003	nd	nd	nd	U	26	0	nd	nd	nd	nd	nd	nd
Mudie et al., 2002	nd	nd	nd	U	40	0	Yes	29	Yes	11	No	0
Nadeau et al., 2013	F	408	0	U	408	0	Yes	290	Yes	70	Yes	48
Ng et al., 2016	F	76	0	U	76	0	1	65	1	11	0	0

Nikamp et al., 2017	F	33	0	U	33	0	1	27	1	6	0	0
Noh et al., 2008	F	25	0	U	25	0	1	13	1	12	0	0
Ordahan et al., 2015	F	50	0	U	50	0	1	41	1	9	0	0
Page et al., 2008	nd	nd	nd	nd	nd	nd	1	7	0	0	0	0
Park D et al., 2018	F	20	0	U	20	0	1	11	1	9	0	0
Park DS et al., 2017	nd	nd	nd	U	20	0	1	13	1	7	0	0
Park et al., 2014	nd	nd	nd	U & B	29	1	nd	nd	nd	nd	nd	nd
Park HK et al., 2018	F	29	0	U	29	0	1	15	1	14	0	0
Park J et al., 2017	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Pollock et al., 2002	nd	nd	nd	U	28	0	Yes	25	Yes	3	No	0
Pomeroy et al., 2001	F & M	nd	nd	U	24	0	nd	nd	nd	nd	nd	nd
Rajaratnam et al., 2013	F	19	0	U	19	0	Yes	16	Yes	3	No	0
Robertson et al., 2010	F	15	0	U	15	0	Yes	8	Yes	7	No	0
Rougier et Boudrahem, 2010	F	39	0	U	39	0	Yes	28	Yes	11	No	0
Salgueiro et Marquez, 2018	nd	nd	nd	U	12	0	1	7	1	5	0	0
Sanchez-Mila et al., 2018	F	26	0	U	26	0	nd	nd	nd	nd	nd	nd
Schmid et al., 2012	nd	nd	nd	nd	nd	nd	Yes	31	nd	nd	Yes	nd
Schuster et al., 2012	F	39	0	U & B	38	1	Yes	30	Yes	9	No	0
Shatil et al., 2005	nd	nd	nd	U	18	0	Yes	14	Yes	4	No	0

Shin et al., 2016	F	24	0	U	24	0	1	5	1	19	0	0
Simons et al., 2009	F	20	0	U	20	0	Yes	17	Yes	3	No	0
Sohn et al., 2015	nd	nd	nd	U	27	0	1	16	1	11	0	0
Song et al., 2014	F	30	0	U	30	0	nd	nd	nd	nd	nd	nd
Stein et al., 2014	F	24	0	nd	nd	nd	1	nd	1	nd	0	0
Suh et al., 2014	nd	nd	nd	nd	nd	nd	Yes	29	Yes	11	Yes	2
Tan et al., 2014	F	45	0	U	45	0	Yes	45	No	0	No	0
Tan et al., 2016	F	58	0	U	58	0	1	30	1	28	0	0
Tian et al., 2014	F	100	0	U	100	0	Yes	68	Yes	32	No	0
Tilikete et al., 2001	F	15	0	U	15	0	Yes	15	No	0	No	0
Tripp and Krakow, 2014	F	30	0	U	30	0	Yes	27	Yes	3	No	0
Tung et al., 2010	F	32	0	U	32	0	nd	nd	nd	nd	nd	nd
Vahlberg et al., 2017	F & M	53	14	nd	nd	nd	1	55	1	12	0	0
VanNes et al., 2006	F	53	0	U	53	0	Yes	38	Yes	15	No	0
Waldron et Bohannon, 1989	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Wang et al., 2017	F	36	0	U	36	0	nd	nd	nd	nd	nd	nd
Wang RY, Lin PY et al., 2007	nd	nd	nd	U	58	0	Yes	39	Yes	19	No	0
Wang RY, Yen LL et al., 2005 part 1	nd	nd	nd	U	42	0	nd	nd	nd	nd	nd	nd
Wang RY, Yen LL et al., 2005 part 2	nd	nd	nd	U	61	0	nd	nd	nd	nd	nd	nd

Wang TC et al., 2015	F	51	0	U	51	0	Yes	nd	Yes	nd	No	0
Xie et al., 2018	F	244	0	U & B	239	5	1	160.608	1	63	0	0
Xing et al., 2007	F & M	nd	nd	nd	nd	nd	Yes	72	No	0	No	0
Yadav et al., 2015	F	24	0	U	24	0	nd	nd	nd	nd	nd	nd
Yeung et al., 2018	nd	nd	nd	U	19	0	1	14	1	5	0	0
Yoo et al., 2010	nd	nd	nd	U	59	0	Yes	29	Yes	30	No	0
Yoo et al., 2018	F	40	0	U	40	0	1	23	1	17	0	0
You et al., 2014	F	37	0	nd	nd	nd	Yes	33	Yes	4	No	0
Yu et Cho, 2016	F	20	0	U	20	0	1	12	1	8	0	0
Yun et al., 2018	nd	nd	nd	U	36	0	1	25	1	11	0	0
Zhang et al., 2015	F	60	0	U	60	0	nd	nd	nd	nd	nd	nd

Abbreviations: F, first; M, multiple; nd, not documented; U, unilateral.

S3E Table. Characteristics of participants for each study included

Study	Description of stroke lesion using brain imagery	Time post-stroke		Eligibility / Inclusion criteria of participants in trials		
		Mean (d)	SD (d)	Acute stroke	Subacute stroke	Chronic stroke
Allison et Dennett, 2007	No imagery used	17.36	17.59	Yes	No	No
Arabzadeh et al., 2018	No imagery used	32.65	15.82	Yes	Yes	No
Askim et al., 2010	No imagery used	14.61	6.94	Yes	No	No
Au-Yeung et al., 2009	No imagery used	1742.16	2635.20	No	No	Yes
Bae et al., 2015	Use of imagery reported without description of lesion	nd	nd	Yes	Yes	No
Barcala et al., 2011	No imagery used	427.00	201.91	No	No	No
Brogardh et al., 2012	No imagery used	1077.24	919.20	No	No	Yes
Bunketorp-Kall et al., 2017	No imagery used	1056.00	484.14	No	No	Yes
Buyukavci et al., 2016	No imagery used	35.91	16.23	No	Yes	No
Büyükvural Şen et al., 2015	No imagery used	91.50	nd	No	Yes	Yes
Cabanas-Valdés et al., 2015	Use of imagery reported without description of lesion	23.25	16.66	Yes	Yes	No
Chan KS et al., 2012	Use of imagery reported without description of lesion	1056.37	986.00	No	No	Yes
Chen CH et al., 2010	Imagery used with description of lesion in text	66.10	41.43	Yes	Yes	No
Chen CL et al., 2015	No imagery used	832.65	957.70	No	No	No
Chen D et al., 2014	Use of imagery reported without description of lesion	20.31	11.71	Yes	Yes	No
Chen IC et al., 2002	Use of imagery reported without description of lesion	101.94	nd	No	No	No
Chen JC et al., 2011	Use of imagery reported without description of lesion	11	nd	Yes	No	No
Chen, 2018	Use of imagery reported without description of lesion	nd	nd	No	Yes	Yes
Chern et al., 2013	No imagery used	nd	nd	No	No	No
Cho HY et al., 2013	No imagery used	441.52	151.33	No	No	Yes
Cho KH et al., 2012	No imagery used	383.84	76.21	No	No	Yes
Cho MK et al., 2015	No imagery used	676.80	340.99	No	No	Yes
Choi HS et al., 2017	No imagery used	422.73	141.91	No	No	Yes
Chu et al., 2015	Use of imagery reported without description of lesion	40.97	33.24	Yes	Yes	No
Chung et al., 2014	No imagery used	767.08	93.55	No	No	Yes
Dault et al., 2003	No imagery used	83.02	32.97	No	No	No
Dujovic et al., 2017	Use of imagery reported without description of lesion	nd	nd	Yes	Yes	Yes
Duncan et al., 1998	No imagery used	61.00	nd	No	Yes	No
Duncan et al., 2003	No imagery used	75.41	27.80	No	Yes	No
Erbil et al., 2018	No imagery used	1059.41	969.41	No	No	Yes
Fernandez-Gonzalo et al., 2016	Use of imagery reported without description of lesion	1429.51	1557.68	No	No	Yes
Ferreira et al., 2017	No imagery used	1347.77	511.35	No	No	Yes
Fritz et al., 2013	No imagery used	1099.66	1056.60	No	No	Yes

Furnari et al., 2014	No imagery used	192.15	42.70	No	No	No
Geiger et al., 2001	No imagery used	115.00	148.90	No	No	No
Ghanjal et al., 2014	Use of imagery reported without description of lesion	nd	nd	No	Yes	No
Globas et al., 2012	Imagery used with description of lesion in text	1985.55	1747.65	No	No	Yes
Goliwas et al., 2017	No imagery used	1345.50	865.15	No	No	Yes
Han et al., 2016	Use of imagery reported without description of lesion	19.95	8.95	Yes	Yes	No
Hart et al., 2004	No imagery used	823.50	nd	No	No	No
Heller et al., 2005	No imagery used	24.70	9.73	Yes	No	No
Hollands et al., 2015	No imagery used	247.36	380.34	Yes	Yes	Yes
Holmgren et al., 2010	No imagery used	132.49	32.65	No	Yes	Yes
Hosseini et al., 2012	No imagery used	588.65	230.28	No	Yes	Yes
Howe et al., 2005	Imagery used with description of lesion in text	24.75	16.50	Yes	Yes	No
Hsieh, 2019	No imagery used	382.78	204.74	No	Yes	Yes
Hsu et al., 2013	No imagery used	234.19	184.53	No	Yes	Yes
Huh et al., 2015	No imagery used	125.44	38.41	No	Yes	Yes
Hung et al., 2016	No imagery used	549.80	381.52	No	No	Yes
Hwang et al., 2015	No imagery used	193.30	18.56	No	No	Yes
Immink et al., 2014	No imagery used	1601.25	1887.95	No	No	Yes
In et al., 2016	No imagery used	397.70	141.85	No	No	Yes
Janssen et al., 2008	No imagery used	466.65	250.81	No	No	Yes
Jung et al., 2015	No imagery used	492.12	125.37	No	No	Yes
Jung et al., 2017	Use of imagery reported without description of lesion	200.69	78.37	No	No	No
Kamps et Schule, 2005	No imagery used	416.18	329.11	No	No	No
Karasu et al., 2018	Use of imagery reported without description of lesion	29.96	nd	Yes	Yes	Yes
Katz-Leurer et al., 2006	No imagery used	<30	nd	Yes	No	No
Khumsapsiri et al., 2018	Use of imagery reported without description of lesion	710.41	712.74	No	Yes	Yes
Kilinc et al., 2015	Use of imagery reported without description of lesion	1907.53	1507.08	Yes	Yes	No
Kim DH et al., 2008	No imagery used	1229.61	810.62	No	No	Yes
Kim JC et Lee, 2018	No imagery used	1157.66	957.66	No	No	Yes
Kim JH et al., 2009	Imagery used with description of lesion in text	764.94	282.50	No	No	Yes
Kim JY et al., 2018	Use of imagery reported without description of lesion	69.77	83.70	Yes	Yes	Yes
Kim SL et Lee, 2018	Imagery used with description of lesion in text	287.77	85.44	No	No	Yes
Kim YH et al., 2004	No imagery used	552.66	907.60	No	Yes	Yes
Kim YM et al., 2009	No imagery used	12.80	7.41	Yes	Yes	No
Knox et al., 2018	No imagery used	66.50	51.59	Yes	Yes	No
Kunkel et al., 2013	Imagery used with description of lesion in text	32.20	nd	Yes	No	No
Kwong et al., 2018	Use of imagery reported without description of lesion	1899.30	1132.28	No	No	Yes
Langhammer et al., 2009	Use of imagery reported without description of lesion	18.80	11.81	Yes	No	No
Lau RWK et al., 2012	No imagery used	1807.99	1409.15	No	No	Yes

Laufer, 2003	Use of imagery reported without description of lesion	77.70	61.70	No	No	No
Lee CH et al., 2014	No imagery used	345.67	137.37	No	No	Yes
Lee D et al., 2016	Use of imagery reported without description of lesion	1206.53	904.16	No	No	Yes
Lee HJ et al., 2018	No imagery used	535.28	118.17	No	No	Yes
Lee MM et al., 2018	No imagery used	100.04	43.51	No	Yes	No
Lee NK et al., 2013	No imagery used	609.09	248.58	No	No	Yes
Lee SH et al., 2012	Use of imagery reported without description of lesion	416.33	184.54	No	No	Yes
Lee SW et al., 2013	No imagery used	1633.22	842.41	No	No	Yes
Liang et al., 2012	No imagery used	12.25	5.98	Yes	No	No
Lin Q et al., 2015	Use of imagery reported without description of lesion	nd	nd	Yes	Yes	No
Lindvall et Forsberg, 2014	No imagery used	1515.79	1497.53	No	No	Yes
Lisinski et al., 2012	Use of imagery reported without description of lesion	518.50	91.50	No	No	No
Liu-Ambrose et Eng, 2015	No imagery used	986.18	401.78	No	No	Yes
Lu et al., 1997	No imagery used	1500.60	1256.60	No	No	No
Lynch et al., 2007	No imagery used	48.23	28.62	No	No	No
Marin et al., 2013	No imagery used	1570.58	886.79	No	No	Yes
Merkert et al., 2011	Use of imagery reported without description of lesion	54.15	203.65	No	No	No
Milczarek et al., 1993	Use of imagery reported without description of lesion	161.71	170.71	No	No	No
Mojica et al., 1988	No imagery used	144.90	nd	No	No	No
Moore JL et al., 2010	No imagery used	396.5	244	No	No	Yes
Morioka et Yagi, 2003	No imagery used	63.52	19.50	No	No	No
Mudie et al., 2002	No imagery used	nd	nd	Yes	Yes	No
Nadeau et al., 2013	Use of imagery reported without description of lesion	63.80	8.50	No	Yes	No
Ng et al., 2016	No imagery used	43.42	19.51	Yes	Yes	No
Nikamp et al., 2017	No imagery used	31.40	6.30	Yes	Yes	No
Noh et al., 2008	No imagery used	812.32	1090.81	No	No	Yes
Ordahan et al., 2015	Use of imagery reported without description of lesion	87.30	26.30	No	Yes	No
Page et al., 2008	No imagery used	1355.12	746.64	No	No	Yes
Park D et al., 2018	Use of imagery reported without description of lesion	338.55	108.81	No	No	Yes
Park DS et al., 2017	No imagery used	379.42	225.81	No	No	Yes
Park et al., 2014	No imagery used	567.91	64.36	No	No	Yes
Park HK et al., 2018	Use of imagery reported without description of lesion	339.59	175.89	No	No	Yes
Park J et al., 2017	No imagery used	nd	nd	Yes	Yes	No
Pollock et al., 2002	Imagery used with description of lesion in text	nd	nd	Yes	Yes	No
Pomeroy et al., 2001	No imagery used	nd	nd	No	No	Yes
Rajaratnam et al., 2013	No imagery used	14.85	6.80	Yes	No	No
Robertson et al., 2010	Use of imagery reported without description of lesion	1716.68	1972.35	No	No	Yes
Rougier et Boudrahem, 2010	Use of imagery reported without description of lesion	92.79	55.63	No	No	No
Salgueiro et Marquez, 2018	No imagery used	1568.75	1091.34	No	No	Yes

Sanchez-Mila et al., 2018	No imagery used	nd	nd	No	No	No
Schmid et al., 2012	No imagery used	1555.50	1232.20	No	No	Yes
Schuster et al., 2012	Imagery used with description of lesion in text	1295.25	1178.92	No	Yes	Yes
Shatil et al., 2005	No imagery used	1528.05	1567.70	No	No	Yes
Shin et al., 2016	Imagery used with description of lesion in text	499.44	262.44	No	No	Yes
Simons et al., 2009	No imagery used	1198.65	1138.26	No	Yes	Yes
Sohn et al., 2015	Use of imagery reported without description of lesion	64.40	57.40	No	No	No
Song et al., 2014	No imagery used	12.90	3.23	Yes	No	No
Stein et al., 2014	Use of imagery reported without description of lesion	68.80	111.01	No	No	Yes
Suh et al., 2014	No imagery used	440.73	150.90	No	No	Yes
Tan et al., 2014	Use of imagery reported without description of lesion	41.46	23.90	Yes	Yes	No
Tan et al., 2016	Use of imagery reported without description of lesion	213.50	114.99	No	Yes	Yes
Tian et al., 2014	No imagery used	34.60	16.47	Yes	Yes	No
Tilikete et al., 2001	Imagery used with description of lesion in text	77.27	nd	Yes	Yes	No
Tripp and Krakow, 2014	Use of imagery reported without description of lesion	45.03	32.99	Yes	Yes	No
Tung et al., 2010	No imagery used	605.43	480.68	No	No	No
Vahlberg et al., 2017	No imagery used	396.50	71.23	No	No	Yes
VanNes et al., 2006	Use of imagery reported without description of lesion	36.59	10.35	Yes	Yes	No
Waldron et Bohannon, 1989	No imagery used	130	211.7	No	No	No
Wang et al., 2017	Imagery used with description of lesion in text	nd	nd	Yes	Yes	No
Wang RY, Lin PY et al., 2007	No imagery used	100.35	35.69	No	Yes	No
Wang RY, Yen LL et al., 2005 part 1	No imagery used	101.00	51.30	Yes	Yes	No
Wang RY, Yen LL et al., 2005 part 2	No imagery used	1043.60	1104.90	No	No	Yes
Wang TC et al., 2015	Use of imagery reported without description of lesion	191.625	487.8841	No	No	Yes
Xie et al., 2018	Use of imagery reported without description of lesion	439.15	615.82	No	Yes	Yes
Xing et al., 2007	Use of imagery reported without description of lesion	19.64	11.88	No	No	No
Yadav et al., 2015	No imagery used	588.50	490.01	No	No	Yes
Yeung et al., 2018	No imagery used	1899.30	1351.43	No	No	Yes
Yoo et al., 2010	No imagery used	45.58	32.07	Yes	Yes	No
Yoo et al., 2018	No imagery used	24.25	nd	Yes	Yes	No
You et al., 2014	Use of imagery reported without description of lesion	24.34	18.96	Yes	Yes	No
Yu et Cho, 2016	No imagery used	384.30	78.63	No	No	Yes
Yun et al., 2018	Use of imagery reported without description of lesion	30.10	7.20	Yes	Yes	No
Zhang et al., 2015	Use of imagery reported without description of lesion	4.52	2.02	Yes	No	No

Abbreviations: nd, not documented.

S4 Table. Overall score of risk of bias and ethic statement for each study included

Study	Overall score of ROB (/14 points)	Ethic committee	Helsinki statement
Allison et Dennett, 2007	9	Yes	No
Arabzadeh et al., 2018	6	Yes	No
Askim et al., 2010	7	Yes	No
Au-Yeung et al., 2009	7	Yes	No
Bae et al., 2015	7	No	No
Barcala et al., 2011	6	Yes	No
Brogardh et al., 2012	12	Yes	Yes
Bunketorp-Kall et al., 2017	8	Yes	No
Buyukavci et al., 2016	8	Yes	Yes
Büyükvural Şen et al., 2015	6	Yes	No
Cabanas-Valdés et al., 2015	10	Yes	Yes
Chan KS et al., 2012	9	No	No
Chen CH et al., 2010	6	Yes	No
Chen CL et al., 2015	8	Yes	No
Chen D et al., 2014	6	No	No
Chen IC et al., 2002	6	No	No
Chen JC et al., 2011	7	Yes	No
Chen, 2018	5	No	No
Chern et al., 2013	6	No	No
Cho HY et al., 2013	9	Yes	No
Cho KH et al., 2012	7	Yes	No
Cho MK et al., 2015	8	Yes	No
Choi HS et al., 2017	6	Yes	Yes
Chu et al., 2015	7	No	No
Chung et al., 2014	8	Yes	No
Dault et al., 2003	5	Yes	No
Dujovic et al., 2017	11	Yes	Yes
Duncan et al., 1998	8	No	No
Duncan et al., 2003	10	Yes	No
Erbil et al., 2018	6	Yes	No
Fernandez-Gonzalo et al., 2016	7	Yes	No
Ferreira et al., 2017	6	Yes	No
Fritz et al., 2013	7	Yes	No
Furnari et al., 2014	7	Yes	No
Geiger et al., 2001	7	Yes	No
Ghanjal et al., 2014	6	Yes	No
Globas et al., 2012	9	Yes	No
Goliwas et al., 2017	6	Yes	No
Han et al., 2016	6	Yes	No
Hart et al., 2004	7	No	No
Heller et al., 2005	7	No	No
Hollands et al., 2015	9	Yes	No
Holmgren et al., 2010	10	Yes	No
Hosseini et al., 2012	8	Yes	No
Howe et al., 2005	7	Yes	No
Hsieh, 2019	8	Yes	Yes
Hsu et al., 2013	8	Yes	No
Huh et al., 2015	7	Yes	Yes
Hung et al., 2016	7	Yes	No
Hwang et al., 2015	9	Yes	No
Immink et al., 2014	9	Yes	No
In et al., 2016	9	Yes	Yes
Janssen et al., 2008	6	Yes	No
Jung et al., 2015	7	Yes	No

Jung et al., 2017	8	Yes	No
Kamps et Schule, 2005	6	Yes	No
Karasu et al., 2018	10	Yes	Yes
Katz-Leurer et al., 2006	8	Yes	No
Khumsapsiri et al., 2018	9	Yes	No
Kilinc et al., 2015	8	Yes	No
Kim DH et al., 2008	7	No	No
Kim JC et Lee, 2018	7	Yes	No
Kim JH et al., 2009	8	Yes	No
Kim JY et al., 2018	6	Yes	No
Kim SL et Lee, 2018	6	Yes	No
Kim YH et al., 2004	7	No	No
Kim YM et al., 2009	8	No	No
Knox et al., 2018	8	Yes	No
Kunkel et al., 2013	8	Yes	No
Kwong et al., 2018	8	Yes	Yes
Langhammer et al., 2009	8	Yes	Yes
Lau RWK et al., 2012	11	Yes	Yes
Laufer, 2003	7	Yes	No
Lee CH et al., 2014	10	Yes	No
Lee D et al., 2016	8	Yes	No
Lee HJ et al., 2018	7	No	No
Lee MM et al., 2018	8	Yes	No
Lee NK et al., 2013	7	Yes	Yes
Lee SH et al., 2012	8	Yes	No
Lee SW et al., 2013	8	Yes	No
Liang et al., 2012	6	Yes	No
Lin Q et al., 2015	8	No	No
Lindvall et Forsberg, 2014	7	Yes	No
Lisinski et al., 2012	7	Yes	No
Liu-Ambrose et Eng, 2015	8	Yes	Yes
Lu et al., 1997	6	Yes	No
Lynch et al., 2007	9	Yes	No
Marin et al., 2013	11	Yes	Yes
Merkert et al., 2011	6	Yes	No
Milczarek et al., 1993	7	No	No
Mojica et al., 1988	8	No	No
Moore JL et al., 2010	6	Yes	No
Morioka et Yagi, 2003	8	No	No
Mudie et al., 2002	7	Yes	No
Nadeau et al., 2013	10	Yes	Yes
Ng et al., 2016	8	Yes	No
Nikamp et al., 2017	5	Yes	No
Noh et al., 2008	9	Yes	Yes
Ordahan et al., 2015	11	Yes	Yes
Page et al., 2008	7	Yes	No
Park D et al., 2018	8	Yes	No
Park DS et al., 2017	9	Yes	No
Park et al., 2014	8	Yes	No
Park HK et al., 2018	7	No	No
Park J et al., 2017	6	Yes	No
Pollock et al., 2002	3	Yes	No
Pomeroy et al., 2001	8	Yes	No
Rajaratnam et al., 2013	10	Yes	No
Robertson et al., 2010	10	Yes	No
Rougier et Boudrahem, 2010	6	Yes	Yes
Salgueiro et Marquez, 2018	6	Yes	No
Sanchez-Mila et al., 2018	10	Yes	No

Schmid et al., 2012	6	Yes	No
Schuster et al., 2012	10	Yes	Yes
Shatil et al., 2005	7	Yes	No
Shin et al., 2016	10	Yes	No
Simons et al., 2009	6	Yes	No
Sohn et al., 2015	6	No	No
Song et al., 2014	7	No	No
Stein et al., 2014	7	Yes	No
Suh et al., 2014	11	Yes	No
Tan et al., 2014	8	Yes	No
Tan et al., 2016	6	Yes	No
Tian et al., 2014	8	No	No
Tilikete et al., 2001	8	No	No
Tripp and Krakow, 2014	9	No	Yes
Tung et al., 2010	10	Yes	No
Vahlberg et al., 2017	8	Yes	Yes
VanNes et al., 2006	6	Yes	No
Waldron et Bohannon, 1989	6	No	No
Wang et al., 2017	8	No	No
Wang RY, Lin PY et al., 2007	8	Yes	No
Wang RY, Yen LL et al., 2005 part 1	7	Yes	No
Wang RY, Yen LL et al., 2005 part 2	7	Yes	No
Wang TC et al., 2015	9	Yes	Yes
Xie et al., 2018	9	Yes	No
Xing et al., 2007	7	No	No
Yadav et al., 2015	7	Yes	No
Yeung et al., 2018	7	Yes	Yes
Yoo et al., 2010	7	No	No
Yoo et al., 2018	8	Yes	No
You et al., 2014	8	Yes	No
Yu et Cho, 2016	6	No	No
Yun et al., 2018	5	Yes	No
Zhang et al., 2015	8	No	No

higher score means lower ROB, lower score means higher ROB

Abbreviations: ROB, risk of bias.

S5 Table. Results of Egger tests detecting bias of publication

Comparison	Outcome	Post-intervention or persisting effects	Number of points	P value
PT vs NT	Balance	Post-intervention effects	40	0.10
PT vs NT	Mediolateral postural deviation EO, crossover RCTs	Post-intervention effects	16	0.70
PT vs NT	Postural stability EO	Post-intervention effects	18	0.44
PT vs NT	Autonomy	Post-intervention effects	16	0.33
PT vs NT	Balance	Persisting effects	12	0.93
PT vs NT	Mediolateral postural deviation EO	Persisting effects	5	0.45
PT vs NT	Postural stability EO	Persisting effects	3	0.58
PT vs NT	Autonomy	Persisting effects	6	0.98
PT vs ST/UC	Balance	Post-intervention effects	51	<0.01
PT vs ST/UC	Mediolateral postural deviation EO, parallel RCTs	Post-intervention effects	5	0.83
PT vs ST/UC	Postural stability EO	Post-intervention effects	18	<0.01
PT vs ST/UC	Autonomy	Post-intervention effects	17	0.03
PT vs ST/UC	Balance	Persisting effects	21	<0.01
PT vs ST/UC	Mediolateral postural deviation EO	Persisting effects	0	NC
PT vs ST/UC	Postural stability EO	Persisting effects	2	NC
PT vs ST/UC	Autonomy	Persisting effects	11	<0.01

Abbreviations: EO, eyes open; NC, not calculable; RCT, randomized controlled trial; ST, sham treatment; UC, usual care; vs, versus

S6 Table. Description of PT

S6A Table. Summary of comparisons

Characteristics	PT versus NT	PT versus ST/UC
Design of comparison		
Direct comparison (e.g. A vs B)	33	34
Comparison "on-top" (e.g. A+B versus C+B)	58	47
Comparator group (control treatment)		
No treatment (NT)	91	NA
Sham treatment (ST)	NA	33
Usual care (UC)	NA	48
Main therapeutic goal of PT		
PT aiming mainly at the recovery of balance (direct PT)	38	7
PT not specifically focused on the recovery of balance (indirect PT)	53	74

Abbreviations: NA, not applicable; NT, no treatment; PT, physical therapy; ST, sham treatment; UC, usual care

S6B Table. Summary of categories of PT investigated in studies included

Comparison PT versus NT	Comparison PT versus ST/UC
Acupuncture (5)	Acupuncture (0)
Assistive devices (19)	Assistive devices (2)
Constraint-induced therapy (4)	Constraint-induced therapy (0)
Functional task-training (32)	Functional task-training (24)
Functional task-training and other intervention (0)	Functional task-training and other intervention (1)
Functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention (14)	Functional task-training associated with musculoskeletal intervention and/or cardiopulmonary intervention (15)
Functional task-training and neurophysiological intervention (1)	Functional task-training and neurophysiological intervention (1)
Musculoskeletal intervention and body awareness therapy (1)	Musculoskeletal intervention and body awareness therapy (0)
Musculoskeletal intervention by active strengthening (3)	Musculoskeletal intervention by active strengthening (6)
Musculoskeletal intervention by electrostimulation (4)	Musculoskeletal intervention by electrostimulation (12)
Musculoskeletal intervention by immobilization (3)	Musculoskeletal intervention by immobilization (1)
Musculoskeletal intervention by mobilization (1)	Musculoskeletal intervention by mobilization (1)
Respiratory training (1)	Respiratory training (1)
Sensory interventions (2)	Sensory interventions (17)
Other intervention (1)	Other intervention (0)

(n) number of comparisons; Abbreviations: NT, no treatment; PT, physical therapy; ST, sham treatment; UC, usual care.

S6C Table. Characteristics of interventions for each study included

Study	Intervention (PT)	Design of comparison	Comparison	Type/nature of PT of comparison	Category of PT
Allison et Dennett, 2007	additional standing practice + CPT versus CPT	A+B vs B	PT vs NT	BT + sit to stand training	FTT and MI and/or CPI
Arabzadeh et al., 2018	task-oriented exercise program versus traditional physiotherapy	A vs B	PT vs ST/UC	FTT + MS	FTT and MI and/or CPI
Askim et al., 2010	intensive motor training after early supported discharge + standard training (PT) versus standard treatment (PT) after early supported discharge	A+B vs B	PT vs NT	FTT + CPI	FTT and MI and/or CPI
Au-Yeung et al., 2009	Tai chi versus exercices	A vs B	PT vs ST/UC	Tai Chi	FTT
Bae et al., 2015	lower-leg flexible kinesiology taping of paralyzed side versus lower-leg inflexible (sham) taping	A vs B	PT vs ST/UC	taping	MI by immobilization
Barcala et al., 2011	Wii Fit program + CPT versus CPT	A+B vs C+B	PT vs ST or UC	BT + VR	FTT alone
Brogardh et al., 2012	whole body vibration (standing static posture) versus sham whole body vibration (standing static posture)	A vs B	PT vs ST or UC	sensory intervention	Sensory intervention
Bunketorp-Kall et al., 2017	multimodal interventions based on rhythm-and-music therapy versus UC	A vs B	PT vs ST/UC	FTT	FTT
Bunketorp-Kall et al., 2017	multimodal interventions based on horse-riding therapy versus UC	A vs B	PT vs ST/UC	BT + FTT	FTT
Buyukavci et al., 2016	trunk balance exercises + CR program versus CR program	A+B vs B	PT vs NT	BT	FTT
Büyükvural Şen et al., 2015	isokinetic strengthening training (knee + ankle) + CR versus CR	A+B vs B	PT vs NT	MS	MI: active strengthening
Cabanas-Valdés et al., 2015	core stability exercises + CT versus CT	A+B vs B	PT vs NT	truncal exercises / core stability exercises	FTT and MI and/or CPI
Chan KS et al., 2012	whole body vibration versus sham vibration	A vs B	PT vs ST or UC	sensory intervention	Sensory intervention
Chen CH et al., 2010	lateral wedge on the paretic side versus no lateral wedge	A vs 0	PT vs NT	constraint-induced therapy	Constraint-induced therapy
Chen CH et al., 2010	lateral wedge on the non paretic side versus no lateral wedge	A vs 0	PT vs NT	constraint-induced therapy	Constraint-induced therapy
Chen CL et al., 2015	anterior ankle-foot orthosis versus no anterior ankle-foot orthosis	A vs 0	PT vs NT	orthoses	Assistive devices

Chen D et al., 2014	FES + routine treatment (medication + basic rehabilitation) versus comfort stimulation	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Chen D et al., 2014	FES + routine treatment (medication + basic rehabilitation) versus comfort stimulation	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Chen IC et al., 2002	Visual feedback BT + CPT + OT versus CPT + OT	A+B vs B	PT vs NT	BT + biofeedback	FTT alone
Chen JC et al., 2011	thermal stimulation + SR versus visits and discussions + SR	A+B vs C+B	PT vs ST or UC	sensory intervention	Sensory intervention
Chen, 2018	Tai Chi Yunshou versus traditional rehabilitation	A vs B	PT vs ST/UC	Tai Chi	FTT
Chern et al., 2013	shoes versus shoes + anterior ankle foot orthosis	A vs 0	PT vs NT	orthoses	Assistive devices
Chern et al., 2013	shoes versus shoes + posterior ankle foot orthosis	A vs 0	PT vs NT	orthoses	Assistive devices
Cho HY et al., 2013	TENS + PT (bobath) versus sham TENS + PT (bobath)	A+B vs C+B	PT vs ST or UC	sensory intervention	Sensory intervention
Cho KH et al., 2012	BT with VR + SR versus SR	A+B vs B	PT vs NT	BT + VR	FTT alone
Cho MK et al., 2015	treadmill GT with FES GM+TA + regular PT versus treadmill GT + sham FES GM+TA + regular PT	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Cho MK et al., 2015	treadmill GT with FES GM+TA + regular PT versus treadmill GT with FES TA + sham FES GM + regular PT	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Cho MK et al., 2015	treadmill GT with FES TA + sham FES GM + regular PT versus treadmill GT + sham FES GM+TA + regular PT	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Choi HS et al., 2017	game-based constraint-induced movement therapy + traditional PT versus traditional PT	A+B vs B	PT vs NT	BT + VR	FTT
Choi HS et al., 2017	General game-based training + traditional PT versus traditional PT	A+B vs B	PT vs NT	BT + VR	FTT
Chu et al., 2015	electroacupuncture stimulation of lateral side of Tianzhu (para-BL 10) + traditional acupuncture + CBT + CRT + routine treatment of neurology versus CBT + CRT + routine treatment of neurology	A+B vs B	PT vs NT	acupuncture	Acupuncture
Chung et al., 2014	GT with FES (GM + TA) versus GT with sham FES (GM + TA)	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Dault et al., 2003	standing balance with visual feedback versus standing balance EO	A vs 0	PT vs NT	BT + biofeedback	FTT alone
Dujovic et al., 2017	Novel multi-pad functional electrical stimulation + CSR versus CSR	A+B vs B	PT vs NT	FES + GT	FTT and MI and/or CPI

Duncan et al., 1998	exercise program at home versus UC at home or outpatient	A vs B	PT vs ST or UC	MS + FTT + NPI + CPI	FTT and MI and/or CPI
Duncan et al., 2003	exercise program at home versus UC at home	A vs B	PT vs ST or UC	MS + CPI + FTT + muscle stretching + active MM + NPI	FTT and MI and/or CPI
Erbil et al., 2018	Robot-assisted training + PT versus PT	A+B vs C+B	PT vs ST/UC	GT + BWS + EMA + biofeedback	FTT and MI and/or CPI
Fernandez-Gonzalo et al., 2016	Eccentric-overload flywheel resistance exercise training program versus daily routines	A vs B	PT vs ST/UC	MS	MI by active strengthening
Ferreira et al., 2017	Insole with corrective elements specifically designed for equinovarus foot on paretic limb (+ an insole without corrective elements on the non-paretic limb) + CPT versus Placebo insoles without corrective elements + CPT	A+B vs C+B	PT vs ST/UC	corrective insole	Assistive devices
Fritz et al., 2013	video games (Wii and PS) versus no treatment	A vs 0	PT vs NT	BT + VR	FTT alone
Furnari et al., 2014	hydrokinesitherapy + CPT versus CPT	A+B vs C+B	PT vs ST/UC	BT + MS + CPI + aquatic environment	FTT and MI and/or CPI
Geiger et al., 2001	balance training with biofeedback + PT versus PT	A+B vs C+B	PT vs ST/UC	BT + biofeedback	FTT
Ghanjal et al., 2014	observation and imitation of functional tasks + standard PT versus standard PT	A+B vs B	PT vs NT	observation and imitation of functional tasks	FTT alone
Ghanjal et al., 2014	observation and imitation of functional tasks + standard PT versus observation of symbols (no functional tasks) + standard PT	A+B vs C+B	PT vs ST or UC	observation and imitation of functional tasks	FTT alone
Globas et al., 2012	aerobic treadmill GT versus CPT	A vs B	PT vs ST or UC	GT + CPI	FTT and MI and/or CPI
Goliwas et al., 2017	Sensorimotor stimulation of the paretic foot + PT versus PT	A+B vs C+B	PT vs ST/UC	sensory intervention (ankle, foot) + BT + MM (ankle, foot) + muscle stretching (ankle, foot) + NPI	FTT + other
Han et al., 2016	Robot-assisted gait training + CR therapy versus CPT + CR therapy	A+B vs C+B	PT vs ST/UC	GT + BWS + EMA + biofeedback	FTT and MI and/or CPI
Hart et al., 2004	Tai Chi Chuan versus balance group exercises	A vs B	PT vs ST or UC	Tai Chi	FTT alone
Heller et al., 2005	BT with biofeedback (barofeedback) + CR (neuromotor therapy) versus CR (neuromotor therapy)	A+B vs B	PT vs NT	BT + biofeedback	FTT alone
Hollands et al., 2015	Treadmill visual cue training + SR versus UC + SR	A+B vs C+B	PT vs ST/UC	GT + cue	FTT

Hollands et al., 2015	Over-ground visual cue training + SR versus UC + SR	A+B vs C+B	PT vs ST/UC	GT + cue	FTT
Holmgren et al., 2010	high intensity functional exercises versus educational program	A vs B	PT vs NT	FTT + exercise + movement + intensive	FTT and MI and/or CPI
Hosseini et al., 2012	mental practice + PT versus PT	A+B vs B	PT vs ST/UC	mental imagery	FTT
Howe et al., 2005	lateral weight transference exercises + UC versus UC	A+B vs B	PT vs NT	BT	FTT alone
Hsieh, 2019	Training with an adaptive foot switch and video games + regular physiotherapy + regular walking versus regular physiotherapy + regular walking	A+B vs B	PT vs NT	ankle movement	MI by mobilization
Hsu et al., 2013	noxious thermal stimulation + PT + OT versus innocuous thermal stimulation + PT + OT	A+B vs C+B	PT vs ST or UC	sensory intervention	Sensory intervention
Huh et al., 2015	balance training with a new lower limb balance control trainer + CR therapy versus CR therapy	A+B vs C+B	PT vs ST/UC	BT + biofeedback	FTT
Hung et al., 2016	Tetrax biofeedback games + conventional outpatient rehabilitation therapy versus conventional outpatient rehabilitation therapy	A+B vs B	PT vs NT	BT + biofeedback	FTT
Hwang et al., 2015	treadmill GT combined with FES using a tilt sensor + CPT versus treadmill GT combined with sham FES using a tilt sensor + CPT	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Immink et al., 2014	yoga (group + home) + usual treatment and lifestyle behavior versus wait list (no treatment) + usual treatment and lifestyle behavior	A+B vs B	PT vs NT	yoga	FTT alone
In et al., 2016	virtual reality reflection therapy (mirror therapy) + CR program versus sham virtual reality reflection therapy + CR program	A+B vs C+B	PT vs ST/UC	mirror therapy (by VR) + FTT	FTT
Janssen et al., 2008	leg cycling exercise with maximally tolerable electrical stimulation versus leg cycling exercise with just sensible electrical stimulation	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Jung et al., 2015	Trunk stabilization training on an unstable surface using visual feedback + general exercises versus general exercises	A+B vs B	PT vs NT	BT + biofeedback	FTT alone
Jung et al., 2017	sit-to-stand training combined with transcutaneous electrical stimulation + CT versus sit-to-stand training combined with sham transcutaneous electrical stimulation + CT	A+B vs C+B	PT vs ST/UC	TENS	sensory intervention
Kamps et Schule, 2005	Cyclic movement training of the lower limb versus CPT + conventional OT	A vs B	PT vs ST or UC	MS + CPI + assistance + resistance + biofeedback	MI: active strengthening
Karasu et al., 2018	Wii Fit-based balance rehabilitation + CR versus CR	A+B vs B	PT vs NT	BT + VR	FTT

Katz-Leurer et al., 2006	Early cycling training + regular rehabilitation versus regular rehabilitation	A+B vs B	PT vs NT	MS	MI: active strengthening
Khumsapsiri et al., 2018	Training using a new multidirectional reach tool + CPT versus CPT	A+B vs B	PT vs NT	BT	FTT
Kilinc et al., 2015	Bobath-based trunk training versus physiotherapy	A vs B	PT vs ST/UC	NPI + FTT	FTT and NPI
Kim DH et al., 2008	Isokinetic strengthening of trunk muscles + NDT and GT versus NDT and GT	A+B vs B	PT vs NT	truncal exercise / core stability exercises	MI: active strengthening
Kim JC et Lee, 2018	action observation physical training versus landscape imagery observation physical training	A+B vs C+B	PT vs ST/UC	observation and imitation of functional tasks	FTT
Kim JH et al., 2009	VR + CPT versus CPT	A+B vs B	PT vs NT	BT + VR	FTT alone
Kim JY et al., 2018	robot-(Morning Walk®) assisted gait training + conventional physiotherapy versus conventional physiotherapy	A+B vs C+B	PT vs ST/UC	GT + BWS + EMA + biofeedback	FTT and MI and/or CPI
Kim SL et Lee, 2018	weight-bearing-based mobilization with movement + UC versus weight-bearing with placebo mobilization with movement + UC	A+B vs C+B	PT vs ST/UC	MM	MI by mobilization
Kim YH et al., 2004	static BT with visual biofeedback versus traditional rehabilitation	A vs B	PT vs ST or UC	BT + biofeedback	FTT alone
Kim YH et al., 2004	dynamic BT with visual biofeedback versus traditional rehabilitation	A vs B	PT vs ST or UC	BT + biofeedback	FTT alone
Kim YM et al., 2009	ES of trunc muscles + ES of lower limb muscles + PT + OT versus ES of lower limb muscles + PT + OT	A+B vs B	PT vs NT	FES	MI by electrostimulation
Knox et al., 2018	task-oriented circuit gait training versus educational therapy	A vs B	PT vs ST/UC	FTT	FTT
Knox et al., 2018	conventional strength training versus educational therapy	A vs B	PT vs ST/UC	MS	MI by active strengthening
Kunkel et al., 2013	Exercises + UC versus UC	A+B vs B	PT vs NT	BT	FTT alone
Kunkel et al., 2013	FES during exercises + UC versus UC	A+B vs B	PT vs NT	BT + FES	FTT and MI and/or CPI
Kwong et al., 2018	Bilateral Transcutaneous Electrical Nerve Stimulation during functional task-oriented training versus Unilateral Transcutaneous Electrical Nerve Stimulation (on paretic lower limb et sham on non-paretic lower limb) during functional task-oriented training	A+B vs C+B	PT vs ST/UC	sensory intervention	Sensory intervention
Langhammer et al., 2009	Specific intensive exercises versus exercises (UC)	A vs B	PT vs ST or UC	MS + CPI + FTT	FTT and MI and/or CPI

Lau RWK et al., 2012	whole body vibration + (while) exercise and BT versus sham whole body vibration + (while) exercise and BT	A+B vs C+B	PT vs ST or UC	sensory intervention	Sensory intervention
Laufer, 2003	Standard cane versus no cane	A vs 0	PT vs NT	Cane	Assistive devices
Laufer, 2003	Quad cane versus no cane	A vs 0	PT vs NT	Cane	Assistive devices
Lee CH et al., 2014	VR + general PT versus general PT	A+B vs B	PT vs NT	BT + VR	FTT alone
Lee D et al., 2016	Mirror Therapy combined with NeuroMuscular Electrical Stimulation + CPT versus CPT	A+B vs B	PT vs NT	FES + mirror therapy	MI by electrostimulation
Lee HJ et al., 2018	diaphragm and deep abdominal muscle exercise versus Traditional exercise	A vs B	PT vs ST/UC	respiratory training	Respiratory training
Lee MM et al., 2018	game-based VR canoe paddling training + CPR versus CPR	A+B vs B	PT vs NT	BT + VR	FTT
Lee NK et al., 2013	Close kinetic chain exercises versus routine activities (no regular exercise program)	A vs B	PT vs ST or UC	MS	MI: active strengthening
Lee NK et al., 2013	Open kinetic chain exercises versus routine activities (no regular exercise program)	A vs B	PT vs ST or UC	MS	MI: active strengthening
Lee SH et al., 2012	Visual feedback BT (standing) + CPT versus CPT	A+B vs B	PT vs NT	BT + biofeedback	FTT alone
Lee SW et al., 2013	Local vibration stimulus training during weight-bearing and weight-shift training + SR versus sham local vibration stimulus training during weight-bearing and weight-shift training + SR	A+B vs C+B	PT vs ST or UC	sensory intervention	Sensory intervention
Liang et al., 2012	Thermal stimulation + PT + OT versus PT + OT + discussion sessions	A+B vs C+B	PT vs ST or UC	sensory intervention	Sensory intervention
Lin Q et al., 2015	Acupuncture + routine rehabilitation training versus routine rehabilitation training	A+B vs B	PT vs NT	acupuncture	Acupuncture
Lindvall et Forsberg, 2014	Body awareness therapy + usual daily activities, ongoing PT or other training versus no treatment + usual daily activities, ongoing PT or other training	A+B vs B	PT vs NT	MM + body awareness therapy	MI and body awareness therapy
Lisinski et al., 2012	BT with visual feedback versus no treatment	A vs 0	PT vs NT	BT + biofeedback	FTT alone
Liu-Ambrose et Eng, 2015	immediate community-based exercises + recreation and leisure activities versus UC	A vs B	PT vs ST or UC	MS + CPI + FTT	FTT and MI and/or CPI
Lu et al., 1997	greater trochanter length cane versus no cane	A vs 0	PT vs NT	Cane	Assistive devices
Lu et al., 1997	wrist crease length cane versus no cane	A vs 0	PT vs NT	Cane	Assistive devices
Lynch et al., 2007	sensory retraining + standard PT versus relaxation + standard standard PT	A+B vs C+B	PT vs ST or UC	sensory intervention + relearning	Sensory intervention
Marin et al., 2013	whole body vibration during isometric position exercises + SR versus isometric position (without vibration) + SR	A+B vs C+B	PT vs ST or UC	sensory intervention	Sensory intervention

Merkert et al., 2011	vibration training + conventional comprehensive geriatric rehabilitation versus conventional comprehensive geriatric rehabilitation	A+B vs B	PT vs NT	sensory intervention	Sensory intervention
Milczarek et al., 1993	four-footed cane versus no cane	A vs 0	PT vs NT	Cane	Assistive devices
Milczarek et al., 1993	standard cane versus no cane	A vs 0	PT vs NT	Cane	Assistive devices
Mojica et al., 1988	ankle-foot orthosis versus no ankle-foot orthosis	A vs 0	PT vs NT	orthoses	Assistive devices
Moore JL et al., 2010	intensive LT (intensity stepping practice + BWS) versus no treatment	A vs 0	PT vs NT	GT + BWS + CPI	FTT and MI and/or CPI
Morioka et Yagi, 2003	perceptual learning exercise + PT and OT versus PT and OT	A+B vs B	PT vs NT	sensory intervention + relearning	Sensory intervention
Mudie et al., 2002	sitting BT with visual feedback + standard PT and OT versus standard PT and OT	A+B vs B	PT vs NT	BT + biofeedback	FTT alone
Mudie et al., 2002	bobath + standard PT and OT versus standard PT and OT	A+B vs B	PT vs NT	BT (NPI)	FTT alone
Mudie et al., 2002	sitting task-related reach training + standard PT and OT versus standard PT and OT	A+B vs B	PT vs NT	BT + task-related reach training	FTT alone
Nadeau et al., 2013	GT + BWS + UC versus UC	A+B vs B	PT vs NT	GT + BWS	FTT and MI and/or CPI
Nadeau et al., 2013	home exercise program + UC versus UC	A+B vs B	PT vs NT	FTT + MS + MM	FTT and MI and/or CPI
Ng et al., 2016	Transcutaneous electrical nerve stimulation during task-oriented balance training + CR versus placebo-TENS during task-oriented balance training + CR	A+B vs C+B	PT vs ST/UC	sensory intervention	Sensory intervention
Nikamp et al., 2017	Early ankle-foot orthosis + UC versus Delayed ankle-foot orthosis + UC	A+B vs B	PT vs NT	orthoses	Assistive devices
Noh et al., 2008	aquatic therapy (Halliwick and Ai Chi methods) versus CT	A vs B	PT vs ST/UC	BT + aquatic environment	FTT
Ordahan et al., 2015	Balance training with balance trainer + CR versus CR	A+B vs B	PT vs NT	BT + biofeedback + verticalization (support)	FTT and MI and/or CPI
Page et al., 2008	bilateral reciprocal locomotor training with device versus home exercice program	A vs B	PT vs ST/UC	MS + EMR	MI by active strengthening
Park D et al., 2018	talus-stabilizing taping versus barefoot	A vs 0	PT vs NT	taping	MI by immobilization
Park D et al., 2018	ankle foot orthosis versus barefoot	A vs 0	PT vs NT	orthosis	Assistive devices

Park DS et al., 2017	virtual reality training using Xbox Kinect + CPT versus CPT	A+B vs B	PT vs NT	BT + VR	FTT
Park et al., 2014	TENS + (during) therapeutic exercises versus placebo TENS + (during) therapeutic exercises	A+B vs C+B	PT vs ST or UC	sensory intervention	Sensory intervention
Park HK et al., 2018	land trunk exercise + aquatic trunk exercises (Halliwick) + CPT versus CPT	A+B vs B	PT vs NT	truncal exercice / core stability exercises + BT + aquatic environment	FTT and MI and/or CPI
Park J et al., 2017	boxing program + CPT versus CPT	A+B vs B	PT vs NT	FTT + muscle stretching	FTT and MI and/or CPI
Pollock et al., 2002	independent practice of motor task training + standard PT (bobath) versus standard PT (bobath)	A+B vs B	PT vs NT	BT + FTT	FTT alone
Pomeroy et al., 2001	weight garments versus no weighted garment	A vs 0	PT vs NT	constraint-induced therapy	Constraint-induced therapy
Rajaratnam et al., 2013	BT with biofeedback + CR versus CR	A+B vs C+B	PT vs ST or UC	BT + VR	FTT alone
Robertson et al., 2010	FES versus no FES	A vs 0	PT vs NT	FES	MI by electrostimulation
Rougier et Boudrahem, 2010	standing balance with visual feedback versus standing balance EO	A vs 0	PT vs NT	BT + biofeedback	FTT alone
Salgueiro et Marquez, 2018	visual and occulomotor training + CT versus CT	A+B vs B	PT vs NT	visual and occulomotor training	visual and occulomotor training
Sanchez-Mila et al., 2018	dry needling + multimodal neuro-rehabilitation (bobath) versus multimodal neuro-rehabilitation (bobath)	A+B vs B	PT vs NT	acupuncture	Acupuncture
Schmid et al., 2012	yoga +/- relaxation audio recording versus no treatment	A vs 0	PT vs NT	yoga	FTT alone
Schuster et al., 2012	PT + embedded motor imagery training versus PT + audio tapes with information related to stroke	A+B vs C+B	PT vs ST or UC	mental imagery	FTT alone
Schuster et al., 2012	PT + added motor imagery training versus PT + audio tapes with information related to stroke	A+B vs C+B	PT vs ST or UC	mental imagery	FTT alone
Shatil et al., 2005	Therapeutic golf rehabilitation (PT + golf) + regular routine versus hand therapy + regular routine (regular routine = no treatment)	A+B vs C+B	PT vs ST or UC	FTT + MS + CPI + MM + muscle stretching	FTT and MI and/or CPI
Shin et al., 2016	Smartphone-based visual feedback trunk control training + CR versus CR	A+B vs B	PT vs NT	BT + biofeedback	FTT
Simons et al., 2009	ankle-foot orthosis versus no ankle-foot orthosis	A vs 0	PT vs NT	orthoses	Assistive devices

Sohn et al., 2015	Bobath sling versus no sling	A vs 0	PT vs NT	Sling	MI by immobilization
Sohn et al., 2015	simple arm sling versus no sling	A vs 0	PT vs NT	Sling	MI by immobilization
Song et al., 2014	tetra-ataxiometric posturography program + CBT versus CBT	A+B vs B	PT vs NT	BT + biofeedback	FTT alone
Song et al., 2014	VR during BT + CBT versus CBT	A+B vs B	PT vs NT	BT + VR	FTT alone
Stein et al., 2014	PT with robotic knee brace versus exercises	A vs B	PT vs ST/UC	FTT + EMA	FTT and MI and/or CPI
Suh et al., 2014	Interferential current therapy + SR versus sham Interferential current therapy + SR	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Tan et al., 2014	four-channel FES (tibialis anterior, quadriceps, hamstrings, and gastrocnemius of the affected leg) + CR versus placebo four-channel FES (tibialis anterior, quadriceps, hamstrings, and gastrocnemius of the affected leg) + CR	A+B vs C+B	PT vs ST or UC	FES	MI by electrostimulation
Tan et al., 2016	Four-channel functional electrical stimulation + medicines and routine rehabilitation training versus Placebo functional electrical stimulation + medicines and routine rehabilitation training	A+B vs C+B	PT vs ST/UC	FES	MI by electrostimulation
Tan et al., 2016	Single channel functional electrical stimulation + medicines and routine rehabilitation training versus Placebo functional electrical stimulation + medicines and routine rehabilitation training	A+B vs C+B	PT vs ST/UC	FES	MI by electrostimulation
Tian et al., 2014	Acupuncture + medical treatment versus medical treatment	A+B vs B	PT vs NT	acupuncture	Other intervention
Tilikete et al., 2001	prism adaptation (optical shift 10 deg to the right) versus sham prism adaptation (no optical shift)	A vs B	PT vs ST or UC	sensory intervention	Sensory intervention
Tilikete et al., 2001	prism adaptation (optical shift 10 deg to the left) versus sham prism adaptation (no optical shift)	A vs B	PT vs ST or UC	sensory intervention	Sensory intervention
Tripp and Krakow, 2014	Halliwick-therapy + CPT versus CPT	A+B vs C+B	PT vs ST or UC	BT + aquatic therapy	FTT alone
Tung et al., 2010	sit-to-stand + general PT versus general PT	A+B vs B	PT vs NT	sit to stand training	FTT alone
Vahlberg et al., 2017	progressive resistance and balance exercise program + motivational group discussions versus regular activities	A vs B	PT vs NT	FTT + MS + CPI	FTT and MI and/or CPI
VanNes et al., 2006	whole body vibration (standing posture) + PT rehabilitation (individualized and group) (+ occupational and speech therapy and psychologic treatment) versus exercise therapy on music + PT rehabilitation (individualized and group) (+ occupational and speech therapy and psychologic treatment)	A+B vs C+B	PT vs ST or UC	sensory intervention	Sensory intervention
Waldron et Bohannon, 1989	cane (cane - elbow 40 deg) versus no cane	A vs 0	PT vs NT	Cane	Assistive devices

Waldron et Bohannon, 1989	cane (cane - elbow 30 deg) versus no cane	A vs 0	PT vs NT	Cane	Assistive devices
Waldron et Bohannon, 1989	cane (cane - elbow 20 deg) versus no cane	A vs 0	PT vs NT	Cane	Assistive devices
Wang et al., 2017	Mirror therapy + CR versus passive or active supplementary training of the lower extremities of the affected side (as mirror therapy) + CR	A+B vs C+B	PT vs ST/UC	mirror therapy	FTT
Wang RY, Lin PY et al., 2007	Ankle-foot orthosis versus no ankle-foot orthosis	A vs 0	PT vs NT	orthoses	Assistive devices
Wang RY, Yen LL et al., 2005 part 1	ankle-foot orthosis versus no ankle-foot orthosis	A vs 0	PT vs NT	orthoses	Assistive devices
Wang RY, Yen LL et al., 2005 part 2	ankle-foot orthosis versus no ankle-foot orthosis	A vs 0	PT vs NT	orthoses	Assistive devices
Wang TC et al., 2015	caregiver-mediated training (home-based intervention) versus routine care + visits or telephone calls	A vs B	PT vs ST or UC	MS + MM + FTT	FTT and MI and/or CPI
Xie et al., 2018	Tai Chi Yunshou exercise versus Balance rehabilitation training	A vs B	PT vs ST/UC	Tai Chi	FTT
Xing et al., 2007	acupuncture + hyperbaric oxygen therapy + conventional drug treatment versus hyperbaric oxygen therapy + conventional drug treatment	A+B vs B	PT vs NT	acupuncture	Other intervention
Yadav et al., 2015	specific balance strategy training versus general balance exercise	A vs B	PT vs ST/UC	BT + muscle stretching + MS	FTT and MI and/or CPI
Yeung et al., 2018	gait training + Robot-assisted ankle foot orthosis with dorsiflexion assistance versus gait training + sham Robot-assisted ankle foot orthosis with dorsiflexion assistance	A vs B	PT vs ST/UC	EMA in orthoses	Assistive devices
Yoo et al., 2010	core strengthening program + CPT versus CPT	A+B vs B	PT vs NT	FTT + truncal exercises / core stability exercises (MS)	FTT and MI and/or CPI
Yoo et al., 2018	bedside respiratory muscle training + CSR versus CSR	A+B vs B	PT vs NT	respiratory training	Respiratory training
You et al., 2014	FES + SR (PT + OT) versus SR (PT + OT)	A+B vs B	PT vs NT	FES	MI by electrostimulation
Yu et Cho, 2016	Virtual reality game + SR program versus SR program	A+B vs B	PT vs NT	BT + VR	FTT
Yun et al., 2018	Robot-assisted gait training versus CPT	A vs B	PT vs ST/UC	GT + BWS + EMA + biofeedback	FTT and MI and/or CPI
Zhang et al., 2015	modified CITUL + routine rehabilitation versus routine rehabilitation	A+B vs B	PT vs NT	CITUL	Constraint-induced therapy

Abbreviations: BT, balance training; BWS, body weight support; CBT, conventional balance training; CITUL, constraint-induced movement therapy of upper limb; CPI, cardiopulmonary intervention; CPT, conventional physical therapy; CPR, conventional physical rehabilitation; CR, conventional rehabilitation; CRT, comprehensive rehabilitation therapy; CSR, conventional stroke rehabilitation; CT, conventional therapy; Deg, degree; EMA, electromechanical assistance; EMR, electromechanical resistance; EO, eyes opened; FES, functional electrostimulation; FTT, functional task training; GM, gluteus medius; GT, gait training; LT, locomotor training; LT-RGO, locomotor training with a robotic gait orthosis; MI, musculoskeletal intervention; MM, musculoskeletal mobilization; MS, muscle strengthening; Nd, not documented; NDT, neurodevelopmental treatment; NPI, neurophysiological intervention; OT, occupational therapy; PT, physical therapy; rTMS, repetitive transcranial magnetic stimulation; SR, standard rehabilitation; TA, tibial anterior; tDCS, transcranial direct current stimulation; TENS, transcutaneous electrical nerve stimulation; UC, usual care; VR, virtual reality

S7 Table. Duration of PT

S7A Table. Summary of duration

	PT versus NT		PT versus ST/UC	
	All interventions (comparison + concomitant therapy)			
	Experimental group	Control group	Experimental group	Control group
	mean +/- standard deviation / median / minimum-maximum			
Mean duration of session (min)	58.3 +/- 76.9 / 48.3 / 0.5-600.0	33.1 +/- 39.0 / 30.0 / 0.0-160.0	67.0 +/- 41.8 / 60.0 / 3.0-236.5	66.8 +/- 44.3 / 60.0 / 3.0-272.0
Number of sessions by week	3.8 +/- 3.0 / 4.0 / 0.8-21.9	2.9 +/- 2.7 / 3.0 / 0.0-14.5	3.5 +/- 1.7 / 3.0 / 0.5-10.0	3.5 +/- 1.7 / 3.0 / 0.1-6.0
Number of weeks	3.7 +/- 2.9 / 3.0 / 1.0-12.0	3.7 +/- 2.9 / 3.0 / 1.0-12.0	6.6 +/- 6.6 / 6.0 / 1.0-52.0	6.3 +/- 5.3 / 6.0 / 1.0-40.0
Total number of sessions	17.4 +/- 22.0 / 15.0 / 1.0-164.0	12.3 +/- 14.4 / 11.0 / 0.0-78.6	21.2 +/- 22.3 / 17.0 / 1.0-160.0	17.9 +/- 14.1 / 15.0 / 1.0-84.0
Total duration (min)	1444.3 +/- 3043.8 / 720.0 / 0.5-25200.0	711.0 +/- 1153.8 / 360.0 / 0.0-7071.0	1402.0 +/- 1282.4 / 960.0 / 3.0-5700.0	1203.0 +/- 1127.7 / 900.0 / 3.0-5700.0
	Comparison only			
	mean +/- standard deviation / median / minimum-maximum			
Mean duration of session (min)	33.1 +/- 67.6 / 20.2 / 0.5-600.0		40.5 +/- 32.0 / 30.0 / 1.0-236.5	
Number of sessions by week	3.3 +/- 1.9 / 3.0 / 1.0-7.5		3.4 +/- 1.7 / 3.0 / 0.5-10.0	
Number of weeks	3.7 +/- 2.9 / 3.0 / 1.0-12.0		6.6 +/- 6.6 / 5.0 / 1.0-52.0	
Total number of sessions	14.3 +/- 14.4 / 12.0 / 1.0-72.0		20.7 +/- 22.3 / 16.0 / 1.0-160.0	
Total duration (min)	811.6 +/- 2821.1 / 300.0 / 0.5-25200.0		911.4 +/- 1054.9 / 570.0 / 3.0-5460.0	
Trial with duration of PT ≥30min per working day	24		43	

Abbreviations: min, minute; NT, no treatment; PT, physical therapy; ST, sham treatment; UC, usual care;

S7B Table. Duration of PT compared for each study included

Study	Type/nature of PT of comparison	Comparison				
		Mean duration of session (min)	Weekly frequency of session	Number of weeks	Number of session	Overall duration (min)
Allison et Dennett, 2007	BT + sit to stand training	45.00	5.00	2.00	10.00	450.00
Arabzadeh et al., 2018	FTT + MS	50.00	3.00	4.00	12.00	600.00
Askim et al., 2010	FTT + CPI	19.09	6.00	12.00	72.00	1374.80
Au-Yeung et al., 2009	Tai Chi	236.50	1.00	12.00	11.30	2838.00
Bae et al., 2015	taping	5.00	1.00	1.00	1.00	5.00
Barcala et al., 2011	BT + VR	30.00	2.00	5.00	10.00	300.00
Brogardh et al., 2012	sensory intervention	45.00	2.00	6.00	12.00	540.00
Bunketorp-Kall et al., 2017	FTT	90.00	2.00	12.00	24.00	2160.00
Bunketorp-Kall et al., 2017	BT + FTT	120.00	2.00	12.00	24.00	2880.00
Buyukavci et al., 2016	BT	120.00	3.00	3.00	9.00	1080.00
Büyükvural Şen et al., 2015	MS	nd	5.00	3.00	nd	nd
Cabanas-Valdés et al., 2015	truncal exercises / core stability exercises	14.76	5.00	5.00	25.00	369.00
Chan KS et al., 2012	sensory intervention	21.00	1.00	1.00	1.00	21.00
Chen CH et al., 2010	constraint-induced therapy	3.00	1.00	1.00	1.00	3.00
Chen CH et al., 2010	constraint-induced therapy	3.00	1.00	1.00	1.00	3.00
Chen CL et al., 2015	orthoses	5.00	1.00	1.00	1.00	5.00
Chen D et al., 2014	FES	30.00	5.00	3.00	15.00	450.00
Chen D et al., 2014	FES	30.00	5.00	3.00	15.00	450.00
Chen IC et al., 2002	BT + biofeedback	20.00	5.00	2.00	10.00	200.00
Chen JC et al., 2011	sensory intervention	48.00	5.00	6.00	30.00	1440.00
Chen, 2018	Tai Chi	nd	nd	6.00	nd	nd
Chern et al., 2013	orthoses	2.00	1.00	1.00	1.00	2.00
Chern et al., 2013	orthoses	2.00	1.00	1.00	1.00	2.00
Cho HY et al., 2013	sensory intervention	60.00	1.00	1.00	1.00	60.00
Cho KH et al., 2012	BT + VR	30.00	3.00	6.00	18.00	540.00
Cho MK et al., 2015	FES	30.00	5.00	4.00	20.00	600.00
Cho MK et al., 2015	FES	30.00	5.00	4.00	20.00	600.00
Cho MK et al., 2015	FES	30.00	5.00	4.00	20.00	600.00
Choi HS et al., 2017	BT + VR	30.00	3.00	4.00	12.00	360.00
Choi HS et al., 2017	BT + VR	30.00	3.00	4.00	12.00	360.00
Chu et al., 2015	acupuncture	nd	5.00	8.00	40.00	nd
Chung et al., 2014	FES	30.00	5.00	6.00	30.00	900.00

Dault et al., 2003	BT + biofeedback	1.50	1.00	1.00	1.00	1.50
Dujovic et al., 2017	FES + GT	30.00	5.00	4.00	20.00	600.00
Duncan et al., 1998	MS + FTT + NPI + CPI	90.00	3.00	12.00	36.00	3240.00
Duncan et al., 2003	MS + CPI + FTT + muscle stretching + active MM + NPI	91.00	2.57	13.00	33.40	3039.00
Erbil et al., 2018	GT + BWS + EMA + biofeedback	30.00	5.00	3.00	15.00	450.00
Fernandez-Gonzalo et al., 2016	MS	20.00	2.00	12.00	24.00	480.00
Ferreira et al., 2017	corrective insole	nd	nd	12.00	nd	nd
Fritz et al., 2013	BT + VR	50.00	4.00	5.00	20.00	1000.00
Furnari et al., 2014	BT + MS + CPI + aquatic environment	60.00	3.00	8.00	24.00	1440.00
Geiger et al., 2001	BT + biofeedback	15.00	2.50	4.00	10.00	150.00
Ghanjal et al., 2014	observation and imitation of functional tasks	15.00	nd	nd	12.00	180.00
Ghanjal et al., 2014	observation and imitation of functional tasks	15.00	nd	nd	12.00	180.00
Globas et al., 2012	GT + CPI	40.00	2.95	13.20	39.00	1560.00
Goliwas et al., 2017	sensory intervention (ankle, foot) + BT + MM (ankle, foot) + muscle stretching (ankle, foot) + NPI	20.00	4.17	6.00	25.00	500.00
Han et al., 2016	GT + BWS + EMA + biofeedback	30.00	5.00	4.00	20.00	600.00
Hart et al., 2004	Tai Chi	60.00	2.00	12.00	24.00	1440.00
Heller et al., 2005	BT + biofeedback	30.00	5.00	7.86	39.29	1178.57
Hollands et al., 2015	GT + cue	60.00	2.00	8.00	16.00	960.00
Hollands et al., 2015	GT + cue	60.00	2.00	8.00	16.00	960.00
Holmgren et al., 2010	FTT + exercise + movement + intensive	72.00	6.00	5.00	30.00	2160.00
Hosseini et al., 2012	mental imagery	15.00	nd	nd	nd	nd
Howe et al., 2005	BT	25.90	nd	4.00	10.00	258.95
Hsieh, 2019	ankle movement	30.00	7.00	10.00	70.00	2100.00
Hsu et al., 2013	sensory intervention	30.00	3.00	8.00	24.00	720.00
Huh et al., 2015	BT + biofeedback	30.00	5.00	2.00	10.00	300.00
Hung et al., 2016	BT + biofeedback	20.00	3.00	6.00	18.00	360.00
Hwang et al., 2015	FES	30.00	5.00	4.00	20.00	600.00
Immink et al., 2014	yoga	57.31	5.20	10.00	52.00	2980.00
In et al., 2016	mirror therapy (by VR) + FTT	30.00	5.00	4.00	20.00	600.00

Janssen et al., 2008	FES	27.50	2.00	6.00	12.00	330.00
Jung et al., 2015	BT + biofeedback	20.00	3.00	4.00	12.00	240.00
Jung et al., 2017	TENS	30.00	5.00	6.00	30.00	900.00
Kamps et Schule, 2005	MS + CPI + assistance + resistance + biofeedback	18.87	10.00	16.00	160.00	3019.00
Karasu et al., 2018	BT + VR	20.00	5.00	4.00	20.00	400.00
Katz-Leurer et al., 2006	MS	25.07	5.00	3.00	15.00	376.00
Khumsapsiri et al., 2018	BT	30.00	3.00	4.00	12.00	360.00
Kilinc et al., 2015	NPI + FTT	60.00	3.00	12.00	36.00	2160.00
Kim DH et al., 2008	truncal exercise / core stability exercises	nd	3.00	4.00	12.00	nd
Kim JC et Lee, 2018	observation and imitation of functional tasks	10.00	3.00	3.00	9.00	90.00
Kim JH et al., 2009	BT + VR	30.00	4.00	4.00	16.00	480.00
Kim JY et al., 2018	GT + BWS + EMA + biofeedback	30.00	5.00	3.00	15.00	450.00
Kim SL et Lee, 2018	MM	80.00	5.00	4.00	20.00	1600.00
Kim YH et al., 2004	BT + biofeedback	30.00	3.00	3.00	9.00	270.00
Kim YH et al., 2004	BT + biofeedback	30.00	3.00	3.00	9.00	270.00
Kim YM et al., 2009	FES	30.00	5.00	3.00	15.00	450.00
Knox et al., 2018	FTT	60.00	0.50	12.00	6.00	360.00
Knox et al., 2018	MS	60.00	0.50	12.00	6.00	360.00
Kunkel et al., 2013	BT	20.38	4.00	2.00	8.00	163.00
Kunkel et al., 2013	BT + FES	24.50	4.00	2.00	8.00	196.00
Kwong et al., 2018	sensory intervention	60.00	2.00	10.00	20.00	1200.00
Langhammer et al., 2009	MS + CPI + FTT	50.00	2.10	52.00	109.20	5460.00
Lau RWK et al., 2012	sensory intervention	10.50	3.00	8.00	24.00	252.00
Laufer, 2003	Cane	0.50	1.00	1.00	1.00	0.50
Laufer, 2003	Cane	0.50	1.00	1.00	1.00	0.50
Lee CH et al., 2014	BT + VR	30.00	3.00	4.00	12.00	360.00
Lee D et al., 2016	FES + mirror therapy	nd	5.00	4.00	20.00	nd
Lee HJ et al., 2018	respiratory training	40.00	5.00	6.00	30.00	1200.00
Lee MM et al., 2018	BT + VR	30.00	3.00	3.00	9.00	450.00
Lee NK et al., 2013	MS	nd	nd	nd	nd	nd
Lee NK et al., 2013	MS	nd	nd	nd	nd	nd
Lee SH et al., 2012	BT + biofeedback	20.00	5.00	4.00	20.00	400.00
Lee SW et al., 2013	sensory intervention	30.00	3.00	6.00	18.00	540.00
Liang et al., 2012	sensory intervention	40.00	5.00	6.00	30.00	1200.00

Lin Q et al., 2015	acupuncture	20.00	5.00	4.00	20.00	400.00
Lindvall et Forsberg, 2014	MM + body awareness therapy	80.00	1.00	8.00	6.00	480.00
Lisinski et al., 2012	BT + biofeedback	nd	nd	2.86	nd	nd
Liu-Ambrose et Eng, 2015	MS + CPI + FTT	60.00	3.00	26.07	78.21	4692.60
Lu et al., 1997	Cane	1.00	1.00	1.00	1.00	1.00
Lu et al., 1997	Cane	1.00	1.00	1.00	1.00	1.00
Lynch et al., 2007	sensory intervention + relearning	30.00	5.00	2.00	10.00	300.00
Marin et al., 2013	sensory intervention	15.08	1.42	12.00	17.00	256.33
Merkert et al., 2011	sensory intervention	4.97	7.50	2.00	15.00	74.54
Milczarek et al., 1993	Cane	0.50	1.00	1.00	1.00	0.50
Milczarek et al., 1993	Cane	0.50	1.00	1.00	1.00	0.50
Mojica et al., 1988	orthoses	5.00	1.00	1.00	1.00	5.00
Moore JL et al., 2010	GT + BWS + CPI	nd	3.50	4.00	14.00	nd
Morioka et Yagi, 2003	sensory intervention + relearning	nd	5.00	2.00	10.00	nd
Mudie et al., 2002	BT + biofeedback	30.00	5.00	2.00	10.00	300.00
Mudie et al., 2002	BT (NPI)	30.00	5.00	2.00	10.00	300.00
Mudie et al., 2002	BT + task-related reach training	30.00	5.00	2.00	10.00	300.00
Nadeau et al., 2013	GT + BWS	76.58	3.00	12.00	33.00	2527.00
Nadeau et al., 2013	FTT + MS + MM	79.31	3.00	12.00	36.00	2855.00
Ng et al., 2016	sensory intervention	60.00	2.00	8.00	16.00	960.00
Nikamp et al., 2017	orthoses	nd	nd	9.00	nd	nd
Noh et al., 2008	BT + aquatic environment	60.00	3.00	8.00	24.00	1440.00
Ordahan et al., 2015	BT + biofeedback + verticalization (support)	20.00	5.00	6.00	30.00	600.00
Page et al., 2008	MS + EMR	38.50	3.00	8.00	24.00	924.00
Park D et al., 2018	taping	15.00	1.00	1.00	1.00	15.00
Park D et al., 2018	orthosis	15.00	1.00	1.00	1.00	15.00
Park DS et al., 2017	BT + VR	30.00	5.00	6.00	30.00	900.00
Park et al., 2014	sensory intervention	30.00	5.00	6.00	30.00	900.00
Park HK et al., 2018	truncal exercice / core stability exercises + BT + aquatic environment	30.00	5.00	4.00	20.00	600.00
Park J et al., 2017	FTT + muscle stretching	30.00	3.00	6.00	18.00	540.00
Pollock et al., 2002	BT + FTT	nd	5.00	4.00	20.00	nd
Pomeroy et al., 2001	constraint-induced therapy	600.00	7.00	6.00	42.00	25200.00
Rajaratnam et al., 2013	BT + VR	20.00	1.00	1.00	1.00	20.00
Robertson et al., 2010	FES	5.00	1.00	1.00	1.00	5.00

Rougier et Boudrahem, 2010	BT + biofeedback	2.67	1.00	1.00	1.00	2.67
Salgueiro et Marquez, 2018	visual and occulomotor training	15.00	1.67	3.00	5.00	75.00
Sanchez-Mila et al., 2018	acupuncture	15.00	1.00	1.00	1.00	15.00
Schmid et al., 2012	yoga	44.20	3.46	8.00	27.00	1193.51
Schuster et al., 2012	mental imagery	15.00	3.00	2.00	6.00	90.00
Schuster et al., 2012	mental imagery	15.00	3.00	2.00	6.00	90.00
Shatil et al., 2005	FTT + MS + CPI + MM + muscle stretching	55.00	3.00	6.00	18.00	990.00
Shin et al., 2016	BT + biofeedback	20.00	3.00	4.00	12.00	240.00
Simons et al., 2009	orthoses	1.50	1.00	1.00	1.00	1.50
Sohn et al., 2015	Sling	13.33	1.00	1.00	1.00	13.33
Sohn et al., 2015	Sling	13.33	1.00	1.00	1.00	13.33
Song et al., 2014	BT + biofeedback	25.00	3.00	3.00	9.00	225.00
Song et al., 2014	BT + VR	25.00	3.00	3.00	9.00	225.00
Stein et al., 2014	FTT + EMA	60.00	3.00	6.00	18.00	1080.00
Suh et al., 2014	FES	60.00	1.00	1.00	1.00	60.00
Tan et al., 2014	FES	30.00	5.00	3.00	15.00	450.00
Tan et al., 2016	FES	30.00	5.00	3.00	15.00	450.00
Tan et al., 2016	FES	30.00	5.00	3.00	15.00	450.00
Tian et al., 2014	acupuncture	30.00	7.00	4.00	28.00	840.00
Tilikete et al., 2001	sensory intervention	3.00	1.00	1.00	1.00	3.00
Tilikete et al., 2001	sensory intervention	3.00	1.00	1.00	1.00	3.00
Tripp and Krakow, 2014	BT + aquatic therapy	45.00	3.00	2.00	6.00	270.00
Tung et al., 2010	sit to stand training	15.00	3.00	4.00	12.00	180.00
Vahlberg et al., 2017	FTT + MS + CPI	75.00	2.50	12.00	30.00	2250.00
VanNes et al., 2006	sensory intervention	1.00	5.00	6.00	30.00	29.89
Waldron et Bohannon, 1989	Cane	15.00	1.00	1.00	1.00	15.00
Waldron et Bohannon, 1989	Cane	15.00	1.00	1.00	1.00	15.00
Waldron et Bohannon, 1989	Cane	15.00	1.00	1.00	1.00	15.00
Wang et al., 2017	mirror therapy	40.00	5.00	6.00	30.00	1200.00
Wang RY, Lin PY et al., 2007	orthoses	5.00	1.00	1.00	1.00	5.00
Wang RY, Yen LL et al., 2005 part 1	orthoses	15.00	1.00	1.00	1.00	15.00
Wang RY, Yen LL et al., 2005 part 2	orthoses	15.00	1.00	1.00	1.00	15.00
Wang TC et al., 2015	MS + MM + FTT	100.00	2.00	12.00	24.00	2400.00
Xie et al., 2018	Tai Chi	60.00	5.00	12.00	60.00	3600.00

Xing et al., 2007	acupuncture	30.00	5.00	4.00	20.00	600.00
Yadav et al., 2015	BT + muscle stretching + MS	60.00	5.00	2.00	10.00	600.00
Yeung et al., 2018	EMA in orthoses	30.00	4.00	5.00	20.00	600.00
Yoo et al., 2010	FTT + truncal exercises / core stability exercises (MS)	30.00	3.00	4.00	12.00	360.00
Yoo et al., 2018	respiratory training	80.00	7.00	3.00	21.00	1680.00
You et al., 2014	FES	30.00	5.00	3.00	15.00	450.00
Yu et Cho, 2016	BT + VR	30.00	3.00	6.00	18.00	540.00
Yun et al., 2018	GT + BWS + EMA + biofeedback	30.00	5.00	3.00	15.00	450.00
Zhang et al., 2015	CITUL	100.00	5.00	6.00	30.00	3000.00

Abbreviations: BT, balance training; BWS, body weight support; CITUL, constraint-induced movement therapy of upper limb; CPI, cardiopulmonary intervention; EMA, electromechanical assistance; EMR, electromechanical resistance; FES, functional electrostimulation; FTT, functional task training; GT, gait training; Min, minute; MM, musculoskeletal mobilization; MS, muscle strengthening; Nd, not documented; NPI, neurophysiological intervention; PT, physical therapy; UC, usual care; VR, virtual reality

S8 Table. Outcome measures

S8A Table. Summary of outcome measures

Measures of outcomes	Number of studies
Balance	
BBS (post-intervention)	98 (68%)
BBS (follow-up)	31 (21%)
PASS (post-intervention)	11 (8%)
PASS (follow-up)	6 (4%)
Autonomy	
Barthel index (post-intervention)	30 (21%)
Barthel index (follow-up)	13 (9%)
ADL (post-intervention)	2 (1%)
IADL (post-intervention)	0 (0%)
IADL (follow-up)	4 (3%)
FIM (post-intervention)	1 (1%)
FIM (follow-up)	3 (2%)
Mediolateral and anteroposterior postural deviation (COP, WBA)	
WB on paretic limb, EO (post-intervention)	23 (16%)
WB on paretic limb, EO (follow-up)	4 (3%)
WB on paretic limb, EC (post-intervention)	2 (1%)
Mediolateral position of COP, EO (post-intervention)	6 (4%)
Anteroposterior position of COP, EO (post-intervention)	5 (3%)
Anteroposterior position of COP, EO (follow-up)	1 (1%)
Postural stability (COP, LOS)	
Sway length EO (post-intervention)	13 (9%)
Sway area EO (post-intervention)	10 (7%)
Sway length EC (post-intervention)	9 (6%)
Velocity COP EO (post-intervention)	9 (6%)
Anteroposterior velocity COP EO (post-intervention)	8 (6%)
Mediolateral velocity COP EO (post-intervention)	8 (6%)
Anteroposterior velocity COP EC (post-intervention)	7 (5%)
LOS, maximum excursion, affected side EO (post-intervention)	7 (5%)
LOS, maximum excursion, anterior, EO (post-intervention)	7 (5%)
LOS, maximum excursion, non-affected side EO (post-intervention)	7 (5%)
Mediolateral velocity COP EC (post-intervention)	7 (5%)
LOS, Movement velocity, affected side EO (post-intervention)	6 (4%)
LOS, Movement velocity, anterior, EO (post-intervention)	6 (4%)
LOS, Movement velocity, non-affected side EO (post-intervention)	6 (4%)
LOS, directional control non-affected side EO (post-intervention)	5 (3%)
LOS, directional control, affected side EO (post-intervention)	5 (3%)
LOS, directional control, anterior, EO (post-intervention)	5 (3%)
LOS, maximum excursion, posterior EO (post-intervention)	5 (3%)
LOS, Movement velocity, posterior EO (post-intervention)	5 (3%)
LOS, directional control posterior EO (post-intervention)	4 (3%)
Sway area EC (post-intervention)	4 (3%)
Velocity COP EC (post-intervention)	4 (3%)
Anteroposterior sway length EO (post-intervention)	3 (2%)
LOS, end-point excursion, affected side, EO (post-intervention)	3 (2%)
LOS, end-point excursion, backward, EO (post-intervention)	3 (2%)
LOS, end-point excursion, forward, EO (post-intervention)	3 (2%)
LOS, end-point excursion, non-affected side, EO (post-intervention)	3 (2%)
Mediolateral sway length EO (post-intervention)	3 (2%)
Anteroposterior variability COP EO (post-intervention)	3 (2%)
Mediolateral variability COP EO (post-intervention)	3 (2%)

Velocity moment EC (post-intervention)	3 (2%)
Velocity moment EO (post-intervention)	3 (2%)
LOS EO (post-intervention)	2 (1%)
LOS, end-point excursion, affected side, EO (follow-up)	2 (1%)
LOS, end-point excursion, backward, EO (follow-up)	2 (1%)
LOS, end-point excursion, forward, EO (follow-up)	2 (1%)
LOS, end-point excursion, non-affected side, EO (follow-up)	2 (1%)
Maximum COP displacement in anteroposterior direction EO (post-intervention)	2 (1%)
Maximum COP displacement in mediolateral direction EO (post-intervention)	2 (1%)
Stability index EO (post-intervention)	2 (1%)
Velocity COP EC (post-intervention)	2 (1%)
Velocity COP EO (post-intervention)	2 (1%)
Anteroposterior sway length EC (post-intervention)	1 (1%)
COP excursion EO (post-intervention)	1 (1%)
LOS, Ankle strategy, EC (follow up)	1 (1%)
LOS, Ankle strategy, EO (follow up)	1 (1%)
LOS, COG alignment, EC (follow up)	1 (1%)
LOS, COG alignment, EO (follow up)	1 (1%)
LOS, Maximal stability, EC (follow up)	1 (1%)
LOS, Maximal stability, EO (follow up)	1 (1%)
LOS, maximum excursion, affected side EO (follow-up)	1 (1%)
LOS, maximum excursion, anterior, EO (follow-up)	1 (1%)
LOS, maximum excursion, non-affected side EO (follow-up)	1 (1%)
LOS, maximum excursion, posterior EO (follow-up)	1 (1%)
LOS, Movement velocity, affected side EO (follow-up)	1 (1%)
LOS, Movement velocity, anterior, EO (follow-up)	1 (1%)
LOS, Movement velocity, non-affected side EO (follow-up)	1 (1%)
LOS, Movement velocity, posterior EO (follow-up)	1 (1%)
LOS, reaction time, affected side, EO (post-intervention)	1 (1%)
LOS, reaction time, affected side, EO (follow-up)	1 (1%)
LOS, reaction time, backward, EO (post-intervention)	1 (1%)
LOS, reaction time, backward, EO (follow-up)	1 (1%)
LOS, reaction time, forward, EO (post-intervention)	1 (1%)
LOS, reaction time, forward, EO (follow-up)	1 (1%)
LOS, reaction time, non-affected side, EO (post-intervention)	1 (1%)
LOS, reaction time, non-affected side, EO (follow-up)	1 (1%)
Maximum COP displacement in anteroposterior direction EC (post-intervention)	1 (1%)
Maximum COP displacement in anteroposterior direction EC (follow-up)	1 (1%)
Maximum COP displacement in anteroposterior direction EO (follow-up)	1 (1%)
Maximum COP displacement in mediolateral direction EC (post-intervention)	1 (1%)
Maximum COP displacement in mediolateral direction EC (follow-up)	1 (1%)
Maximum COP displacement in mediolateral direction EO (follow-up)	1 (1%)
Mediolateral sway length EC (post-intervention)	1 (1%)
Stability index EC (post-intervention)	1 (1%)
Sway area EC (follow-up)	1 (1%)
Sway length EC (follow-up)	1 (1%)
Sway length EO (follow-up)	1 (1%)
Anteroposterior variability COP EC (post-intervention)	1 (1%)
Mediolateral variability COP EC (post-intervention)	1 (1%)

Abbreviations: ADL, activities of daily living; BBS, berg balance scale; COP, center of pressure; EC, eyes closed; EO, eyes open; FIM, functional independence measure; IADL, instrumental activities of daily living; LOS, limit of stability; PASS, postural assessment scale for stroke; NT, no treatment; ST, sham treatment; UC, usual care; WB, weight bearing; WBA, weight bearing asymmetry

S8B Table. Characteristics of outcome measures for each study included

Study	Outcomes	Post-intervention assessment	Follow-up assessment
Allison et Dennett, 2007	RMA, TCT, BBS	2w	12 w
Askim et al., 2010	BBS, MAS, BI, ST, 5mWT, SIS, Borg, time spent on home exercises, the training diaries, adverse events	12w	26 w
Barcala et al., 2011	BBS, X and Y sway COP	5w	No
Brogardh et al., 2012	strength (knee), mAS (hip, knee, ankle), BBS, TUG, 6MWT, 10mWT, SIS	6w	No
Büyükvural Şen et al., 2015	FIM, SS-QOL, 10mWT, 6MWT, TUG, SCT, BBS, RMI, Strength (knee, ankle)	3w	No
Cabanas-Valdés et al., 2015	TIS, The Function in Sitting Test, BBA, BBS, PASS, BI, Tinetti	5w	No
Chan KS et al., 2012	mAS, H-reflex, Hmax/Max, deep tendon reflex of the Achilles tendon, VAS, TUG, 10mWT, BWD, pressure (foot area)	21min	No
Chen CH et al., 2010	gait, WBD (Symmetry index)	few min	No
Chen CL et al., 2015	LOS (Movement velocity, Maximum excursion, Directional control), RWS	few min	No
Chen D et al., 2014	FMA-LL, BBA, BBS, PASS, MBI	3w	No
Chen IC et al., 2002	Brunstrom, FIM, LOS (Maximal stability, ankle strategy, COG alignment, Axis velocity, directional control and end point excursion)	No	6m + 2w
Chen JC et al., 2011	FMA-LE, MRC-LE, mMAS, PASS-TC, BBS, FAC, mAS (hip, knee and ankle), AE	6w	No
Chern et al., 2013	COP total path excursion, maximum COP displacement, bilateral weight bearing difference, 10mWT and voluntary weight shifting	few min	No
Cho HY et al., 2013	COP sway length, MAS, hand strength	90min	1d
Cho KH et al., 2012	X and Y COP velocity, BBS, TUG	6w	No
Cho MK et al., 2015	gait (spatiotemporal parameters), 6MWT, BBS, strength, MMT	4w	No
Chung et al., 2014	gait (spatiotemporal parameters), strength, BBS	6w	No
Dault et al., 2003	COP sway, weight shifting	post-intervention	No
Duncan et al., 1998	OPS, FMA, BI, IADL, MOS-36, 10mWT, 6MWT, BBS, JTHF	12w	No

Duncan et al., 2003	OPS, FMA, strength (Grip, ankle, knee extension), WMT, 10mWT, BBS, FR, 6MWT, EST, AE	12 to 14w	No
Fritz et al., 2013	FMA, BBS, DGI, 6MWT, 3mWT, SIS, TUG	5w	3m
Ghanjal et al., 2014	TUG, 6MWT, BI, BBS	nd (after 12 sessions)	No
Globas et al., 2012	peak V02, 6MWT, 10mW, 5CR, BBS, RMI, SF-12	3w	No
Hart et al., 2004	Romberg test, EFAP, BBS, TUG, Standing on the unaffected leg, DHP	12w	No
Heller et al., 2005	FMA-LL, AS, PASS, FIM, FAC, gait	9w	No
Howe et al., 2005	LRT, STS test, COP sway	4w	8w
Hsu et al., 2013	LE-STREAM, MOB-STREAM, FAC, BI, PASS , MAS	8w	12w
Hwang et al., 2015	TUG, BBS, 10mWT, Muscle architecture	4w	No
Immink et al., 2014	9HPT, MAS, BBS, 2MWD, CGS, GDS15, STAI, SIS	10w	No
Janssen et al., 2008	6MWT, BBS, RMI, V02 max, POmax, MVC IL, MVC CL, HR	6w	No
Jung et al., 2015	TIS, mFRT, X and Y sway velocity	4w	No
Kamps et Schule, 2005	10mWT, 2MWT, 6MWT, TUG, Tinetti, BBS	16w	No
Katz-Leurer et al., 2006	PASS, FMA-LL, FIM, MAS, Standing Balance test	3w	6w
Kim DH et al., 2008	strength, TUG, BBS, 10mWT, step-up	4w	No
Kim JH et al., 2009	BBS, 10mWT, mMAS, gait (spatiotemporal parameters), mean balance, COP sway (area, path, maximal sway velocity, X and Y sway angle)	4w	No
Kim YH et al., 2004	COP sway	3w	No
Kim YM et al., 2009	PASS, BBS, TCT, mBI, MI	3w	No
Kunkel et al., 2013	WBD, max weight transferred, 10mWT, BBS, RMI, acceptability	2w	4w
Langhammer et al., 2009	IADL, MAS, 6MWT, BBS, TUG, strength, AS, heart rate, interview	12m	4y
Lau RWK et al., 2012	BBS, LOS (MVL, EPE, MXE, DCL), 10mWT, 6MWT, strength, ABC, falls	8w	1m + 8w
Laufer, 2003	Sway Index, BWD	few min	No
Lee CH et al., 2014	TUG, BBS, gait (spatiotemporal parameters)	4w	No
Lee NK et al., 2013	MVIC, Y and X sway velocities	6w + 1d	No
Lee SH et al., 2012	FAC, 10mWT, TUG, BBS, mBI, MMT	4w	No

Lee SW et al., 2013	COP sway (velocity and length)	6w	No
Liang et al., 2012	FMA-LE, MRC-LE, FAC, BBS, mMAS, BI	6w	12m
Lindvall et Forsberg, 2014	TUG, TUG Cognitive Test, 6MWT, BBS, Timed-stands Test, ABC, SF-36	9w	14w
Lisinski et al., 2012	WBD, COP sway (X and Y velocity), Brunnström scale	20d	No
Liu-Ambrose et Eng, 2015	Stroop Test, Trail Making Tests, verbal digits forward and backward tests, GDS, 6MWT, BBS	6m	No
Lu et al., 1997	COP sway (maximum sway, total travel distance, mean travel speed of the COP), gait	post-intervention	No
Lynch et al., 2007	Light touch (wmes-Weinstein monofilaments), DPT, BBS, 10mWT, 14mWT, ILAS	2w	4w
Marin et al., 2013	muscle architecture, strength (knee), BBS	12w	No
Merkert et al., 2011	BBS, BI, F-test, Tinetti, TUG	2w	No
Milczarek et al., 1993	COP sway travel, X and Y COP position	post-intervention	No
Mojica et al., 1988	body sway, X and Y COP position, gait (spatiotemporal parameters)	15min	No
Moore JL et al., 2010	gait speed, 12MWT, 02 cost (gait), Peak treadmill velocity, peak VO2, BBS, TUG, number of step	4w	No
Morioka et Yagi, 2003	COP sway (total locus length, enveloped area, and rectangular area)	2w	No
Mudie et al., 2002	WBD, BI	2w	14w
Nadeau et al., 2013	gait (speed), 6MWT, step activity, FMA, BBS, ABC, SIS, falls, AE	4m	No
Park et al., 2014	mAS (ankle), COP sway velocity and speed moment, TUG, gait (spatiotemporal parameters)	6w	No
Pollock et al., 2002	SI, maximum weight transference	4w	6w
Pomeroy et al., 2001	BBS, gait (spatiotemporal parameters), patient experience	6w	No
Rajaratnam et al., 2013	FRT, BBS, TUG, COP sway	60min	No
Robertson et al., 2010	ABC, BBS, TUG, 10mWT, gait speed, toe height (foot clearance)	few min	No
Rougier et Boudrahem, 2010	COP sway (area, velocity, variance, DC, mean time interval, mean square distances), X and Y COP position	post-intervention	No
Schmid et al., 2012	mRS, BBS, ABC, FoF, SS-QoL	8w	No
Schuster et al., 2012	motor task (time), CMSA, Stage of the motor task (Bergland and Lake), Imagination inflation (time), EBI, BBS, KVIQ, Imaprax software, ABC, diary (motivation), 11-point VAS	2w	4w
Shatil et al., 2005	golf performance, COP excursion velocity, peak arm acceleration, EMG, BBS, CMPCI, SIP	6w	No

Simons et al., 2009	BBS, TUG, TBT, 10mWT, FAC, WBD (static and dynamic), DBC	few min	No
Song et al., 2014	BBS, FI, SI, WDI	3w	No
Suh et al., 2014	mAS, FRT, BBS, TUG, 10mWT	2h 30min	No
Tan et al., 2014	FMA-LL, PASS, BBS, BI, FAC	3w	3m + 3w
Tian et al., 2014	track length, peripheral square, track length of per unit square, left-right offset and rectangle square, Mean-X, Mean-Y, Max-X, Max-Y, LSKG, SSKG, LFS, SI, WDI	4w	No
Tilikete et al., 2001	X and Y COP position, COP sway area	3min	No
Tripp and Krakow, 2014	BBS, FRT, FAC, RMI	2w	No
Tung et al., 2010	BBS, WBD, LOS (MXE, DCL), strength	4w	No
VanNes et al., 2006	BBS, BI, TCT, RMI, FAC, MI, Somatosensory threshold, AE	6w	12w
Waldron et Bohannon, 1989	WBD	15min	No
Wang RY, Lin PY et al., 2007	gait (spatiotemporal parameters), WBD, LOS (MXE, MVL)	few min	No
Wang RY, Yen LL et al., 2005 part 1	WBD, COP sway, LOS (MVL, DCL, MXE), sit-to-stand test (rising time, weight transfer and COP sway), BBS, 10mWT	15min	No
Wang RY, Yen LL et al., 2005 part 2	WBD, COP sway, LOS (MVL, DCL, MXE), sit-to-stand test (rising time, weight transfer and COP sway), BBS, 10mWT	15min	No
Wang TC et al., 2015	BBS, 10mWT, 6MWT, SIS, BI, caregiver burden test	12w	No
Xing et al., 2007	BBS, Brunnstrom	2 to 3w	No
Yoo et al., 2010	BBS, TIS, TCT (K-MMSE et K-MBI for experimental group only)	4w	No
You et al., 2014	CSS, FMA-LE, PASS, BBS, mBI	3w	No
Zhang et al., 2015	mBI, FMA, BBS	6w	12w
Au-Yeung et al., 2009	LOS (reaction time and EPE), SOT, TUG	12w	18w
Furnari et al., 2014	length of the ball (COP), index of energy expenditure, plantar load for each foot, Plantar Surface for each foot, gait (spatiotemporal parameters)	8w	No
Geiger et al., 2001	TUG, BBS	4w	No
Hollands et al., 2015	gait (spatiotemporal parameters), time to turn 180°, adaptability of gait (success rate in target stepping), FMA-LE, SF-12, TUG, FAC, Falls Efficacy Scale, BBS	8w	12w
Holmgren et al., 2010	BBS, BI, FES-I, number of falls, FAI-3, Borg scale	5w	3m
Hosseini et al., 2012	TUG, BBS	nd	nd
Kilinc et al., 2015	BBS, STREAM, TIS, FRT, 10mWT, TUG	12w	No

Noh et al., 2008	BBS , WBA, strength, mMAS	No	12w
Page et al., 2008	FMA-LL, BBS	8w	No
Stein et al., 2014	TUG, BBS, 10mWT, 6MWT, Five-Times-Sit-to-Stand test, EFAP, California Functional Evaluation 40	6w	19w
In et al., 2016	BBS, FRT, TUG, posturography (medial-lateral distance, anterior-posterior distance, and total sway distance), 10mWT	4w	No
Kwong et al., 2018	ankle and knee muscle strength, BBS, TUG, Step Test and the Lower Extremity Motor Coordination Test	10w	3m + 10w
Arabzadeh et al., 2018	BBS, the postural sway parameters, including COP path length and COP area, and WBA	4w	No
Kim JY et al., 2018	FAC, Motricity index (lower limb subscale), 10mWT, mBI, RMI, BBS	3w	No
Erbil et al., 2018	TUG, BBS, mAS, Tardieu Scale, Rivermead Visual Gait Assessment	No	12w
Park HK et al., 2018	TIS, PASS-3L (5 items), BBS-3L (7 items), FRT, mBI	4w	No
Xie et al., 2018	BBS, Single leg stance test (SLST), FMA, mBI, 36-Item Short-Form health survey, Beck depression inventory, Modified falls efficacy scale, TUG	12w	24w
Choi HS et al., 2017	WBA, the deviation of the COP (the medial-lateral axis distance, and anteroposterior axis distance, sway mean velocity, sway area), FRT, mFRT, TUG	4w	No
Lee D et al., 2016	strength of the lower extremity, mAS, BBS, TUG, 6MWT	4w	No
Fernandez-Gonzalo et al., 2016	maximal dynamic and isometric force and power tests, and m. quadriceps femoris cross sectional area and volume (MRI), BBS, TUG, Dual-task cost on walking, mAS	3m	No
Dujovic et al., 2017	10mWT (gait speed), FMA, BBS, BI	4w	No
Yeung et al., 2018	FAC, FMA, MAS, BBS, 10mWT, 6MWT, gait analysis	5w	10w
Yun et al., 2018	BLS, BBS, PASS, FMA, K-mBI, Somatosensory Evoked potentials	3w	7w
Han et al., 2016	brachial-ankle Pulse wave velocity, cardiopulmonary fitness (VO2, respiratory exchange ratio, the peak values of each of these parameters and peak heart rate, instantaneous systolic blood pressure (SBP) and diastolic blood pressure (DBP). Resting and peak SBP and DBP values, resting and peak heart rate values, peak RER, and duration of exercise treadmill test, K-mBI, BBS, FMA-LL, FAC	4w	No
Vahlberg et al., 2017	BBS, Short Physical Performance Battery (balance, gait speed and the ability to rise from a seated position five times), 6MWT, 10mWT, PASE, EQ-5D, Geriatric Depression Scale-20, Fall-related self-efficacy	12w	15m
Knox et al., 2018	BBS, 6mWT, 10mWT (comfortable and fast speed), TUG	12w	24w
Goliwas et al., 2017	SI, BBS, FMA-LL, mAS, Exteroceptive sensation	6w	No
Shin et al., 2016	mFRT, TIS, TUG, posturography (ML and AP sway speed, velocity moment)	4w	No
Kim SL et Lee, 2018	weight-bearing lunge test, COP sway path length, COP sway speed, TUG, DGI	4w	No

Khumsapsiri et al., 2018	LOS (MMVL, EPE, MXE), WBA, FAB	4w	8w
Yu et Cho, 2016	BBS, TUG, mBI	6w	No
Sohn et al., 2015	overall index, AP index, ML index, BBS, TIS	15min	No
Hsieh, 2019	10mWT, maximum CoP sway in the AP direction, maximum CoP sway in the ML direction, sway area	10w	No
Ferreira et al., 2017	AP COP, ML COP	12w	No
Kim JC et Lee, 2018	WDI, LOS (LOS-surface area, LOS-area ratio), TUG, DGI	3w	No
Park D et al., 2018	Static balance ability, TUG, gait (spatiotemporal parameters)	15min	No
Buyukavci et al., 2016	Brunnstrom, TIS, BBS, FIM, RMI	No	3m
Hung et al., 2016	Adherence, safety, and satisfaction, TUG, FRT, Physiologic Profile Assessment Subtests, WBA	6w	No
Lee MM et al., 2018	COP path length, COP sway velocity, mFRT, MFT	5w	No
Yoo et al., 2018	pulmonary function (FVC, FEV1, Peak flow), NIHSS, mBI, BBS, FMA, K-MMSE, incidence of pneumonia	3w	No
Karasu et al., 2018	BBS, FRT, PASS, TUG, SBI, Postural sway, FIM (locomotion and transfert)	4w	8w
Bunketorp-Kall et al., 2017	SIS, TUG, BBS, the Bäckstrand, Dahlberg and Liljenäs Balance Scale, Hand strength, Barrow Neurological Institute screen, working memory (letter–number sequencing test)	12w	6m
Wang et al., 2017	Brunnstrom staging of motor function of lower extremity, BBS, FAC, FIM (transporting as well as walking part), BOLD-fMRI scan	6w	No
Park DS et al., 2017	FMA-LL, BBS, TUG, 10mWT	6w	No
Jung et al., 2017	Postural sway distance, strength (hip, knee and ankle), Composite Spasticity Score	6w	No
Ordahan et al., 2015	BBS, TUG, FIM	6w	No
Nikamp et al., 2017	10mWT, BBS, 6MWT, TUG, stairs test, FAC, RMI, BI	9w	No
Chen, 2018	Body composition, mood state scale, flexibility, muscle endurance, and maximum oxygen uptake, BBS, single-legged standing ability test, motor evoked potentials, EEG	6w	No
Sanchez-Mila et al., 2018	mAS, FMA, LOS (MVL, MXE, EPE, DCL), equitest	60min	No
Ng et al., 2016	BBS, 6MWT, RMI, TUG, SF-36	8w	8w + 3m
Bae et al., 2015	BBS, COP sway area, LOS	few min	No
Lee HJ et al., 2018	10mWT, 6MWT, TUG, BBS	6w	No
Park J et al., 2017	MFT, strength, BBS, pCOP velocity moment, COP AP sway, COP ML sway, 10mWT, SS-QOL	6w	No
Yadav et al., 2015	BBS, TUG	2w	No
Huh et al., 2015	BBS, FAC, 6MWT, TUG, K-mBI, MMT	2w	No

Lin Q et al., 2015	FMA, BBS, BI	4w	No
Salgueiro et Marquez, 2018	BBS, TUG, COP ML displacement, COP AP displacement, COP sway velocity, X COP, Y COP	3w	No
Chu et al., 2015	BBS, Sheikh Trunk Control Scale, FMA-LL, Holden FAC, 10mWT	8w	No
Tan et al., 2016	FMA-LL, 10mWT, BBS, mBI, EMG	No	6w

Abbreviations: 10mWT, 10-meter walking Test; 2 MWT, 2 minutes walking test; 2MWD, two-minute walking distance; 3mWT, 3-meter walking test; 5CR, the 5-chair-rise test; 5mTW, the 5-meter timed walk; 5mWT, 5-meter walking test; 6MWT, 6 minutes walking test; 9HPT, 9-hole peg test; ABC, activities-specific balance confidence scale; AE, adverse effects; AP, anteroposterior; AS, ashworth scale; BBA, brunel balance assessment; BBS, berg balance scale; BC, balance coefficient; BI, barthel index; BWD, body weight distribution; CGS, comfortable gait speed; CMPCI, chedoke-McMaster postural control inventory; d, day; DBC, dynamic balance contribution; DC, dependency coefficient; DCL, directional control; DGI, dynamic gait index; DHP, duke health profile; DPT, the distal proprioception test; EBI, extended barthel index; EFAP, emory functional ambulation profile; EMG, electromyogram; EPE, end point excursions; ES, electrostimulation; EST, exercise stress test; FAC, functional ambulation category; FI, falling index; FIM, functional Independence measure; FMA-LE, lower limb part of fugl-meyer assessment; FoF, fear or fall; FR, functional reach; GDS15, geriatric depression scale 15-item; H, hour; IADL, instrumental activity of daily living; ILAS, iowa level of assistance scale; JTHF, jebsen test of hand function; LE-STREAM, lower extremity part of stroke rehabilitation assessment of movement measure; LFS, square ratio of weight shift; LOS, limit of stability; LSKG, weight shift distance; M, month; MAS, motor assessment scale; mAS, modified ashworth scale; Max, maximum; Max-X, maximum of X axis weight shift distance; Max-Y, maximum of Y axis weight shift distance; mBI, modified barthel index; Mean-X, mean of X axis weight shift distance; Mean-Y, mean of Y axis weight shift distance; MEP, motor evoked potentials; mFRT, modified functional reach test; MFT, manual function test; MI, Motricity index; MI-LE, lower limb part of motricity Index; Min, minute; ML, mediolateral; mMAS, modified motor assessment scale; MMT, manual muscle test; MOB-STREAM, the mobility subscale of the stroke rehabilitation assessment of movement measure; MOS-36, 36-item short-form health survey (SF-36); MRC-LE, the medical research council scale for lower extremity; MRI, magnetic resonance imaging; MVC CL, isometric maximal voluntary contractions of contralateral leg; MVC IL, isometric maximal voluntary contractions of ipsilateral leg; MVIC, maximum voluntary isometric contraction; MVL, movement velocity; MXE, maximum excursion; NRS, numerical rating scales; Num, number; OPS, orpington prognostic scale; PASS, postural assessment scale for stroke; PASS-TC, items on trunk control of postural assessment scale for stroke; POMA, tinetti performance oriented mobility assessment; RMA, rivermead motor assessment; RMI, rivermead mobility index; RWS, rhythmic weight shift; SC, sway coefficient; SCT, stair-climbing test; SF-12, the 12-item short form health survey; SI, symmetry index; SIP, sickness impact profile; SIS, stroke impact scale; SIS-16, 16 items of stroke impact scale; SS-QOL, stroke specific quality of life scale; SSKG, weight shift square; ST, step test; STAI, state trait anxiety inventory; TCT, trunk control test; TIS, trunk impairment scale; TUG, time up and go test; UC, usual Care; VAS, visual analogue scale; W, week; WDI, weight distribution index; WMT, wolf motor function; X, mediolateral; Y, anteroposterior

S9 Table. Results of subgroup analyses according to the time since post-stroke

Outcome or Subgroup	Studies, No.	Participants, No.	Statistical Method	Effect Estimate SMD (95% CI)	Heterogeneity I^2 & test for subgroup differences Chi^2
1. PT versus no treatment, post-intervention effect					
1.1 Balance	37	1721	Fixed	0.46 [0.37; 0.56]	19.1% SgD: Chi2 p=0.50
1.1.1 Acute and subacute stroke	15	1032	Fixed	0.45 [0.33; 0.58]	44.1%
1.1.2 Chronic stroke	16	464	Fixed	0.54 [0.35; 0.74]	0%
1.1.3 Mixed or not determined	6	225	Fixed	0.35 [0.09; 0.62]	0%
1.2 Mediolateral postural deviation, EO	11	430	Fixed	-0.23 [-0.36; -0.09]	0% SgD: Chi2 p=0.34
1.2.1 Acute and subacute stroke	3	120	Fixed	-0.39 [-0.66; -0.13]	0%
1.2.2 Chronic stroke	1	61	Fixed	-0.13 [-0.49; 0.22]	NA
1.2.3 Mixed or not determined	7	249	Fixed	-0.17 [-0.35; 0.00]	2.6%
1.3 Postural stability, EO	16	504	Random	0.48 [0.25; 0.70]	29.3% SgD: Chi2 p=1.00
1.3.1 Acute and subacute stroke	4	186	Random	0.50 [0.21; 0.80]	0%
1.3.2 Chronic stroke	6	139	Random	0.48 [-0.09; 1.05]	60.3%
1.3.3 Mixed or not determined	6	179	Random	0.50 [0.14; 0.86]	26%
1.4 Autonomy	15	941	Fixed	0.36 [0.23; 0.49]	0% SgD: Chi2 p=0.68
1.4.1 Acute and subacute stroke	9	754	Fixed	0.33 [0.19; 0.48]	0%
1.4.2 Chronic stroke	3	89	Fixed	0.43 [0.01; 0.86]	41.6%
1.4.3 Mixed or not determined	3	98	Fixed	0.50 [0.09; 0.90]	0%
2. PT versus no treatment, persisting effect					
2.1 Balance	11	493	Random	0.29 [-0.02; 0.59]	60.2% SgD: Chi2 p=0.64
2.1.1 Acute and subacute stroke	6	295	Random	0.16 [-0.07; 0.40]	71.4%
2.1.2 Chronic stroke	3	141	Random	0.44 [0.11; 0.78]	0%
2.1.3 Mixed or not determined	2	57	Random	0.38 [-0.16; 0.92]	73.0%
2.2 Mediolateral postural deviation, EO	3	50	Fixed	-0.44 [-1.05; 0.16]	0% SgD: Chi2 p=0.47
2.2.1 Acute and subacute stroke	2	36	Fixed	-0.28 [-1.03; 0.47]	0%
2.2.2 Chronic stroke	0	0	Fixed	Not estimable	NA
2.2.3 Mixed or not determined	1	16	Fixed	-0.75 [-1.77; 0.28]	NA
2.3 Postural stability, EO	3	80	Fixed	0.31 [-0.14; 0.76]	12.1%

					SgD: Chi2 NA
2.3.1 Acute and subacute stroke	0	0	Fixed	Not estimable	NA
2.3.2 Chronic stroke	0	0	Fixed	Not estimable	NA
2.3.3 Mixed or not determined	3	80	Fixed	0.31 [-0.14; 0.76]	12.1%
2.4 Autonomy	6	312	Fixed	0.36 [0.13; 0.58]	0% SgD: Chi2 p=0.97
2.4.1 Acute and subacute stroke	5	278	Fixed	0.36 [0.12; 0.59]	0%
2.4.2 Chronic stroke	0	0	Fixed	Not estimable	NA
2.4.3 Mixed or not determined	1	34	Fixed	0.37 [-0.31; 1.05]	NA
3. PT versus sham treatment/usual care, post-intervention effect					
3.1 Balance	46	2051	Random	0.43 [0.28; 0.59]	60.9% SgD: Chi2 p=0.16
3.1.1 Acute and subacute stroke	15	753	Random	0.36 [0.14; 0.58]	50%
3.1.2 Chronic stroke	21	793	Random	0.60 [0.35; 0.86]	64.5%
3.1.3 Mixed or not determined	10	505	Random	0.22 [-0.10; 0.55]	57.4%
3.2 Mediolateral postural deviation, EO	4	122	Fixed	-0.15 [-0.52; 0.21]	38.2% SgD: Chi2 p=0.11
3.2.1 Acute and subacute stroke	1	15	Fixed	0.13 [-0.97; 1.23]	0%
3.2.2 Chronic stroke	2	67	Fixed	-0.50 [-0.99; -0.01]	36.9%
3.2.3 Mixed or not determined	1	40	Fixed	0.32 [-0.30; 0.94]	NA
3.3 Postural stability, EO	15	574	Random	0.96 [0.55; 1.37]	77.9% SgD: Chi2 p=0.09
3.3.1 Acute and subacute stroke	3	65	Random	0.24 [-0.26; 0.74]	0%
3.3.2 Chronic stroke	10	429	Random	0.83 [0.49; 1.17]	58.2%
3.3.3 Mixed or not determined	2	80	Random	3.34 [-1.72; 8.40]	97.4%
3.4 Autonomy	15	805	Random	0.26 [0.01; 0.51]	61.1% SgD: Chi2 p=0.02
3.4.1 Acute and subacute stroke	9	360	Random	0.24 [0.02; 0.45]	75%
3.4.2 Chronic stroke	1	51	Random	0.74 [0.17; 1.30]	NA
3.4.3 Mixed or not determined	5	394	Random	-0.02 [-0.22; 0.18]	36%
4. PT versus sham treatment/usual care, persisting effect					
4.1 Balance	18	1150	Fixed	0.18 [0.06; 0.30]	48.8% SgD: Chi2 p=0.23
4.1.1 Acute and subacute stroke	7	407	Fixed	0.24 [0.04; 0.44]	40%
4.1.2 Chronic stroke	6	367	Fixed	0.27 [0.05; 0.48]	51%
4.1.3 Mixed or not determined	5	376	Fixed	0.03 [-0.18; 0.24]	59%
4.2 Postural stability, EO	2	178	Fixed	0.32 [0.02; 0.62]	0% SgD: Chi2 NA

4.2.1 Acute and subacute stroke	0	0	Fixed	Not estimable	NA
4.2.2 Chronic stroke	2	178	Fixed	0.32 [0.02; 0.62]	0%
4.2.3 Mixed or not determined	0	0	Fixed	Not estimable	NA
4.3 Autonomy	9	551	Fixed	-0.00 [-0.17; 0.17]	26% SgD: Chi2 p=0.36
4.3.1 Acute and subacute stroke	5	187	Fixed	0.11 [-0.18; 0.39]	0%
4.3.2 Chronic stroke	0	0	Fixed	Not estimable	NA
4.3.3 Mixed or not determined	4	364	Fixed	-0.06 [-0.27; 0.15]	49.5%

Autonomy: combination of barthel index, functional independence measure, activities of daily living and instrumental activities of daily living scales.

Mediolateral postural deviation: combination of weight bearing asymmetry and mediolateral position of center of pressure

Abbreviations: ADL, activities of daily living; BBS, berg balance scale; CI, confidence interval; COP, center of pressure; CPI, cardiopulmonary intervention; EO, eyes open; EC, eyes closed; IADL, instrumental activities of daily living; FIM, functional independence measure; FTT, functional task training; MD, mean difference; MS, muscle strengthening; MM, musculoskeletal mobilization; NA, not applicable; NPI, neurophysiological intervention; PASS, postural assessment scale for stroke; PT, physical therapy; RCT, randomized controlled trials; SgD, subgroup difference; SMD, standardized mean difference; X, mediolateral position of COP; Y, anteroposterior position of COP; WB, weight bearing.

S10 Table. Results of subgroup analyses according to the location of stroke lesion

Outcome or Subgroup	Studies, No.	Participants, No.	Statistical Method	Effect Estimate SMD (95% CI)	Heterogeneity I^2 & test for subgroup differences Chi^2
1. PT versus no treatment, post-intervention effect					
1.1 Balance	37	1721	Fixed	0.46 [0.37; 0.56]	19.1% SgD: Chi2 p=0.71
1.1.1 Supratentorial stroke	3	114	Fixed	0.53 [0.16; 0.91]	0%
1.1.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
1.1.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
1.1.4 Mixed or not determined	34	1607	Fixed	0.46 [0.36; 0.56]	23.2%
1.2 Mediolateral postural deviation, EO	11	430	Fixed	-0.23 [-0.36; -0.09]	0% SgD: Chi2 p=0.08
1.2.1 Supratentorial stroke	2	80	Fixed	0.02 [-0.29; 0.33]	0%
1.2.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
1.2.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
1.2.4 Mixed or not determined	9	350	Fixed	-0.28 [-0.44; -0.13]	0%
1.3 Postural stability, EO	16	504	Fixed	0.47 [0.29; 0.65]	29.3% SgD: Chi2 p=0.96
1.3.1 Supratentorial stroke	2	40	Fixed	0.49 [-0.15; 1.12]	0.9%
1.3.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
1.3.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
1.3.4 Mixed or not determined	14	464	Fixed	0.47 [0.28; 0.66]	34.9%
1.4 Autonomy	15	941	Fixed	0.36 [0.23; 0.49]	0% SgD: Chi2 p=0.62
1.4.1 Supratentorial stroke	2	64	Fixed	0.24 [-0.25; 0.73]	0%
1.4.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
1.4.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
1.4.4 Mixed or not determined	13	877	Fixed	0.37 [0.23; 0.51]	0%
2. PT versus no treatment, persisting effect					
2.1 Balance	11	493	Random	0.29 [-0.02; 0.59]	60.2% SgD: Chi2 NA
2.1.1 Supratentorial stroke	0	0	Random	Not estimable	NA
2.1.2 Brainstem stroke	0	0	Random	Not estimable	NA
2.1.3 Cerebellum stroke	0	0	Random	Not estimable	NA
2.1.4 Mixed or not determined	11	493	Random	0.29 [-0.02; 0.59]	60.2%
2.2 Mediolateral postural deviation, EO	3	50	Fixed	-0.44 [-1.05; 0.16]	0%

					SgD: Chi2 p=0.47
2.2.1 Supratentorial stroke	1	16	Fixed	-0.75 [-1.77; 0.28]	NA
2.2.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
2.2.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
2.2.4 Mixed or not determined	1	34	Fixed	-0.28 [-1.03; 0.47]	0%
2.3 Postural stability, EO	3	80	Fixed	0.31 [-0.14; 0.76]	12.1% SgD: Chi2 p=0.14
2.3.1 Supratentorial stroke	2	57	Fixed	0.11 [-0.42; 0.63]	0%
2.3.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
2.3.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
2.3.4 Mixed or not determined	1	23	Fixed	0.87 [0.01; 1.74]	NA
2.4 Autonomy	6	312	Fixed	0.36 [0.13; 0.58]	0% SgD: Chi2 NA
2.4.1 Supratentorial stroke	0	0	Fixed	Not estimable	NA
2.4.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
2.4.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
2.4.4 Mixed or not determined	6	312	Fixed	0.36 [0.13; 0.58]	0%
3. PT versus sham treatment/usual care, post-intervention effect					
3.1 Balance	46	2051	Random	0.43 [0.28; 0.59]	60.9% SgD: Chi2 p=0.27
3.1.1 Supratentorial stroke	7	318	Random	0.26 [-0.06; 0.58]	49.5%
3.1.2 Brainstem stroke	0	0	Random	Not estimable	NA
3.1.3 Cerebellum stroke	0	0	Random	Not estimable	NA
3.1.4 Mixed or not determined	39	1733	Random	0.47 [0.30; 0.64]	62.6%
3.2 Mediolateral postural deviation, EO	4	122	Fixed	-0.15 [-0.52; 0.21]	38.2% SgD: Chi2 p=0.59
3.2.1 Supratentorial stroke	1	15	Fixed	0.13 [-0.97; 1.23]	0%
3.2.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
3.2.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
3.2.4 Mixed or not determined	3	107	Fixed	-0.19 [-0.57; 0.20]	64.9%
3.3 Postural stability, EO	15	574	Random	0.96 [0.55; 1.37]	77.9% SgD: Chi2 p=0.46
3.3.1 Supratentorial stroke	1	15	Random	0.54 [-0.58; 1.66]	0%
3.3.2 Brainstem stroke	0	0	Random	Not estimable	NA
3.3.3 Cerebellum stroke	0	0	Random	Not estimable	NA
3.3.4 Mixed or not determined	14	559	Random	1.00 [0.56; 1.43]	80.5%
3.4 Autonomy	15	805	Random	0.26 [0.01; 0.51]	61.1%

					SgD: Chi2 p=0.62
3.4.1 Supratentorial stroke	6	278	Random	0.19 [-0.13; 0.51]	43.8%
3.4.2 Brainstem stroke	0	0	Random	Not estimable	NA
3.4.3 Cerebellum stroke	0	0	Random	Not estimable	NA
3.4.4 Mixed or not determined	9	527	Random	0.32 [-0.05; 0.69]	68.9%
4. PT versus sham treatment/usual care, persisting effect					
4.1 Balance	18	1150	Fixed	0.18 [0.06; 0.30]	48.8% SgD: Chi2 p=0.36
4.1.1 Supratentorial stroke	3	121	Fixed	0.02 [-0.34; 0.38]	3%
4.1.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
4.1.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
4.1.4 Mixed or not determined	15	1029	Fixed	0.20 [0.07; 0.33]	53%
4.2 Postural stability, EO	2	178	Fixed	0.32 [0.02; 0.62]	0% SgD: Chi2 NA
4.2.1 Supratentorial stroke	0	0	Fixed	Not estimable	NA
4.2.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
4.2.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
4.2.4 Mixed or not determined	2	178	Fixed	0.32 [0.02; 0.62]	0%
4.3 Autonomy	9	551	Fixed	-0.00 [-0.17; 0.17]	26% SgD: Chi2 p=0.84
4.3.1 Supratentorial stroke	3	121	Fixed	0.03 [-0.33; 0.39]	3.9%
4.3.2 Brainstem stroke	0	0	Fixed	Not estimable	NA
4.3.3 Cerebellum stroke	0	0	Fixed	Not estimable	NA
4.3.4 Mixed or not determined	6	430	Fixed	-0.01 [-0.21; 0.18]	38.6%

Autonomy: combination of barthel index, functional independence measure, activities of daily living and instrumental activities of daily living scales.

Mediolateral postural deviation: combination of weight bearing asymmetry and mediolateral position of center of pressure

Abbreviations: ADL, activities of daily living; BBS, berg balance scale; CI, confidence interval; COP, center of pressure; CPI, cardiopulmonary intervention; EO, eyes open; EC, eyes closed; IADL, instrumental activities of daily living; FIM, functional independence measure; FTT, functional task training; MD, mean difference; MS, muscle strengthening; MM, musculoskeletal mobilization; NA, not applicable; NPI, neurophysiological intervention; PASS, postural assessment scale for stroke; PT, physical therapy; RCT, randomized controlled trials; SgD, subgroup difference; SMD, standardized mean difference; X, mediolateral position of COP; Y, anteroposterior position of COP; WB, weight bearing.

S11 Table. Summary of findings and quality of the evidence

S11A Table. For PT compared to no treatment

Physical therapy compared to no treatment after stroke

Patient or population: Adult stroke patients
Intervention: Physical therapy
Comparison: No treatment

Outcomes	Standardized mean difference [95% CI]	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Balance Post-intervention effects	0.46 [0.37; 0.56]	37 studies, 1721 participants	⊕⊕⊕⊖ moderate	Low heterogeneity. Many studies had high and unclear risks of bias, but sensitive analyses based on the methodological quality did not change the direction of the effect.
Balance Persisting effects	0.29 [-0.02; 0.59]	11 studies, 493 participants	⊕⊖⊖⊖⊖ very low	Substantial heterogeneity. Many studies had high and unclear risks of bias.
Mediolateral postural deviation EO Post-intervention effects	-0.23 [-0.36; -0.09]	11 studies, 329 participants	⊕⊕⊖⊖ low	No heterogeneity. Most studies had high and unclear risks of bias.
Mediolateral postural deviation, EO Persisting effects	-0.28 [-1.03, 0.47]	2 studies, 34 participants	⊕⊖⊖⊖ very low	No heterogeneity. Most studies had high and unclear risks of bias.
Postural stability, EO Post-intervention effects	0.47 [0.29; 0.65]	16 studies, 504 participants	⊕⊕⊖⊖ low	Low heterogeneity. Many studies had high and unclear risks of bias.
Postural stability, EO Persisting effects	0.31 [-0.14, 0.76]	3 studies, 80 participants	⊕⊖⊖⊖ very low	Low heterogeneity. Studies had high and unclear risks of bias.
Autonomy Post-intervention effects	0.36 [0.23, 0.49]	15 studies, 941 participants	⊕⊕⊕⊖ moderate	No heterogeneity. Many studies had high and unclear risks of bias, but sensitive analyses based on the methodological quality did not change the direction of the effect.
Autonomy Persisting effects	0.36 [0.13; 0.58]	6 studies, 312 participants	⊕⊖⊖⊖ very low	No heterogeneity. Many studies had high and unclear risks of bias.

EO, eyes open; CI, Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

S11B Table. For PT compared to sham treatment/usual care

Physical therapy compared to sham treatment or usual care after stroke

Patient or population: Adult stroke patients
Intervention: Physical therapy
Comparison: sham treatment or usual care

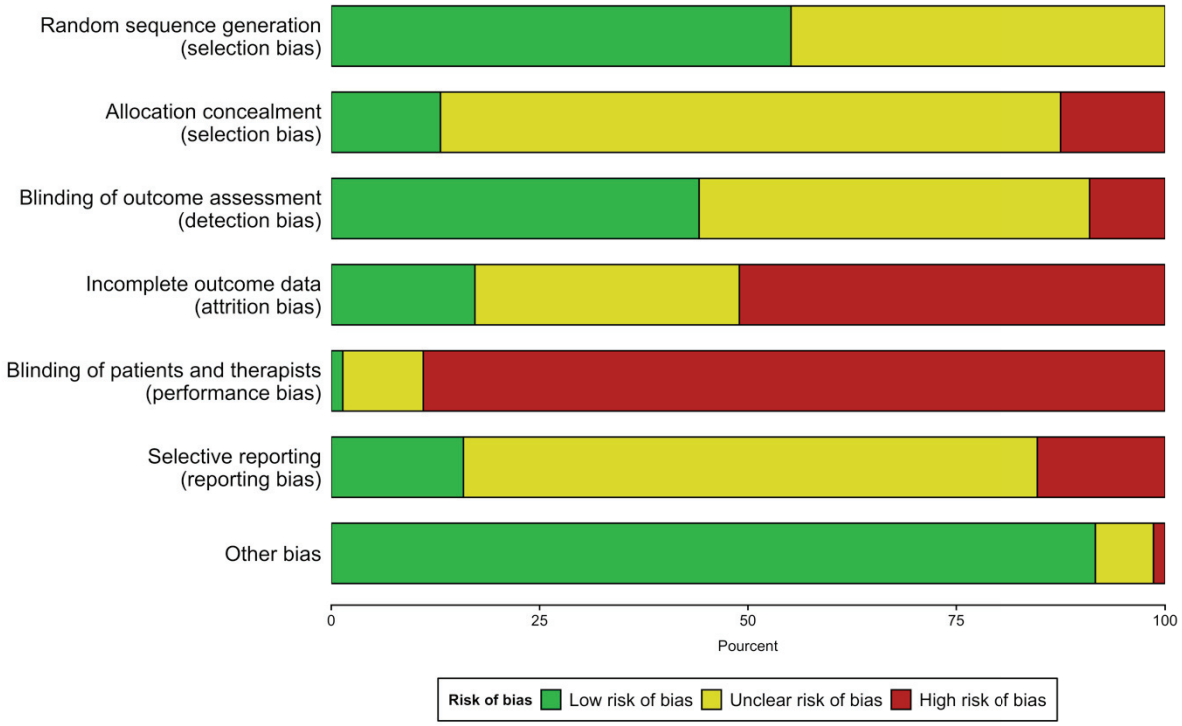
Outcomes	Standardized mean difference (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Balance Post-intervention effects	0.43 [0.28; 0.59]	46 studies, 2051 participants	⨁⨁⊖⊖ low	Substantial heterogeneity. Many studies had high or unclear risks of bias.
Balance Persisting effects	0.18 [0.06; 0.30]	18 studies, 1150 participants	⨁⊖⊖⊖ very low	Moderate heterogeneity. Many studies had high and unclear risks of bias. Potential publication bias.
Mediolateral postural deviation, EO Post-intervention effects	-0.15 [-0.52; 0.21]	4 studies, 122 participants	⨁⊖⊖⊖ very low	Moderate heterogeneity. Most studies had high and unclear risks of bias.
Mediolateral postural deviation, EO Persisting effects	NA	0 study, 0 participant	NA	No data
Postural stability, EO Post-intervention effects	0.96 [0.55; 1.37]	15 studies, 574 participants	⨁⊖⊖⊖ very low	Substantial heterogeneity. Most studies had high or unclear risks of bias.
Postural stability, EO Persisting effects	0.32 [0.02, 0.62]	2 studies, 178 participants	⨁⊖⊖⊖ very low	No heterogeneity. Studies had high and unclear risks of bias.
Autonomy Post-intervention effects	0.26 [0.01; 0.51]	16 studies, 805 participants	⨁⊖⊖⊖ very low	Substantial heterogeneity. Many studies had high or unclear risks of bias.
Autonomy Persisting effects	-0.002 [-0.17; 0.17]	9 studies, 551 participants	⨁⊖⊖⊖ very low	Low heterogeneity. Many studies had high or unclear risks of bias. Potential publication bias.

EO, eyes open; CI, Confidence interval; NA, Not applicable

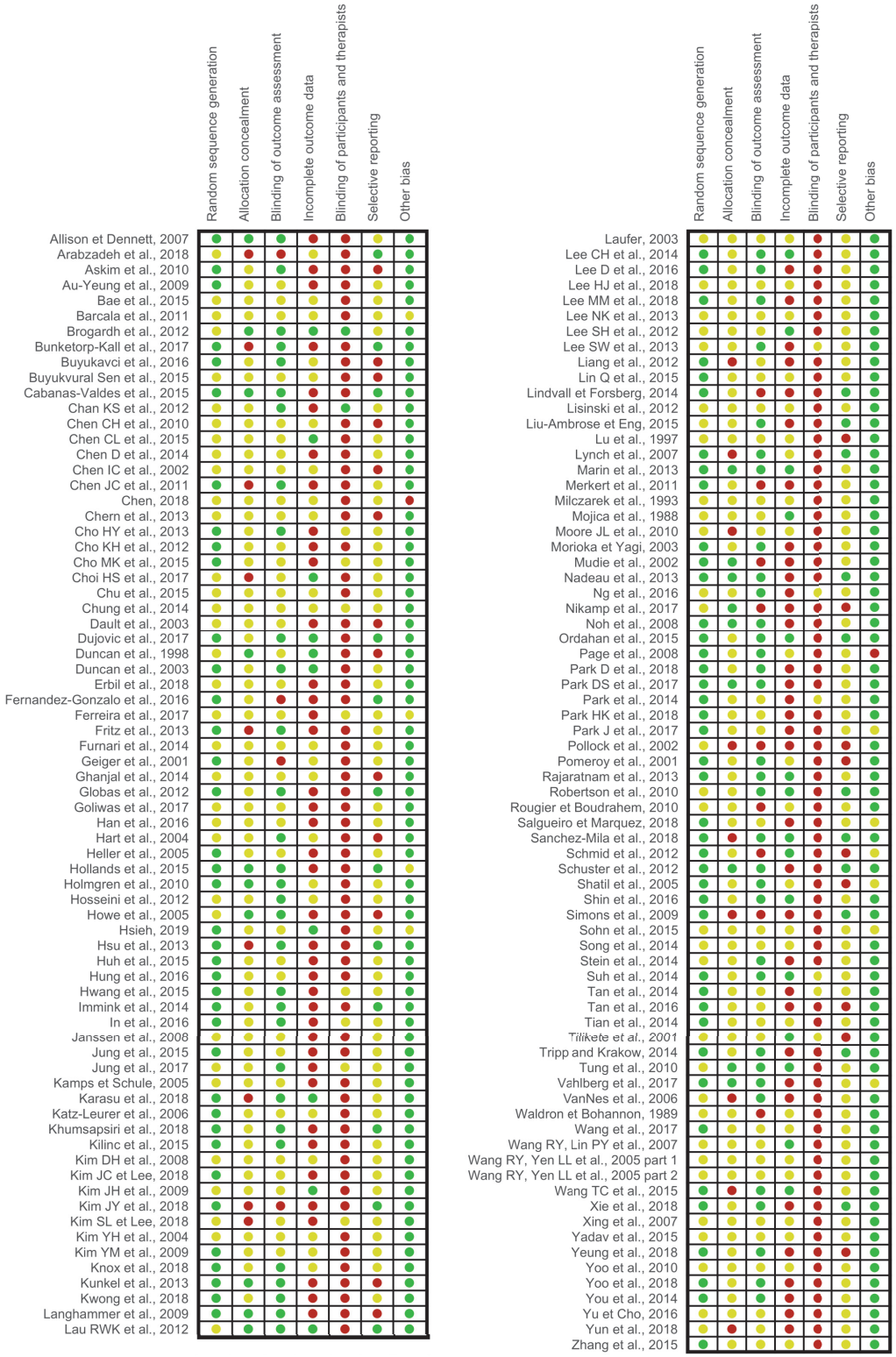
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

S1 Fig. Risk of bias

S1A Fig. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



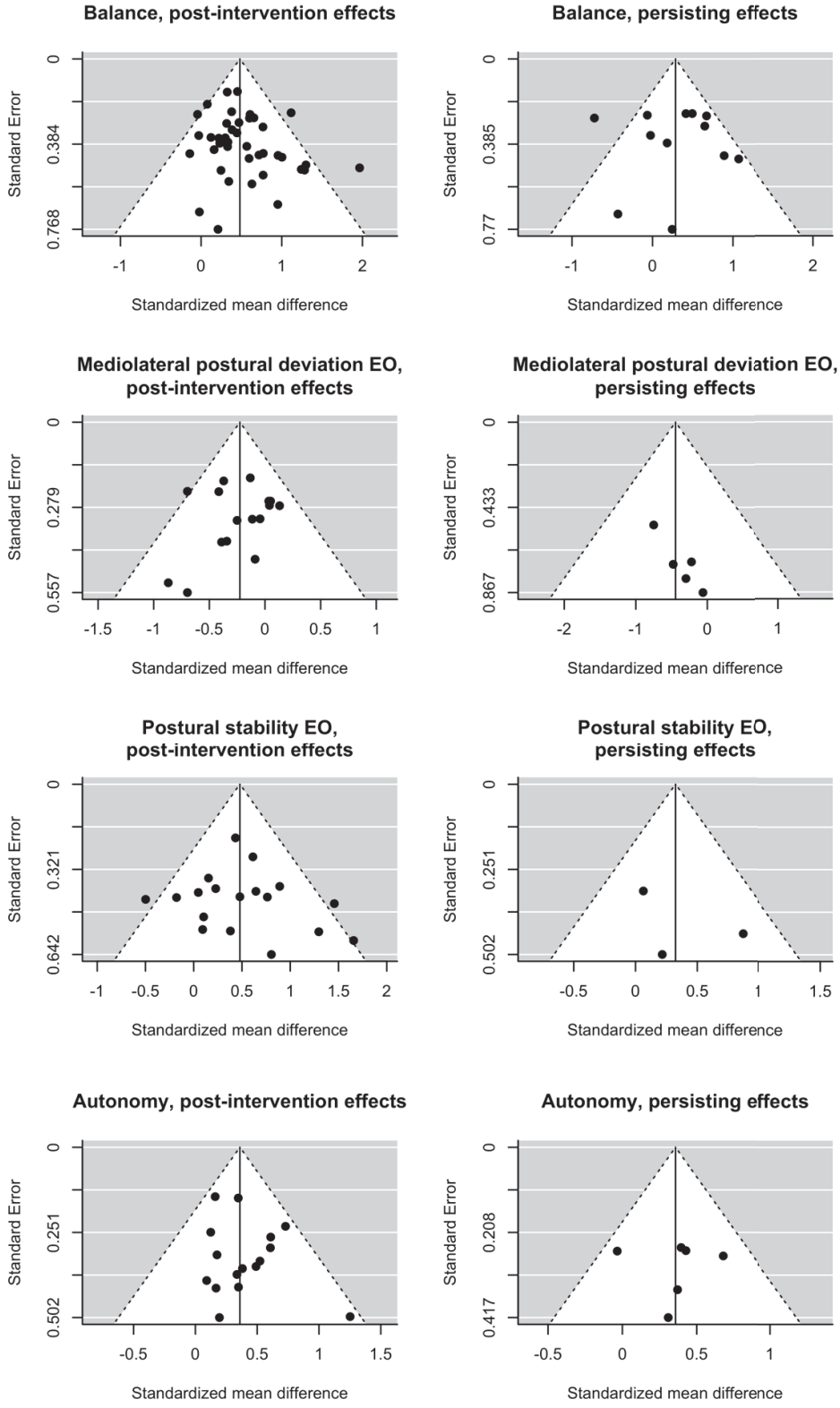
S1B Fig. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Judgements about risk of bias: Green color means low risk, yellow color means unclear risk and red color means high risk.

S2 Fig. Funnel plots

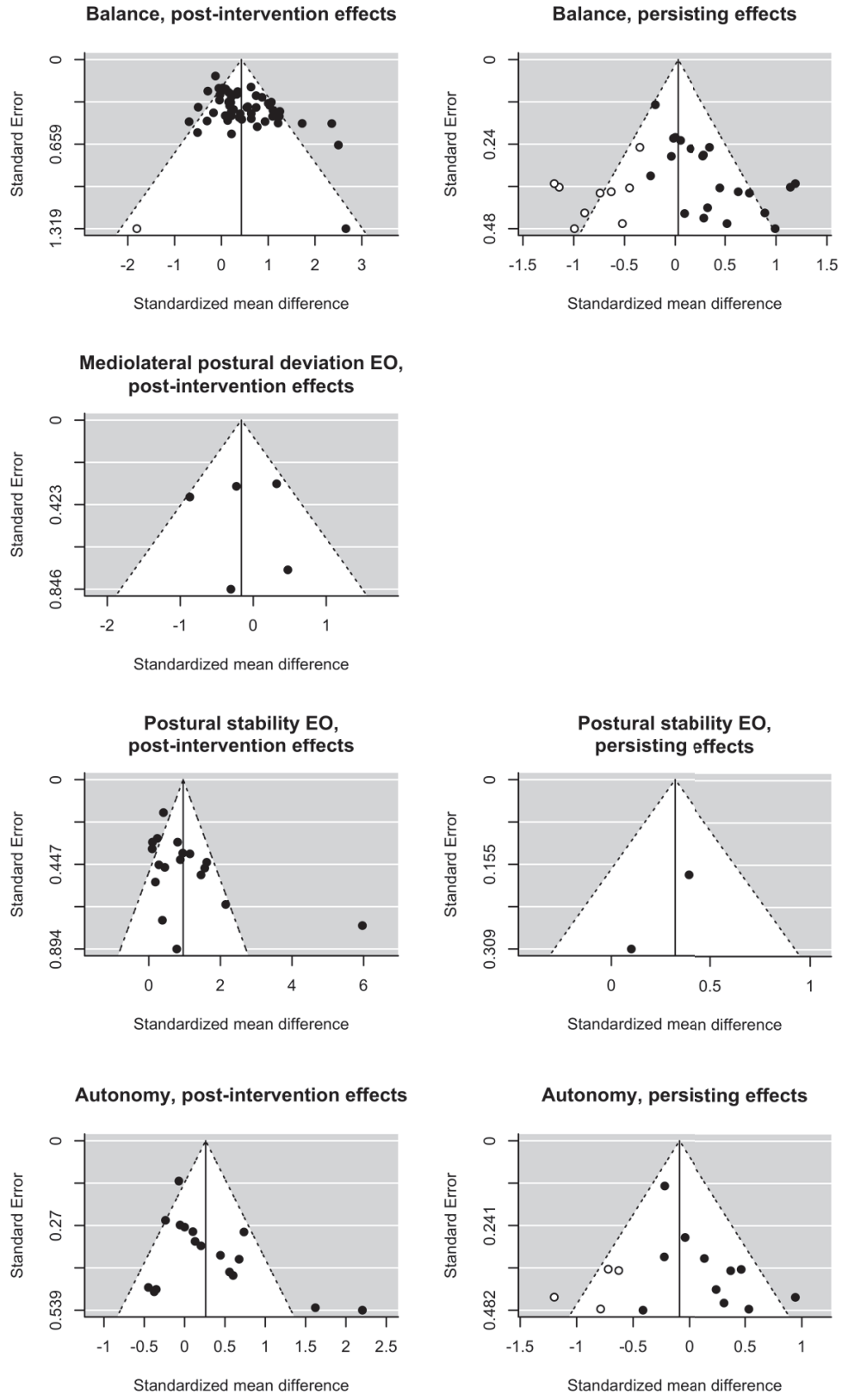
S2A Fig. Funnel plots of comparison PT versus no treatment



Legend: Dotted line: 95% confidence interval; black filled circle: study

Abbreviations: EO, eyes open

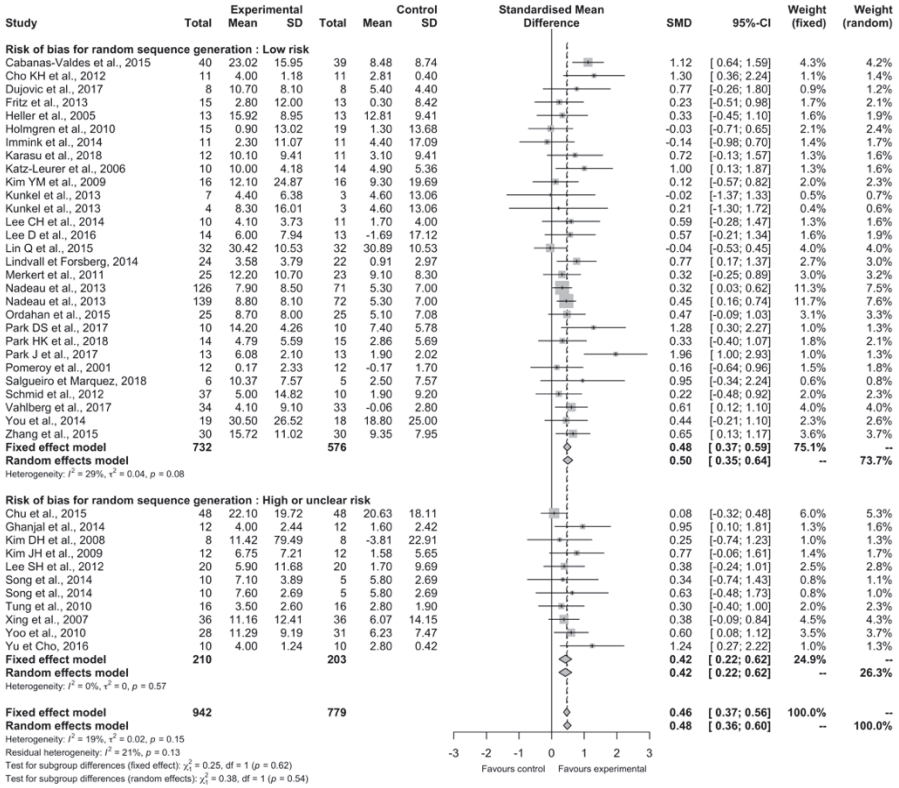
S2B Fig. Funnel plots of comparison PT versus sham treatment/usual care

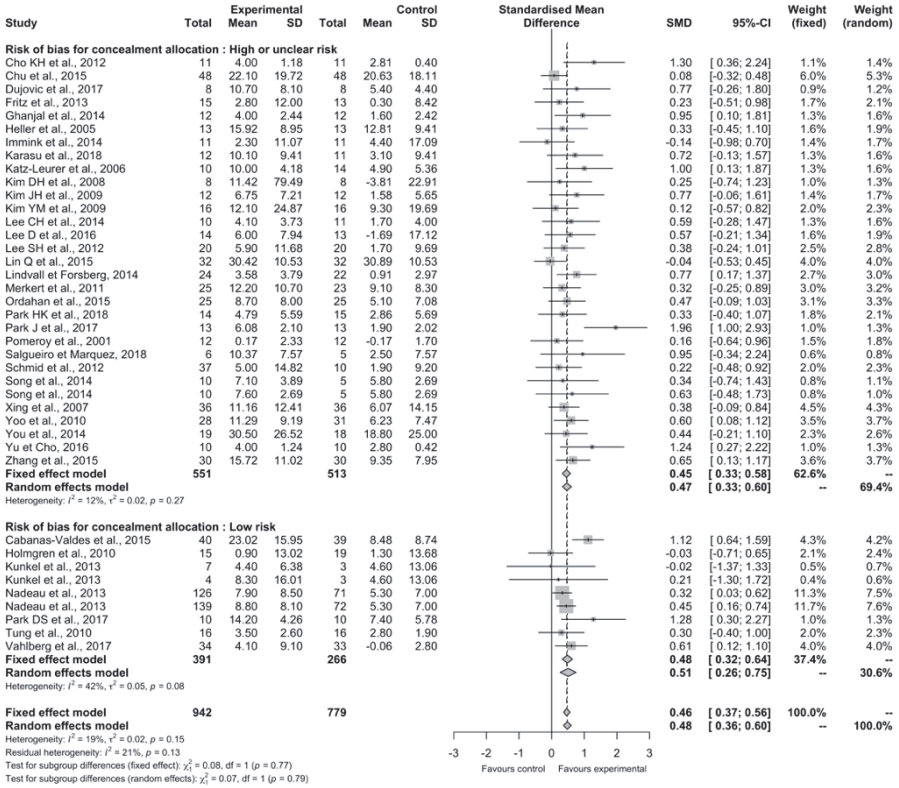


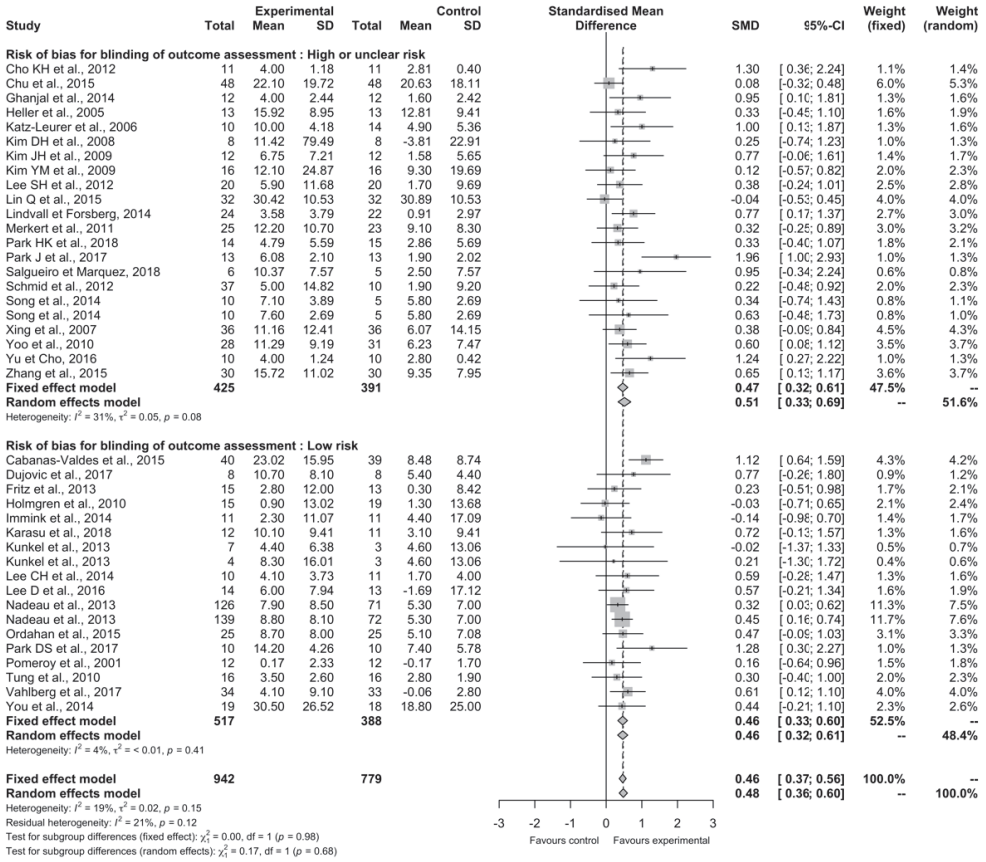
Legend: Dotted line: 95% confidence interval; black filled circle: study; white filled circle: "missing" study

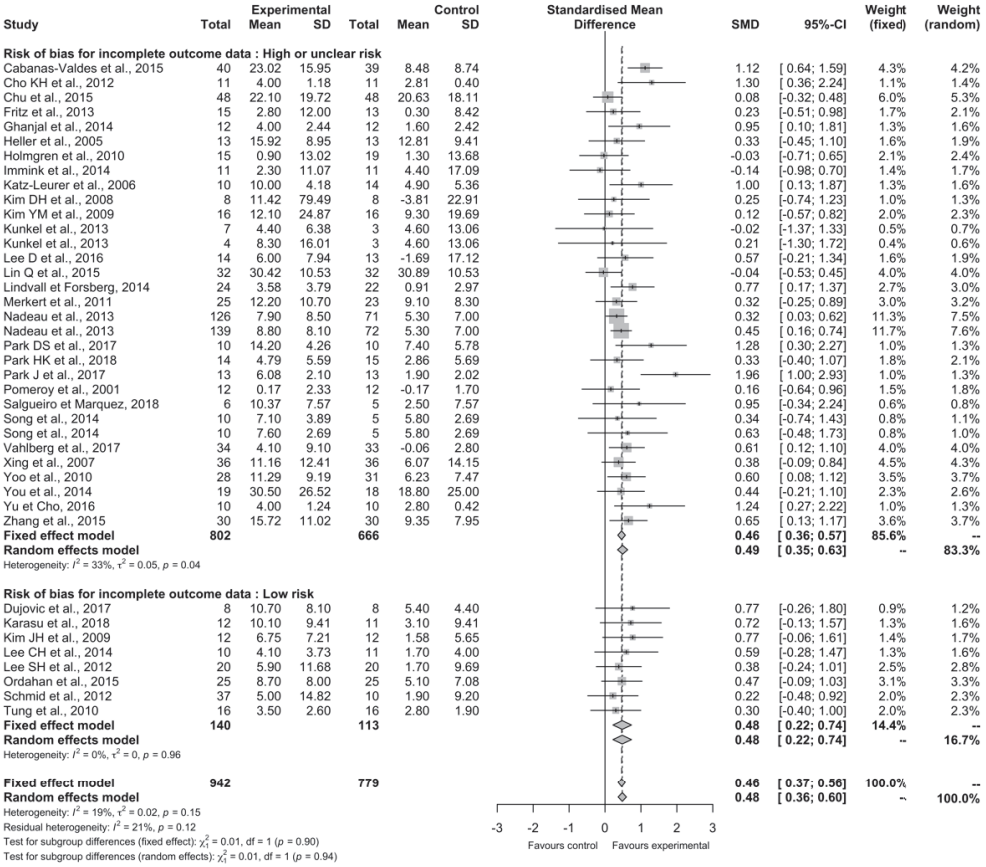
Abbreviations: EO, eyes open

S3 Fig. Forest plot of physical therapy versus no treatment. Outcome: Balance, post-intervention effects. Subgroup: risk of bias






Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Total
Mean
SD
SMD
95%-CI
Risk of bias for blinding of outcome assessment : High or unclear risk
Cho KH et al., 2012 11 4.00 1.18 11 2.81 0.40 1.30 [0.36; 2.24] 1.1% 1.4%
Chu et al., 2015 48 22.10 19.72 48 20.63 18.11 0.08 [-0.32; 0.48] 6.0% 5.3%
Ghanjal et al., 2014 12 4.00 2.44 12 1.60 2.42 0.95 [0.10; 1.81] 1.3% 1.6%
Heller et al., 2005 13 15.92 8.95 13 12.81 9.41 0.33 [-0.45; 1.10] 1.6% 1.9%
Katz-Leurer et al., 2006 10 10.00 4.18 14 4.90 5.36 1.00 [0.13; 1.87] 1.3% 1.6%
Kim DH et al., 2008 8 11.42 79.49 8 -3.81 22.91 0.25 [-0.74; 1.23] 1.0% 1.3%
Kim JH et al., 2009 12 6.75 7.21 12 1.58 5.65 0.77 [-0.06; 1.61] 1.4% 1.7%
Kim YM et al., 2009 16 12.10 24.87 16 9.30 19.69 0.12 [-0.57; 0.82] 2.0% 2.3%
Lee SH et al., 2012 20 5.90 11.68 20 1.70 9.69 0.38 [-0.24; 1.01] 2.5% 2.8%
Lin Q et al., 2015 32 30.42 10.53 32 30.89 10.53 -0.04 [-0.53; 0.45] 4.0% 4.0%
Lindvall et Forsberg, 2014 24 3.58 3.79 22 0.91 2.97 0.77 [0.17; 1.37] 2.7% 3.0%
Merkert et al., 2011 25 12.20 10.70 23 9.10 8.30 0.32 [-0.25; 0.89] 3.0% 3.2%
Park HK et al., 2018 14 4.79 5.59 15 2.86 5.69 0.33 [-0.40; 1.07] 1.8% 2.1%
Park J et al., 2017 13 6.08 2.10 13 1.90 2.02 1.96 [1.00; 2.93] 1.0% 1.3%
Salgueiro et Marquez, 2018 6 10.37 7.57 5 2.50 7.57 0.95 [-0.34; 2.24] 0.6% 0.8%
Schmid et al., 2012 37 5.00 14.82 10 1.90 9.20 0.22 [-0.48; 0.92] 2.0% 2.3%
Song et al., 2014 10 7.10 3.89 5 5.80 2.69 0.34 [-0.74; 1.43] 0.8% 1.1%
Song et al., 2014 10 7.60 2.69 5 5.80 2.69 0.63 [-0.48; 1.73] 0.8% 1.0%
Xing et al., 2007 36 11.16 12.41 36 6.07 14.15 0.38 [-0.09; 0.84] 4.5% 4.3%
Yoo et al., 2010 28 11.29 9.19 31 6.23 7.47 0.60 [0.08; 1.12] 3.5% 3.7%
Yu et Cho, 2016 10 4.00 1.24 10 2.80 0.42 1.24 [0.27; 2.22] 1.0% 1.3%
Zhang et al., 2015 30 15.72 11.02 30 9.35 7.95 0.65 [0.13; 1.17] 3.6% 3.7%
Fixed effect model 425 391 0.47 [0.32; 0.61] 47.5% --
Random effects model 0.51 [0.33; 0.69] -- 51.6%
Heterogeneity: I^2 = 31%, τ^2 = 0.05, p = 0.08
Risk of bias for blinding of outcome assessment : Low risk
Cabanas-Valdes et al., 2015 40 23.02 15.95 39 8.48 8.74 1.12 [0.64; 1.59] 4.3% 4.2%
Dujovic et al., 2017 8 10.70 8.10 8 5.40 4.40 0.77 [-0.26; 1.80] 0.9% 1.2%
Fritz et al., 2013 15 2.80 12.00 13 0.30 8.42 0.23 [-0.51; 0.98] 1.7% 2.1%
Holmgren et al., 2010 15 0.90 13.02 19 1.30 13.68 -0.03 [-0.71; 0.65] 2.1% 2.4%
Immink et al., 2014 11 2.30 11.07 11 4.40 17.09 -0.14 [-0.98; 0.70] 1.4% 1.7%
Karasu et al., 2018 12 10.10 9.41 11 3.10 9.41 0.72 [-0.13; 1.57] 1.3% 1.6%
Kunkel et al., 2013 7 4.40 6.38 3 4.60 13.06 -0.02 [-1.37; 1.33] 0.5% 0.7%
Kunkel et al., 2013 4 8.30 16.01 3 4.60 13.06 0.21 [-1.30; 1.72] 0.4% 0.6%
Lee CH et al., 2014 10 4.10 3.73 11 1.70 4.00 0.59 [-0.28; 1.47] 1.3% 1.6%
Lee D et al., 2016 14 6.00 7.94 13 -1.69 17.12 0.57 [-0.21; 1.34] 1.6% 1.9%
Nadeau et al., 2013 126 7.90 8.50 71 5.30 7.00 0.32 [0.03; 0.62] 11.3% 7.5%
Nadeau et al., 2013 139 8.80 8.10 72 5.30 7.00 0.45 [0.16; 0.74] 11.7% 7.6%
Ordahan et al., 2015 25 8.70 8.00 25 5.10 7.08 0.47 [-0.09; 1.03] 3.1% 3.3%
Park DS et al., 2017 10 14.20 4.26 10 7.40 5.78 1.28 [0.30; 2.27] 1.0% 1.3%
Pomeroy et al., 2001 12 0.17 2.33 12 -0.17 1.70 0.16 [-0.64; 0.96] 1.5% 1.8%
Tung et al., 2010 16 3.50 2.60 16 2.80 1.90 0.30 [-0.40; 1.00] 2.0% 2.3%
Vahlberg et al., 2017 34 4.10 9.10 33 -0.06 2.80 0.61 [0.12; 1.10] 4.0% 4.0%
You et al., 2014 19 30.50 26.52 18 18.80 25.00 0.44 [-0.21; 1.10] 2.3% 2.6%
Fixed effect model 517 388 0.46 [0.33; 0.60] 52.5% --
Random effects model 0.46 [0.32; 0.61] -- 48.4%
Heterogeneity: I^2 = 4%, τ^2 = < 0.01, p = 0.41
Fixed effect model 942 779 0.46 [0.37; 0.56] 100.0% --
Random effects model 0.48 [0.36; 0.60] -- 100.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.02, p = 0.15
Residual heterogeneity: I^2 = 21%, p = 0.12
Test for subgroup differences (fixed effect): χ^2_1 = 0.00, df = 1 (p = 0.98)
Test for subgroup differences (random effects): χ^2_1 = 0.17, df = 1 (p = 0.68)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Total
Mean
SD
SMD
95%-CI
Risk of bias for incomplete outcome data : High or unclear risk
Cabanas-Valdes et al., 2015 40 23.02 15.95 39 8.48 8.74 1.12 [0.64; 1.59] 4.3% 4.2%
Cho KH et al., 2012 11 4.00 1.18 11 2.81 0.40 1.30 [0.36; 2.24] 1.1% 1.4%
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Fritz et al., 2013 15 2.80 12.00 13 0.30 8.42 0.23 [-0.51; 0.98] 1.7% 2.1%
Ghanjal et al., 2014 12 4.00 2.44 12 1.60 2.42 0.95 [0.10; 1.81] 1.3% 1.6%
Heller et al., 2005 13 15.92 8.95 13 12.81 9.41 0.33 [-0.45; 1.10] 1.6% 1.9%
Holmgren et al., 2010 15 0.90 13.02 19 1.30 13.68 -0.03 [-0.71; 0.65] 2.1% 2.4%
Immink et al., 2014 11 2.30 11.07 11 4.40 17.09 -0.14 [-0.98; 0.70] 1.4% 1.7%
Katz-Leurer et al., 2006 10 10.00 4.18 14 4.90 5.36 1.00 [0.13; 1.87] 1.3% 1.6%
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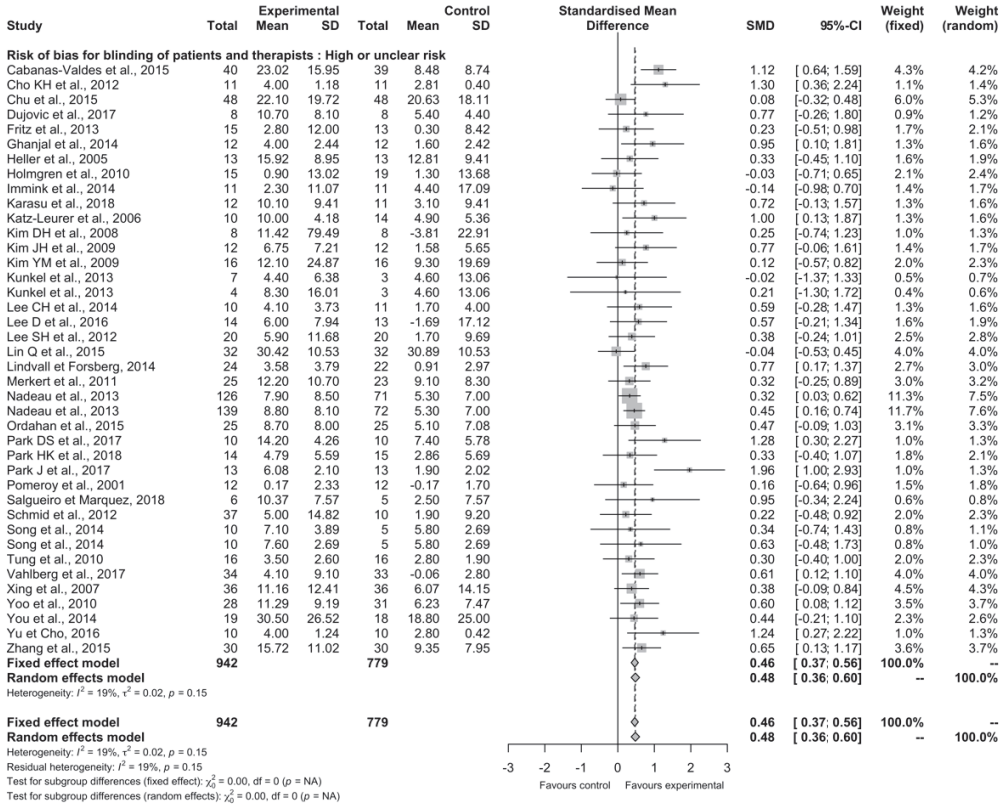
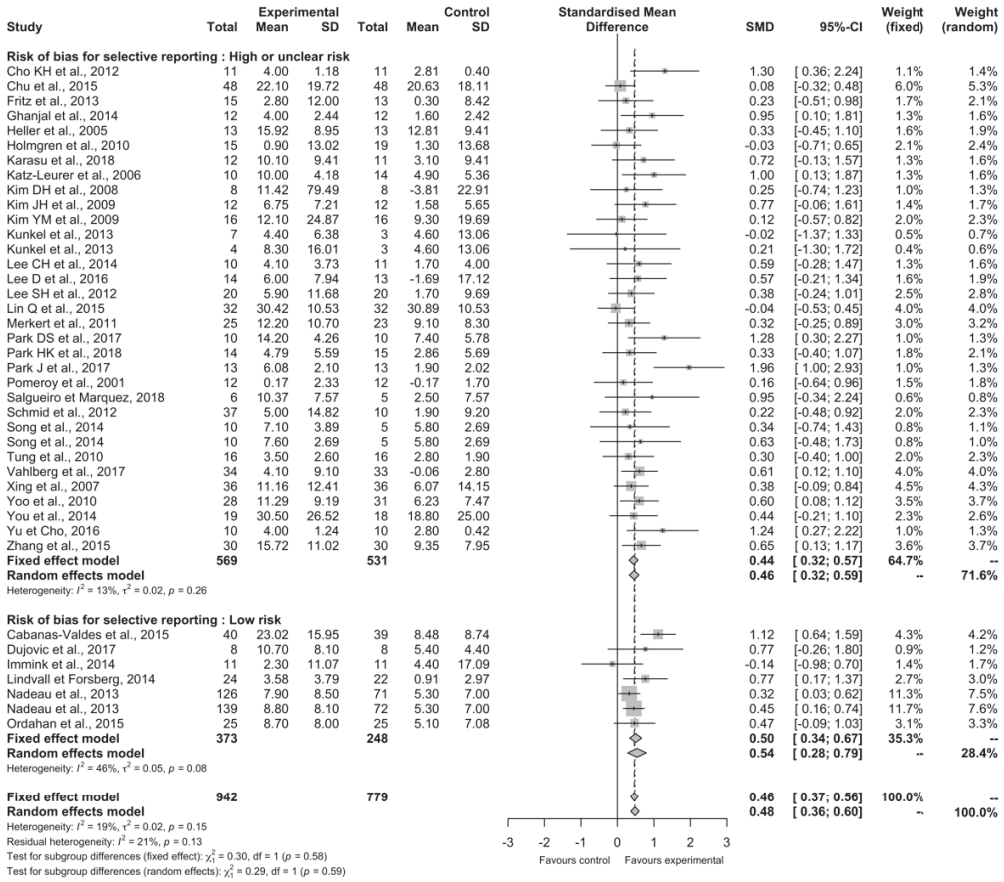
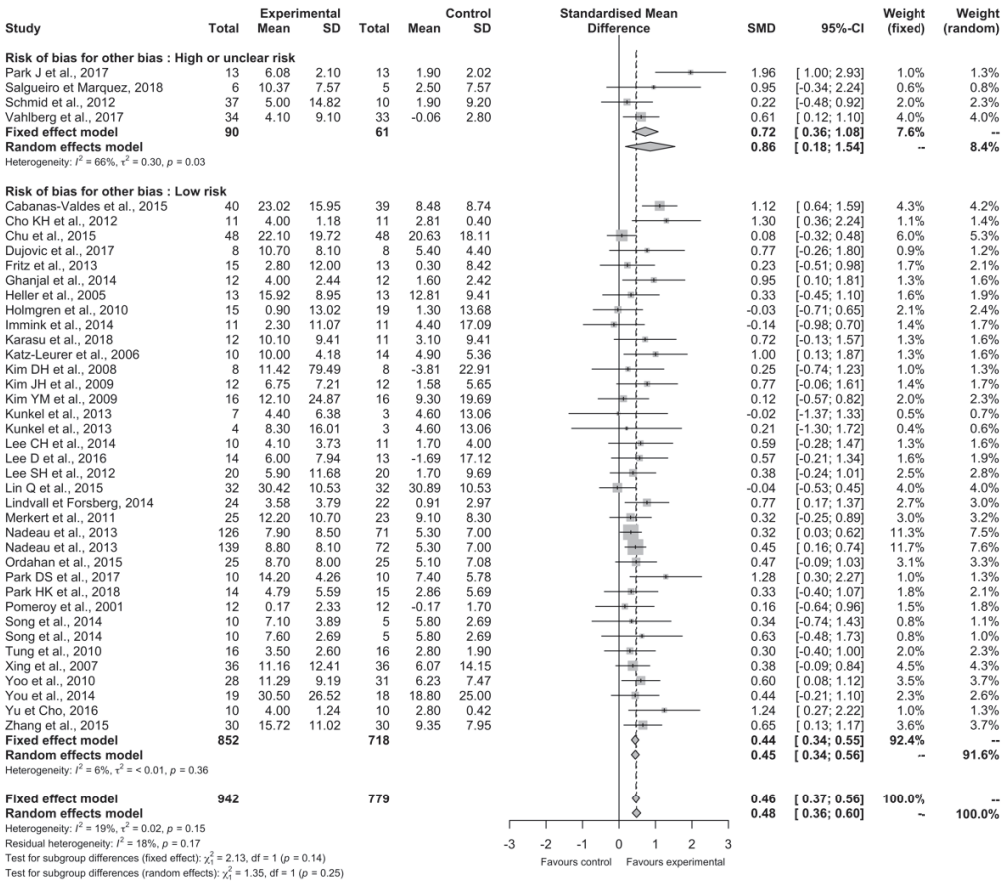
Kim YM et al., 2009 16 12.10 24.87 16 9.30 19.69 0.12 [-0.57; 0.82] 2.0% 2.3%
Kunkel et al., 2013 7 4.40 6.38 3 4.60 13.06 -0.02 [-1.37; 1.33] 0.5% 0.7%
Kunkel et al., 2013 4 8.30 16.01 3 4.60 13.06 0.21 [-1.30; 1.72] 0.4% 0.6%
Lee D et al., 2016 14 6.00 7.94 13 -1.69 17.12 0.57 [-0.21; 1.34] 1.6% 1.9%
Lin Q et al., 2015 32 30.42 10.53 32 30.89 10.53 -0.04 [-0.53; 0.45] 4.0% 4.0%
Lindvall et Forsberg, 2014 24 3.58 3.79 22 0.91 2.97 0.77 [0.17; 1.37] 2.7% 3.0%
Merkert et al., 2011 25 12.20 10.70 23 9.10 8.30 0.32 [-0.25; 0.89] 3.0% 3.2%
Nadeau et al., 2013 126 7.90 8.50 71 5.30 7.00 0.32 [0.03; 0.62] 11.3% 7.5%
Nadeau et al., 2013 139 8.80 8.10 72 5.30 7.00 0.45 [0.16; 0.74] 11.7% 7.6%
Park DS et al., 2017 10 14.20 4.26 10 7.40 5.78 1.28 [0.30; 2.27] 1.0% 1.3%
Park HK et al., 2018 14 4.79 5.59 15 2.86 5.69 0.33 [-0.40; 1.07] 1.8% 2.1%
Park J et al., 2017 13 6.08 2.10 13 1.90 2.02 1.96 [1.00; 2.93] 1.0% 1.3%
Pomeroy et al., 2001 12 0.17 2.33 12 -0.17 1.70 0.16 [-0.64; 0.96] 1.5% 1.8%
Salgueiro et Marquez, 2018 6 10.37 7.57 5 2.50 7.57 0.95 [-0.34; 2.24] 0.6% 0.8%
Song et al., 2014 10 7.10 3.89 5 5.80 2.69 0.34 [-0.74; 1.43] 0.8% 1.1%
Song et al., 2014 10 7.60 2.69 5 5.80 2.69 0.63 [-0.48; 1.73] 0.8% 1.0%
Vahlberg et al., 2017 34 4.10 9.10 33 -0.06 2.80 0.61 [0.12; 1.10] 4.0% 4.0%
Xing et al., 2007 36 11.16 12.41 36 6.07 14.15 0.38 [-0.09; 0.84] 4.5% 4.3%
Yoo et al., 2010 28 11.29 9.19 31 6.23 7.47 0.60 [0.08; 1.12] 3.5% 3.7%
You et al., 2014 19 30.50 26.52 18 18.80 25.00 0.44 [-0.21; 1.10] 2.3% 2.6%
Yu et Cho, 2016 10 4.00 1.24 10 2.80 0.42 1.24 [0.27; 2.22] 1.0% 1.3%
Zhang et al., 2015 30 15.72 11.02 30 9.35 7.95 0.65 [0.13; 1.17] 3.6% 3.7%
Fixed effect model 802 666 0.46 [0.36; 0.57] 85.6% --
Random effects model 0.49 [0.35; 0.63] -- 83.3%
Heterogeneity: I^2 = 33%, τ^2 = 0.05, p = 0.04
Risk of bias for incomplete outcome data : Low risk
Dujovic et al., 2017 8 10.70 8.10 8 5.40 4.40 0.77 [-0.26; 1.80] 0.9% 1.2%
Karasu et al., 2018 12 10.10 9.41 11 3.10 9.41 0.72 [-0.13; 1.57] 1.3% 1.6%
Kim JH et al., 2009 12 6.75 7.21 12 1.58 5.65 0.77 [-0.06; 1.61] 1.4% 1.7%
Lee CH et al., 2014 10 4.10 3.73 11 1.70 4.00 0.59 [-0.28; 1.47] 1.3% 1.6%
Lee SH et al., 2012 20 5.90 11.68 20 1.70 9.69 0.38 [-0.24; 1.01] 2.5% 2.8%
Ordahan et al., 2015 25 8.70 8.00 25 5.10 7.08 0.47 [-0.09; 1.03] 3.1% 3.3%
Schmid et al., 2012 37 5.00 14.82 10 1.90 9.20 0.22 [-0.48; 0.92] 2.0% 2.3%
Tung et al., 2010 16 3.50 2.60 16 2.80 1.90 0.30 [-0.40; 1.00] 2.0% 2.3%
Fixed effect model 140 113 0.48 [0.22; 0.74] 14.4% --
Random effects model 0.48 [0.22; 0.74] -- 16.7%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.96
Fixed effect model 942 779 0.46 [0.37; 0.56] 100.0% --
Random effects model 0.48 [0.36; 0.60] -- 100.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.02, p = 0.15
Residual heterogeneity: I^2 = 21%, p = 0.12
Test for subgroup differences (fixed effect): χ^2_1 = 0.01, df = 1 (p = 0.90)
Test for subgroup differences (random effects): χ^2_1 = 0.01, df = 1 (p = 0.94)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

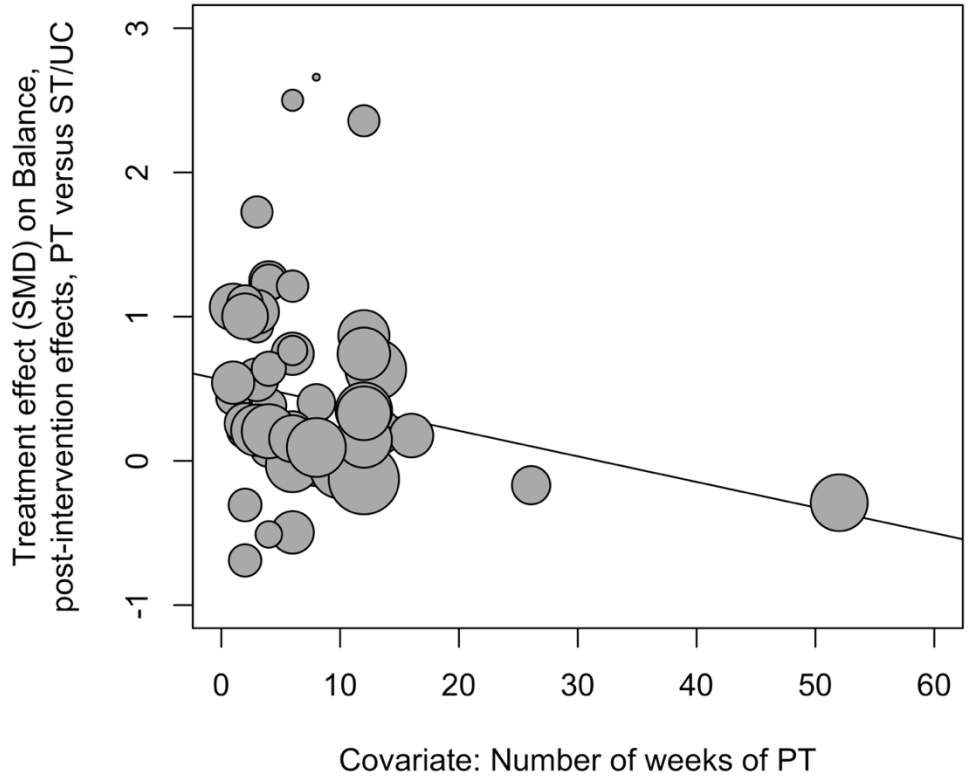

Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for blinding of patients and therapists : High or unclear risk
Cabanas-Valdes et al., 2015 40 23.02 15.95 39 8.48 8.74 1.12 [0.64; 1.59] 4.3% 4.2%
Cho KH et al., 2012 11 4.00 1.18 11 2.81 0.40 1.30 [0.36; 2.24] 1.1% 1.4%
Chu et al., 2015 48 22.10 19.72 48 20.63 18.11 0.08 [-0.32; 0.48] 6.0% 5.3%
Dujovic et al., 2017 8 10.70 8.10 8 5.40 4.40 0.77 [-0.26; 1.80] 0.9% 1.2%
Fritz et al., 2013 15 2.80 12.00 13 0.30 8.42 0.23 [-0.51; 0.98] 1.7% 2.1%
Ghanjal et al., 2014 12 4.00 2.44 12 1.60 2.42 0.95 [0.10; 1.81] 1.3% 1.6%
Heller et al., 2005 13 15.92 8.95 13 12.81 9.41 0.33 [-0.45; 1.10] 1.6% 1.9%
Holmgren et al., 2010 15 0.90 13.02 19 1.30 13.68 -0.03 [-0.71; 0.65] 2.1% 2.4%
Immink et al., 2014 11 2.30 11.07 11 4.40 17.09 -0.14 [-0.98; 0.70] 1.4% 1.7%
Karasu et al., 2018 12 10.10 9.41 11 3.10 9.41 0.72 [-0.13; 1.57] 1.3% 1.6%
Katz-Leurer et al., 2006 10 10.00 4.18 14 4.90 5.36 1.00 [0.13; 1.87] 1.3% 1.6%
Kim DH et al., 2008 8 11.42 79.49 8 -3.81 22.91 0.25 [-0.74; 1.23] 1.0% 1.3%
Kim JH et al., 2009 12 6.75 7.21 12 1.58 5.65 0.77 [-0.06; 1.61] 1.4% 1.7%
Kim YM et al., 2009 16 12.10 24.87 16 9.30 19.69 0.12 [-0.57; 0.82] 2.0% 2.3%
Kunkel et al., 2013 7 4.40 6.38 3 4.60 13.06 -0.02 [-1.37; 1.33] 0.5% 0.7%
Kunkel et al., 2013 4 8.30 16.01 3 4.60 13.06 0.21 [-1.30; 1.72] 0.4% 0.6%
Lee CH et al., 2014 10 4.10 3.73 11 1.70 4.00 0.59 [-0.28; 1.47] 1.3% 1.6%
Lee D et al., 2016 14 6.00 7.94 13 -1.69 17.12 0.57 [-0.21; 1.34] 1.6% 1.9%
Lee SH et al., 2012 20 5.90 11.68 20 1.70 9.69 0.38 [-0.24; 1.01] 2.5% 2.8%
Lin Q et al., 2015 32 30.42 10.53 32 30.89 10.53 -0.04 [-0.53; 0.45] 4.0% 4.0%
Lindvall et Forsberg, 2014 24 3.58 3.79 22 0.91 2.97 0.77 [0.17; 1.37] 2.7% 3.0%
Merkert et al., 2011 25 12.20 10.70 23 9.10 8.30 0.32 [-0.25; 0.89] 3.0% 3.2%
Nadeau et al., 2013 126 7.90 8.50 71 5.30 7.00 0.32 [0.03; 0.62] 11.3% 7.5%
Nadeau et al., 2013 139 8.80 8.10 72 5.30 7.00 0.45 [0.16; 0.74] 11.7% 7.6%
Ordahan et al., 2015 25 8.70 8.00 25 5.10 7.08 0.47 [-0.09; 1.03] 3.1% 3.3%
Park DS et al., 2017 10 14.20 4.26 10 7.40 5.78 1.28 [0.30; 2.27] 1.0% 1.3%
Park HK et al., 2018 14 4.79 5.59 15 2.86 5.69 0.33 [-0.40; 1.07] 1.8% 2.1%
Park J et al., 2017 13 6.08 2.10 13 1.90 2.02 1.96 [1.00; 2.93] 1.0% 1.3%
Pomeroy et al., 2001 12 0.17 2.33 12 -0.17 1.70 0.16 [-0.64; 0.96] 1.5% 1.8%
Salgueiro et Marquez, 2018 6 10.37 7.57 5 2.50 7.57 0.95 [-0.34; 2.24] 0.6% 0.8%
Schmid et al., 2012 37 5.00 14.82 10 1.90 9.20 0.22 [-0.48; 0.92] 2.0% 2.3%
Song et al., 2014 10 7.10 3.89 5 5.80 2.69 0.34 [-0.74; 1.43] 0.8% 1.1%
Song et al., 2014 10 7.60 2.69 5 5.80 2.69 0.63 [-0.48; 1.73] 0.8% 1.0%
Tung et al., 2010 16 3.50 2.60 16 2.80 1.90 0.30 [-0.40; 1.00] 2.0% 2.3%
Vahlberg et al., 2017 34 4.10 9.10 33 -0.06 2.80 0.61 [0.12; 1.10] 4.0% 4.0%
Xing et al., 2007 36 11.16 12.41 36 6.07 14.15 0.38 [-0.09; 0.84] 4.5% 4.3%
Yoo et al., 2010 28 11.29 9.19 31 6.23 7.47 0.60 [0.08; 1.12] 3.5% 3.7%
You et al., 2014 19 30.50 26.52 18 18.80 25.00 0.44 [-0.21; 1.10] 2.3% 2.6%
Yu et Cho, 2016 10 4.00 1.24 10 2.80 0.42 1.24 [0.27; 2.22] 1.0% 1.3%
Zhang et al., 2015 30 15.72 11.02 30 9.35 7.95 0.65 [0.13; 1.17] 3.6% 3.7%
Fixed effect model 942 779 0.46 [0.37; 0.56] 100.0% --
Random effects model 0.48 [0.36; 0.60] -- 100.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.02, p = 0.15
Fixed effect model 942 779 0.46 [0.37; 0.56] 100.0% --
Random effects model 0.48 [0.36; 0.60] -- 100.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.02, p = 0.15
Residual heterogeneity: I^2 = 19%, p = 0.15
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for selective reporting : High or unclear risk
Cho KH et al., 2012 11 4.00 1.18 11 2.81 0.40 1.30 [0.36; 2.24] 1.1% 1.4%
Chu et al., 2015 48 22.10 19.72 48 20.63 18.11 0.08 [-0.32; 0.48] 6.0% 5.3%
Fritz et al., 2013 15 2.80 12.00 13 0.30 8.42 0.23 [-0.51; 0.98] 1.7% 2.1%
Ghanjal et al., 2014 12 4.00 2.44 12 1.60 2.42 0.95 [0.10; 1.81] 1.3% 1.6%
Heller et al., 2005 13 15.92 8.95 13 12.81 9.41 0.33 [-0.45; 1.10] 1.6% 1.9%
Holmgren et al., 2010 15 0.90 13.02 19 1.30 13.68 -0.03 [-0.71; 0.65] 2.1% 2.4%
Karasu et al., 2018 12 10.10 9.41 11 3.10 9.41 0.72 [-0.13; 1.57] 1.3% 1.6%
Katz-Leurer et al., 2006 10 10.00 4.18 14 4.90 5.36 1.00 [0.13; 1.87] 1.3% 1.6%
Kim DH et al., 2008 8 11.42 79.49 8 -3.81 22.91 0.25 [-0.74; 1.23] 1.0% 1.3%
Kim JH et al., 2009 12 6.75 7.21 12 1.58 5.65 0.77 [-0.06; 1.61] 1.4% 1.7%
Kim YM et al., 2009 16 12.10 24.87 16 9.30 19.69 0.12 [-0.57; 0.82] 2.0% 2.3%
Kunkel et al., 2013 7 4.40 6.38 3 4.60 13.06 -0.02 [-1.37; 1.33] 0.5% 0.7%
Kunkel et al., 2013 4 8.30 16.01 3 4.60 13.06 0.21 [-1.30; 1.72] 0.4% 0.6%
Lee CH et al., 2014 10 4.10 3.73 11 1.70 4.00 0.59 [-0.28; 1.47] 1.3% 1.6%
Lee D et al., 2016 14 6.00 7.94 13 -1.69 17.12 0.57 [-0.21; 1.34] 1.6% 1.9%
Lee SH et al., 2012 20 5.90 11.68 20 1.70 9.69 0.38 [-0.24; 1.01] 2.5% 2.8%
Lin Q et al., 2015 32 30.42 10.53 32 30.89 10.53 -0.04 [-0.53; 0.45] 4.0% 4.0%
Merkert et al., 2011 25 12.20 10.70 23 9.10 8.30 0.32 [-0.25; 0.89] 3.0% 3.2%
Park DS et al., 2017 10 14.20 4.26 10 7.40 5.78 1.28 [0.30; 2.27] 1.0% 1.3%
Park HK et al., 2018 14 4.79 5.59 15 2.86 5.69 0.33 [-0.40; 1.07] 1.8% 2.1%
Park J et al., 2017 13 6.08 2.10 13 1.90 2.02 1.96 [1.00; 2.93] 1.0% 1.3%
Pomeroy et al., 2001 12 0.17 2.33 12 -0.17 1.70 0.16 [-0.64; 0.96] 1.5% 1.8%
Salgueiro et Marquez, 2018 6 10.37 7.57 5 2.50 7.57 0.95 [-0.34; 2.24] 0.6% 0.8%
Schmid et al., 2012 37 5.00 14.82 10 1.90 9.20 0.22 [-0.48; 0.92] 2.0% 2.3%
Song et al., 2014 10 7.10 3.89 5 5.80 2.69 0.34 [-0.74; 1.43] 0.8% 1.1%
Song et al., 2014 10 7.60 2.69 5 5.80 2.69 0.63 [-0.48; 1.73] 0.8% 1.0%
Tung et al., 2010 16 3.50 2.60 16 2.80 1.90 0.30 [-0.40; 1.00] 2.0% 2.3%
Vahlberg et al., 2017 34 4.10 9.10 33 -0.06 2.80 0.61 [0.12; 1.10] 4.0% 4.0%
Xing et al., 2007 36 11.16 12.41 36 6.07 14.15 0.38 [-0.09; 0.84] 4.5% 4.3%
Yoo et al., 2010 28 11.29 9.19 31 6.23 7.47 0.60 [0.08; 1.12] 3.5% 3.7%
You et al., 2014 19 30.50 26.52 18 18.80 25.00 0.44 [-0.21; 1.10] 2.3% 2.6%
Yu et Cho, 2016 10 4.00 1.24 10 2.80 0.42 1.24 [0.27; 2.22] 1.0% 1.3%
Zhang et al., 2015 30 15.72 11.02 30 9.35 7.95 0.65 [0.13; 1.17] 3.6% 3.7%
Fixed effect model 569 531 0.44 [0.32; 0.57] 64.7% --
Random effects model 0.46 [0.32; 0.59] -- 71.6%
Heterogeneity: I^2 = 13%, τ^2 = 0.02, p = 0.26
Risk of bias for selective reporting : Low risk
Cabanas-Valdes et al., 2015 40 23.02 15.95 39 8.48 8.74 1.12 [0.64; 1.59] 4.3% 4.2%
Dujovic et al., 2017 8 10.70 8.10 8 5.40 4.40 0.77 [-0.26; 1.80] 0.9% 1.2%
Immink et al., 2014 11 2.30 11.07 11 4.40 17.09 -0.14 [-0.98; 0.70] 1.4% 1.7%
Lindvall et Forsberg, 2014 24 3.58 3.79 22 0.91 2.97 0.77 [0.17; 1.37] 2.7% 3.0%
Nadeau et al., 2013 126 7.90 8.50 71 5.30 7.00 0.32 [0.03; 0.62] 11.3% 7.5%
Nadeau et al., 2013 139 8.80 8.10 72 5.30 7.00 0.45 [0.16; 0.74] 11.7% 7.6%
Ordahan et al., 2015 25 8.70 8.00 25 5.10 7.08 0.47 [-0.09; 1.03] 3.1% 3.3%
Fixed effect model 373 248 0.50 [0.34; 0.67] 35.3% --
Random effects model 0.54 [0.28; 0.79] -- 28.4%
Heterogeneity: I^2 = 46%, τ^2 = 0.05, p = 0.08
Fixed effect model 942 779 0.46 [0.37; 0.56] 100.0% --
Random effects model 0.48 [0.36; 0.60] -- 100.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.02, p = 0.15
Residual heterogeneity: I^2 = 21%, p = 0.13
Test for subgroup differences (fixed effect): χ^2_1 = 0.30, df = 1 (p = 0.58)
Test for subgroup differences (random effects): χ^2_1 = 0.29, df = 1 (p = 0.59)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for other bias : High or unclear risk
Park J et al., 2017 13 6.08 2.10 13 1.90 2.02 1.96 [1.00; 2.93] 1.0% 1.3%
Salgueiro et Marquez, 2018 6 10.37 7.57 5 2.50 7.57 0.95 [-0.34; 2.24] 0.6% 0.8%
Schmid et al., 2012 37 5.00 14.82 10 1.90 9.20 0.22 [-0.48; 0.92] 2.0% 2.3%
Vahlberg et al., 2017 34 4.10 9.10 33 -0.06 2.80 0.61 [0.12; 1.10] 4.0% 4.0%
Fixed effect model 90 61 0.72 [0.36; 1.08] 7.6% --
Random effects model 0.86 [0.18; 1.54] -- 8.4%
Heterogeneity: I^2 = 66%, τ^2 = 0.30, p = 0.03
Risk of bias for other bias : Low risk
Cabanas-Valdes et al., 2015 40 23.02 15.95 39 8.48 8.74 1.12 [0.64; 1.59] 4.3% 4.2%
Cho KH et al., 2012 11 4.00 1.18 11 2.81 0.40 1.30 [0.36; 2.24] 1.1% 1.4%
Chu et al., 2015 48 22.10 19.72 48 20.63 18.11 0.08 [-0.32; 0.48] 6.0% 5.3%
Dujovic et al., 2017 8 10.70 8.10 8 5.40 4.40 0.77 [-0.26; 1.80] 0.9% 1.2%
Fritz et al., 2013 15 2.80 12.00 13 0.30 8.42 0.23 [-0.51; 0.98] 1.7% 2.1%
Ghanjal et al., 2014 12 4.00 2.44 12 1.60 2.42 0.95 [0.10; 1.81] 1.3% 1.6%
Heller et al., 2005 13 15.92 8.95 13 12.81 9.41 0.33 [-0.45; 1.10] 1.6% 1.9%
Holmgren et al., 2010 15 0.90 13.02 19 1.30 13.68 -0.03 [-0.71; 0.65] 2.1% 2.4%
Immink et al., 2014 11 2.30 11.07 11 4.40 17.09 -0.14 [-0.98; 0.70] 1.4% 1.7%
Karasu et al., 2018 12 10.10 9.41 11 3.10 9.41 0.72 [-0.13; 1.57] 1.3% 1.6%
Katz-Leurer et al., 2006 10 10.00 4.18 14 4.90 5.36 1.00 [0.13; 1.87] 1.3% 1.6%
Kim DH et al., 2008 8 11.42 79.49 8 -3.81 22.91 0.25 [-0.74; 1.23] 1.0% 1.3%
Kim JH et al., 2009 12 6.75 7.21 12 1.58 5.65 0.77 [-0.06; 1.61] 1.4% 1.7%
Kim YM et al., 2009 16 12.10 24.87 16 9.30 19.69 0.12 [-0.57; 0.82] 2.0% 2.3%
Kunkel et al., 2013 7 4.40 6.38 3 4.60 13.06 -0.02 [-1.37; 1.33] 0.5% 0.7%
Kunkel et al., 2013 4 8.30 16.01 3 4.60 13.06 0.21 [-1.30; 1.72] 0.4% 0.6%
Lee CH et al., 2014 10 4.10 3.73 11 1.70 4.00 0.59 [-0.28; 1.47] 1.3% 1.6%
Lee D et al., 2016 14 6.00 7.94 13 -1.69 17.12 0.57 [-0.21; 1.34] 1.6% 1.9%
Lee SH et al., 2012 20 5.90 11.68 20 1.70 9.69 0.38 [-0.24; 1.01] 2.5% 2.8%
Lin Q et al., 2015 32 30.42 10.53 32 30.89 10.53 -0.04 [-0.53; 0.45] 4.0% 4.0%
Lindvall et Forsberg, 2014 24 3.58 3.79 22 0.91 2.97 0.77 [0.17; 1.37] 2.7% 3.0%
Merkert et al., 2011 25 12.20 10.70 23 9.10 8.30 0.32 [-0.25; 0.89] 3.0% 3.2%
Nadeau et al., 2013 126 7.90 8.50 71 5.30 7.00 0.32 [0.03; 0.62] 11.3% 7.5%
Nadeau et al., 2013 139 8.80 8.10 72 5.30 7.00 0.45 [0.16; 0.74] 11.7% 7.6%
Ordahan et al., 2015 25 8.70 8.00 25 5.10 7.08 0.47 [-0.09; 1.03] 3.1% 3.3%
Park DS et al., 2017 10 14.20 4.26 10 7.40 5.78 1.28 [0.30; 2.27] 1.0% 1.3%
Park HK et al., 2018 14 4.79 5.59 15 2.86 5.69 0.33 [-0.40; 1.07] 1.8% 2.1%
Pomeroy et al., 2001 12 0.17 2.33 12 -0.17 1.70 0.16 [-0.64; 0.96] 1.5% 1.8%
Song et al., 2014 10 7.10 3.89 5 5.80 2.69 0.34 [-0.74; 1.43] 0.8% 1.1%
Song et al., 2014 10 7.60 2.69 5 5.80 2.69 0.63 [-0.48; 1.73] 0.8% 1.0%
Tung et al., 2010 16 3.50 2.60 16 2.80 1.90 0.30 [-0.40; 1.00] 2.0% 2.3%
Xing et al., 2007 36 11.16 12.41 36 6.07 14.15 0.38 [-0.09; 0.84] 4.5% 4.3%
Yoo et al., 2010 28 11.29 9.19 31 6.23 7.47 0.60 [0.08; 1.12] 3.5% 3.7%
You et al., 2014 19 30.50 26.52 18 18.80 25.00 0.44 [-0.21; 1.10] 2.3% 2.6%
Yu et Cho, 2016 10 4.00 1.24 10 2.80 0.42 1.24 [0.27; 2.22] 1.0% 1.3%
Zhang et al., 2015 30 15.72 11.02 30 9.35 7.95 0.65 [0.13; 1.17] 3.6% 3.7%
Fixed effect model 852 718 0.44 [0.34; 0.55] 92.4% --
Random effects model 0.45 [0.34; 0.56] -- 91.6%
Heterogeneity: I^2 = 6%, τ^2 = < 0.01, p = 0.36
Fixed effect model 942 779 0.46 [0.37; 0.56] 100.0% --
Random effects model 0.48 [0.36; 0.60] -- 100.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.02, p = 0.15
Residual heterogeneity: I^2 = 18%, p = 0.17
Test for subgroup differences (fixed effect): χ^2_1 = 2.13, df = 1 (p = 0.14)
Test for subgroup differences (random effects): χ^2_1 = 1.35, df = 1 (p = 0.25)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

S4 Fig. Meta-regression of effects of PT according to duration of PT

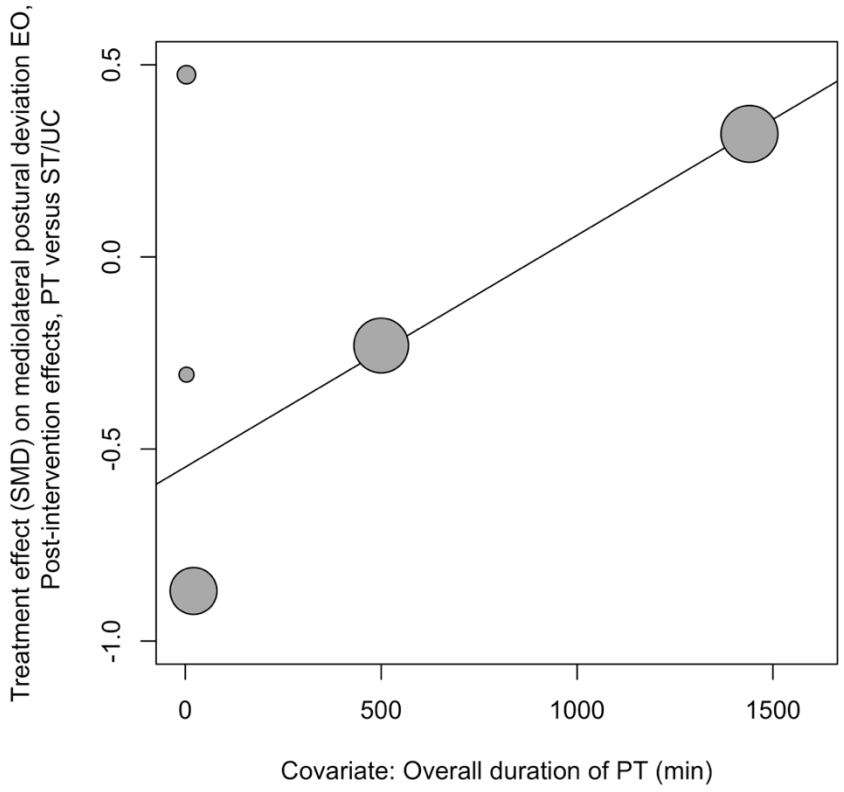
S4A Fig. Meta-regression between the post-intervention effects and the number of weeks of PT. Comparison: PT compared to ST/UC. Outcome: Balance




```
Mixed-Effects Model (k = 49; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity):     0.1482 (SE = 0.0598)
tau (square root of estimated tau^2 value):             0.3849
I^2 (residual heterogeneity / unaccounted variability): 57.65%
H^2 (unaccounted variability / sampling variability):   2.36
R^2 (amount of heterogeneity accounted for):            12.16%

Test for Residual Heterogeneity:
QE(df = 47) = 110.9701, p-val < .0001

Test of Moderators (coefficient 2):
QM(df = 1) = 4.1981, p-val = 0.0405

Model Results:

          estimate      se     zval    pval    ci.lb    ci.ub
intrcpt     0.5640  0.1062   5.3099  <.0001   0.3558   0.7722  ***
NUM_WEEK   -0.0177  0.0087  -2.0489  0.0405  -0.0347  -0.0008    *

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Abbreviations: PT, physical therapy; SMD, standardized mean difference; ST, sham treatment; UC, usual care

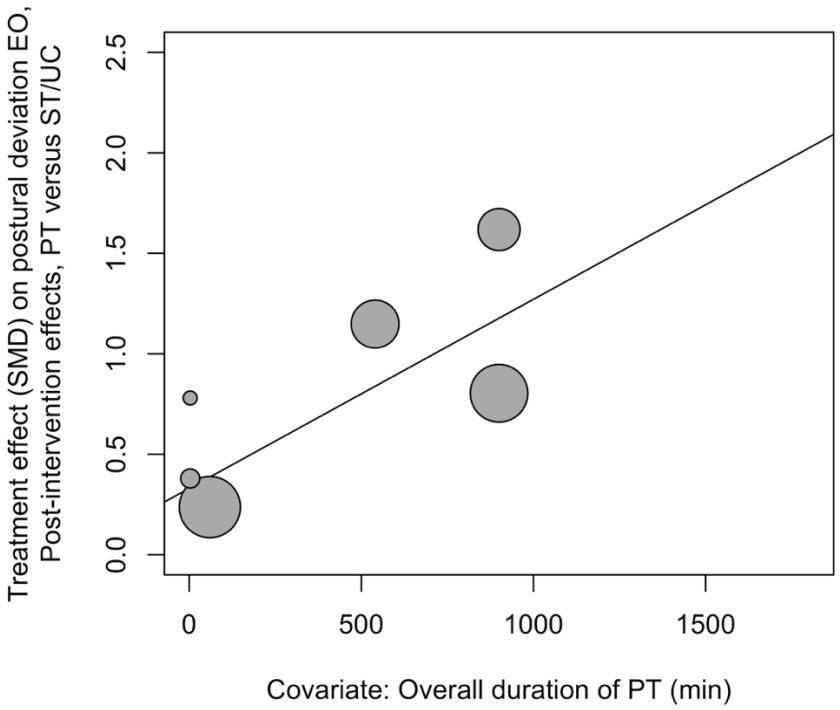
S4B Fig. Meta-regression between the post-intervention effects and the overall duration of PT. Comparison: PT compared to ST/UC. Outcome: mediolateral postural deviation EO




```
Mixed-Effects Model (k = 5; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity):     0 (SE = 0.1889)
tau (square root of estimated tau^2 value):             0
I^2 (residual heterogeneity / unaccounted variability): 0.00%
H^2 (unaccounted variability / sampling variability):   1.00
R^2 (amount of heterogeneity accounted for):            100.00%

Test for Residual Heterogeneity:
QE(df = 3) = 2.6931, p-val = 0.4414

Test of Moderators (coefficient 2):
QM(df = 1) = 3.7752, p-val = 0.0520

Model Results:

           estimate      se     zval    pval    ci.lb    ci.ub
intrcpt     -0.5471  0.2753  -1.9870  0.0469  -1.0867  -0.0074  *
TOTAL_TIME   0.0006  0.0003   1.9430  0.0520  -0.0000   0.0012  .

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Abbreviations: EO, eyes open; PT, physical therapy; SMD, standardized mean difference; ST, sham treatment; UC, usual care

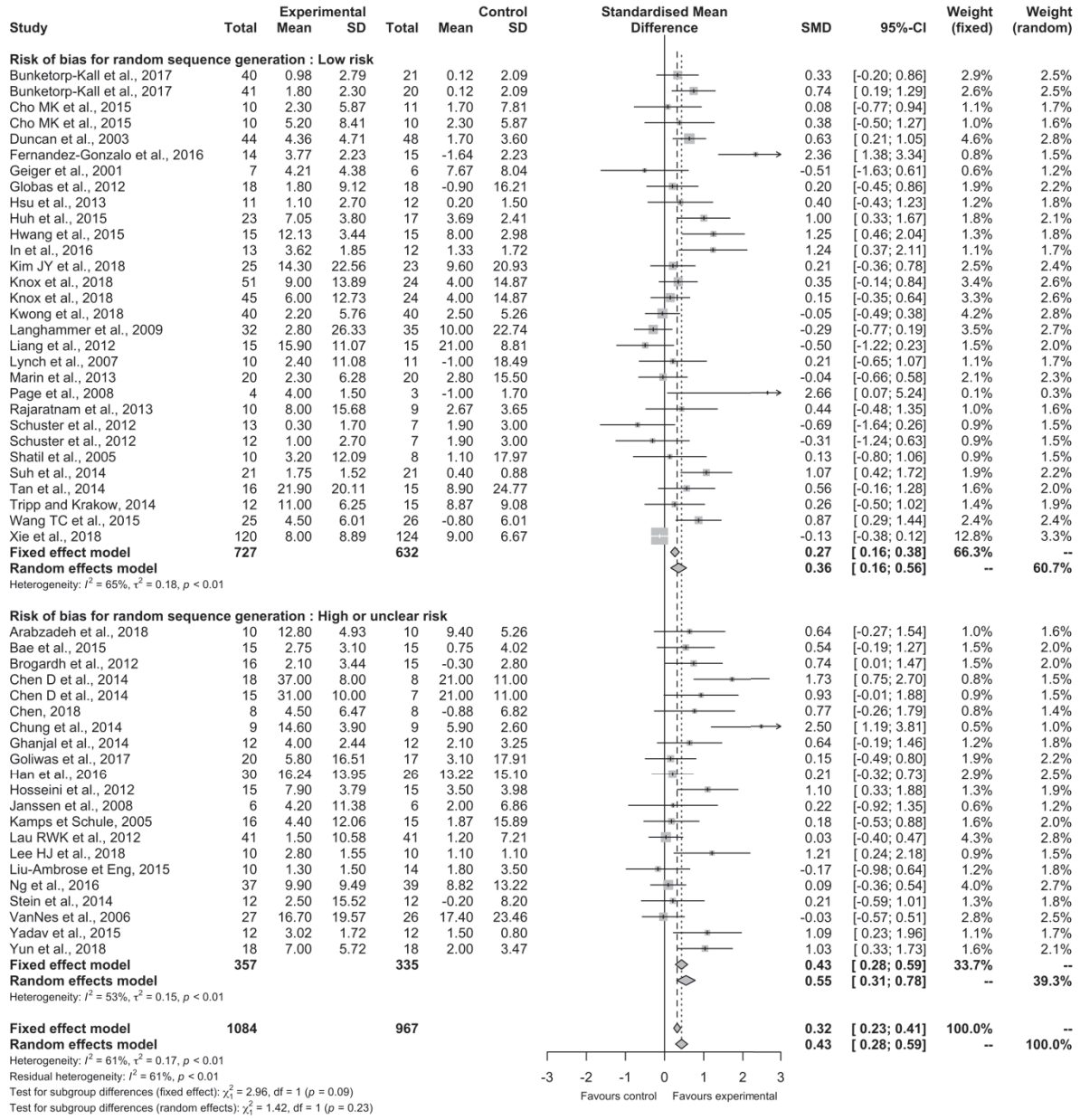
S4C Fig. Meta-regression between the post-intervention effects and the overall duration of PT for the subgroup of sensory interventions. Comparison: PT compared to ST/UC. Outcome: postural stability EO

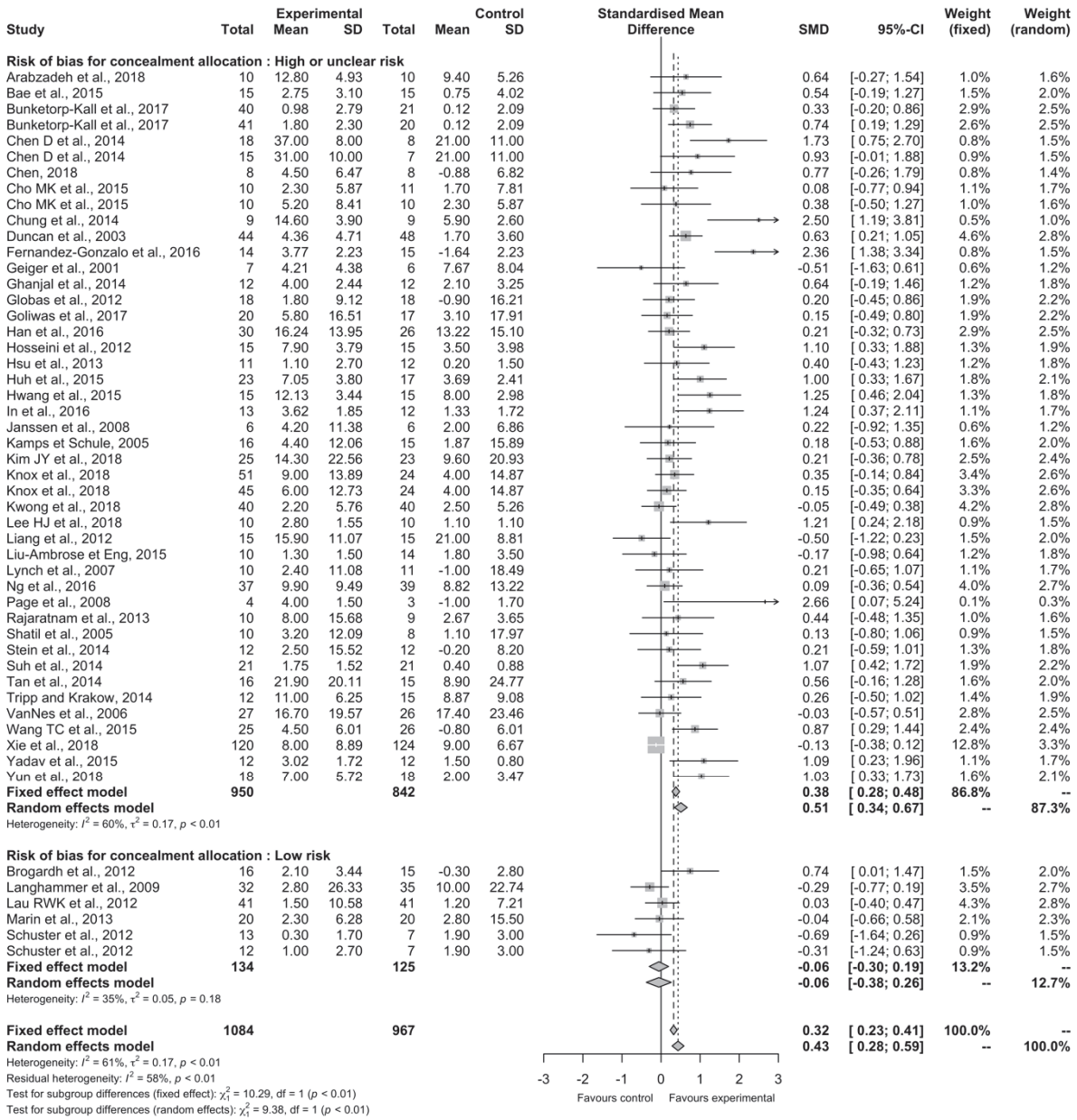


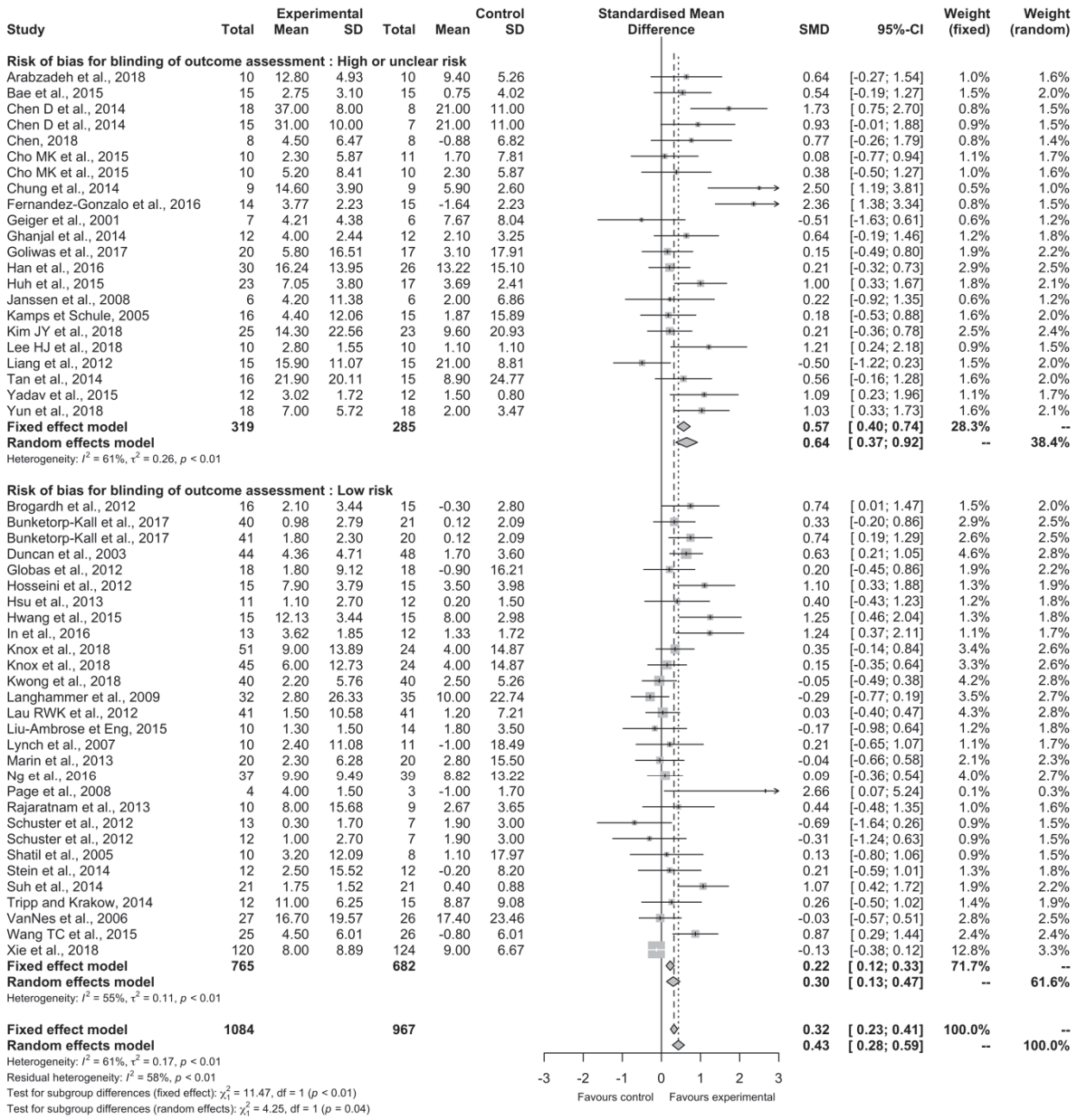

```
Mixed-Effects Model (k = 6; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity):     0 (SE = 0.1507)
tau (square root of estimated tau^2 value):             0
I^2 (residual heterogeneity / unaccounted variability): 0.00%
H^2 (unaccounted variability / sampling variability):   1.00
R^2 (amount of heterogeneity accounted for):            100.00%

Test for Residual Heterogeneity:
QE(df = 4) = 3.4135, p-val = 0.4911

Test of Moderators (coefficient 2):
QM(df = 1) = 4.5067, p-val = 0.0338

Model Results:

              estimate      se    zval    pval    ci.lb   ci.ub
intrcpt         0.3301  0.2790  1.1831  0.2368  -0.2167  0.8768
TOTAL_TIME_SI   0.0009  0.0004  2.1229  0.0338   0.0001  0.0018  *

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Abbreviations: EO, eyes open; PT, physical therapy; SMD, standardized mean difference; ST, sham treatment; UC, usual care

S5 Fig. Forest plot of physical therapy versus sham treatment/usual care. Outcome: Balance, post-intervention effects. Subgroup: risk of bias




Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for concealment allocation : High or unclear risk
Arabzadeh et al., 2018 10 12.80 4.93 10 9.40 5.26 0.64 [-0.27; 1.54] 1.0% 1.6%
Bae et al., 2015 15 2.75 3.10 15 0.75 4.02 0.54 [-0.19; 1.27] 1.5% 2.0%
Bunketorp-Kall et al., 2017 40 0.98 2.79 21 0.12 2.09 0.33 [-0.20; 0.86] 2.9% 2.5%
Bunketorp-Kall et al., 2017 41 1.80 2.30 20 0.12 2.09 0.74 [0.19; 1.29] 2.6% 2.5%
Chen D et al., 2014 18 37.00 8.00 8 21.00 11.00 1.73 [0.75; 2.70] 0.8% 1.5%
Chen D et al., 2014 15 31.00 10.00 7 21.00 11.00 0.93 [-0.01; 1.88] 0.9% 1.5%
Chen, 2018 8 4.50 6.47 8 -0.88 6.82 0.77 [-0.26; 1.79] 0.8% 1.4%
Cho MK et al., 2015 10 2.30 5.87 11 1.70 7.81 0.08 [-0.77; 0.94] 1.1% 1.7%
Cho MK et al., 2015 10 5.20 8.41 10 2.30 5.87 0.38 [-0.50; 1.27] 1.0% 1.6%
Chung et al., 2014 9 14.60 3.90 9 5.90 2.60 2.50 [1.19; 3.81] 0.5% 1.0%
Duncan et al., 2003 44 4.36 4.71 48 1.70 3.60 0.63 [0.21; 1.05] 4.6% 2.8%
Fernandez-Gonzalo et al., 2016 14 3.77 2.23 15 -1.64 2.23 2.36 [1.38; 3.34] 0.8% 1.5%
Geiger et al., 2001 7 4.21 4.38 6 7.67 8.04 -0.51 [-1.63; 0.61] 0.6% 1.2%
Ghanjal et al., 2014 12 4.00 2.44 12 2.10 3.25 0.64 [-0.19; 1.46] 1.2% 1.8%
Globas et al., 2012 18 1.80 9.12 18 -0.90 16.21 0.20 [-0.45; 0.86] 1.9% 2.2%
Goliwas et al., 2017 20 5.80 16.51 17 3.10 17.91 0.15 [-0.49; 0.80] 1.9% 2.2%
Han et al., 2016 30 16.24 13.95 26 13.22 15.10 0.21 [-0.32; 0.73] 2.9% 2.5%
Hosseini et al., 2012 15 7.90 3.79 15 3.50 3.98 1.10 [0.33; 1.88] 1.3% 1.9%
Hsu et al., 2013 11 1.10 2.70 12 0.20 1.50 0.40 [-0.43; 1.23] 1.2% 1.8%
Huh et al., 2015 23 7.05 3.80 17 3.69 2.41 1.00 [0.33; 1.67] 1.8% 2.1%
Hwang et al., 2015 15 12.13 3.44 15 8.00 2.98 1.25 [0.46; 2.04] 1.3% 1.8%
In et al., 2016 13 3.62 1.85 12 1.33 1.72 1.24 [0.37; 2.11] 1.1% 1.7%
Janssen et al., 2008 6 4.20 11.38 6 2.00 6.86 0.22 [-0.92; 1.35] 0.6% 1.2%
Kamps et Schule, 2005 16 4.40 12.06 15 1.87 15.89 0.18 [-0.53; 0.88] 1.6% 2.0%
Kim JY et al., 2018 25 14.30 22.56 23 9.60 20.93 0.21 [-0.36; 0.78] 2.5% 2.4%
Knox et al., 2018 51 9.00 13.89 24 4.00 14.87 0.35 [-0.14; 0.84] 3.4% 2.6%
Knox et al., 2018 45 6.00 12.73 24 4.00 14.87 0.15 [-0.35; 0.64] 3.3% 2.6%
Kwong et al., 2018 40 2.20 5.76 40 2.50 5.26 -0.05 [-0.49; 0.38] 4.2% 2.8%
Lee HJ et al., 2018 10 2.80 1.55 10 1.10 1.10 1.21 [0.24; 2.18] 0.9% 1.5%
Liang et al., 2012 15 15.90 11.07 15 21.00 8.81 -0.50 [-1.22; 0.23] 1.5% 2.0%
Liu-Ambrose et Eng, 2015 10 1.30 1.50 14 1.80 3.50 -0.17 [-0.98; 0.64] 1.2% 1.8%
Lynch et al., 2007 10 2.40 11.08 11 -1.00 18.49 0.21 [-0.65; 1.07] 1.1% 1.7%
Ng et al., 2016 37 9.90 9.49 39 8.82 13.22 0.09 [-0.36; 0.54] 4.0% 2.7%
Page et al., 2008 4 4.00 1.50 3 -1.00 1.70 2.66 [0.07; 5.24] 0.1% 0.3%
Rajaratnam et al., 2013 10 8.00 15.68 9 2.67 3.65 0.44 [-0.48; 1.35] 1.0% 1.6%
Shatil et al., 2005 10 3.20 12.09 8 1.10 17.97 0.13 [-0.80; 1.06] 0.9% 1.5%
Stein et al., 2014 12 2.50 15.52 12 -0.20 8.20 0.21 [-0.59; 1.01] 1.3% 1.8%
Suh et al., 2014 21 1.75 1.52 21 0.40 0.88 1.07 [0.42; 1.72] 1.9% 2.2%
Tan et al., 2014 16 21.90 20.11 15 8.90 24.77 0.56 [-0.16; 1.28] 1.6% 2.0%
Tripp and Krakow, 2014 12 11.00 6.25 15 8.87 9.08 0.26 [-0.50; 1.02] 1.4% 1.9%
VanNes et al., 2006 27 16.70 19.57 26 17.40 23.46 -0.03 [-0.57; 0.51] 2.8% 2.5%
Wang TC et al., 2015 25 4.50 6.01 26 -0.80 6.01 0.87 [0.29; 1.44] 2.4% 2.4%
Xie et al., 2018 120 8.00 8.89 124 9.00 6.67 -0.13 [-0.38; 0.12] 12.8% 3.3%
Yadav et al., 2015 12 3.02 1.72 12 1.50 0.80 1.09 [0.23; 1.96] 1.1% 1.7%
Yun et al., 2018 18 7.00 5.72 18 2.00 3.47 1.03 [0.33; 1.73] 1.6% 2.1%
Fixed effect model 950 842 0.38 [0.28; 0.48] 86.8% --
Random effects model 0.51 [0.34; 0.67] -- 87.3%
Heterogeneity: I^2 = 60%, τ^2 = 0.17, p < 0.01
Risk of bias for concealment allocation : Low risk
Brogardh et al., 2012 16 2.10 3.44 15 -0.30 2.80 0.74 [0.01; 1.47] 1.5% 2.0%
Langhammer et al., 2009 32 2.80 26.33 35 10.00 22.74 -0.29 [-0.77; 0.19] 3.5% 2.7%
Lau RWK et al., 2012 41 1.50 10.58 41 1.20 7.21 0.03 [-0.40; 0.47] 4.3% 2.8%
Marin et al., 2013 20 2.30 6.28 20 2.80 15.50 -0.04 [-0.66; 0.58] 2.1% 2.3%
Schuster et al., 2012 13 0.30 1.70 7 1.90 3.00 -0.69 [-1.64; 0.26] 0.9% 1.5%
Schuster et al., 2012 12 1.00 2.70 7 1.90 3.00 -0.31 [-1.24; 0.63] 0.9% 1.5%
Fixed effect model 134 125 -0.06 [-0.30; 0.19] 13.2% --
Random effects model -0.06 [-0.38; 0.26] -- 12.7%
Heterogeneity: I^2 = 35%, τ^2 = 0.05, p = 0.18
Fixed effect model 1084 967 0.32 [0.23; 0.41] 100.0% --
Random effects model 0.43 [0.28; 0.59] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.17, p < 0.01
Residual heterogeneity: I^2 = 58%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 10.29, df = 1 (p < 0.01)
Test for subgroup differences (random effects): χ^2_1 = 9.38, df = 1 (p < 0.01)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Study
Experimental Total Mean SD
Control Total Mean SD
Standardised Mean Difference
SMD 95%-CI
Weight (fixed) Weight (random)
Risk of bias for blinding of outcome assessment : High or unclear risk
Arabzadeh et al., 2018 10 12.80 4.93 10 9.40 5.26 0.64 [-0.27; 1.54] 1.0% 1.6%
Bae et al., 2015 15 2.75 3.10 15 0.75 4.02 0.54 [-0.19; 1.27] 1.5% 2.0%
Chen D et al., 2014 18 37.00 8.00 8 21.00 11.00 1.73 [0.75; 2.70] 0.8% 1.5%
Chen D et al., 2014 15 31.00 10.00 7 21.00 11.00 0.93 [-0.01; 1.88] 0.9% 1.5%
Chen, 2018 8 4.50 6.47 8 -0.88 6.82 0.77 [-0.26; 1.79] 0.8% 1.4%
Cho MK et al., 2015 10 2.30 5.87 11 1.70 7.81 0.08 [-0.77; 0.94] 1.1% 1.7%
Cho MK et al., 2015 10 5.20 8.41 10 2.30 5.87 0.38 [-0.50; 1.27] 1.0% 1.6%
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Geiger et al., 2001 7 4.21 4.38 6 7.67 8.04 -0.51 [-1.63; 0.61] 0.6% 1.2%
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Lee HJ et al., 2018 10 2.80 1.55 10 1.10 1.10 1.21 [0.24; 2.18] 0.9% 1.5%
Liang et al., 2012 15 15.90 11.07 15 21.00 8.81 -0.50 [-1.22; 0.23] 1.5% 2.0%
Tan et al., 2014 16 21.90 20.11 15 8.90 24.77 0.56 [-0.16; 1.28] 1.6% 2.0%
Yadav et al., 2015 12 3.02 1.72 12 1.50 0.80 1.09 [0.23; 1.96] 1.1% 1.7%
Yun et al., 2018 18 7.00 5.72 18 2.00 3.47 1.03 [0.33; 1.73] 1.6% 2.1%
Fixed effect model 319 285 0.57 [0.40; 0.74] 28.3% --
Random effects model 0.64 [0.37; 0.92] -- 38.4%
Heterogeneity: I^2 = 61%, τ^2 = 0.26, p < 0.01
Risk of bias for blinding of outcome assessment : Low risk
Brogardh et al., 2012 16 2.10 3.44 15 -0.30 2.80 0.74 [0.01; 1.47] 1.5% 2.0%
Bunketorp-Kall et al., 2017 40 0.98 2.79 21 0.12 2.09 0.33 [-0.20; 0.86] 2.9% 2.5%
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Globas et al., 2012 18 1.80 9.12 18 -0.90 16.21 0.20 [-0.45; 0.86] 1.9% 2.2%
Hosseini et al., 2012 15 7.90 3.79 15 3.50 3.98 1.10 [0.33; 1.88] 1.3% 1.9%
Hsu et al., 2013 11 1.10 2.70 12 0.20 1.50 0.40 [-0.43; 1.23] 1.2% 1.8%
Hwang et al., 2015 15 12.13 3.44 15 8.00 2.98 1.25 [0.46; 2.04] 1.3% 1.8%
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Knox et al., 2018 51 9.00 13.89 24 4.00 14.87 0.35 [-0.14; 0.84] 3.4% 2.6%
Knox et al., 2018 45 6.00 12.73 24 4.00 14.87 0.15 [-0.35; 0.64] 3.3% 2.6%
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Langhammer et al., 2009 32 2.80 26.33 35 10.00 22.74 -0.29 [-0.77; 0.19] 3.5% 2.7%
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Liu-Ambrose et Eng, 2015 10 1.30 1.50 14 1.80 3.50 -0.17 [-0.98; 0.64] 1.2% 1.8%
Lynch et al., 2007 10 2.40 11.08 11 -1.00 18.49 0.21 [-0.65; 1.07] 1.1% 1.7%
Marin et al., 2013 20 2.30 6.28 20 2.80 15.50 -0.04 [-0.66; 0.58] 2.1% 2.3%
Ng et al., 2016 37 9.90 9.49 39 8.82 13.22 0.09 [-0.36; 0.54] 4.0% 2.7%
Page et al., 2008 4 4.00 1.50 3 -1.00 1.70 2.66 [0.07; 5.24] 0.1% 0.3%
Rajaratnam et al., 2013 10 8.00 15.68 9 2.67 3.65 0.44 [-0.48; 1.35] 1.0% 1.6%
Schuster et al., 2012 13 0.30 1.70 7 1.90 3.00 -0.69 [-1.64; 0.26] 0.9% 1.5%
Schuster et al., 2012 12 1.00 2.70 7 1.90 3.00 -0.31 [-1.24; 0.63] 0.9% 1.5%
Shatil et al., 2005 10 3.20 12.09 8 1.10 17.97 0.13 [-0.80; 1.06] 0.9% 1.5%
Stein et al., 2014 12 2.50 15.52 12 -0.20 8.20 0.21 [-0.59; 1.01] 1.3% 1.8%
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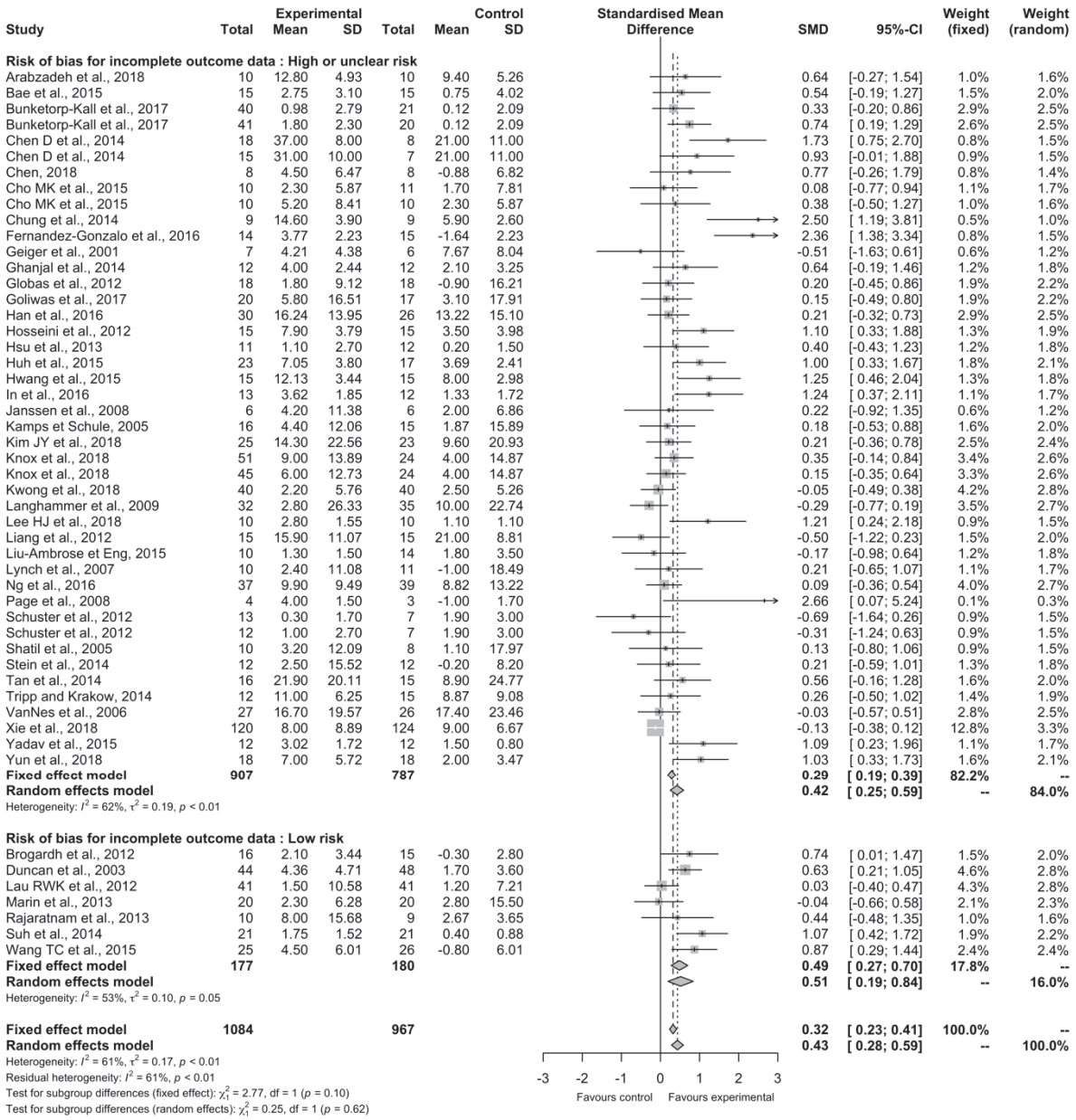
Wang TC et al., 2015 25 4.50 6.01 26 -0.80 6.01 0.87 [0.29; 1.44] 2.4% 2.4%
Xie et al., 2018 120 8.00 8.89 124 9.00 6.67 -0.13 [-0.38; 0.12] 12.8% 3.3%
Fixed effect model 765 682 0.22 [0.12; 0.33] 71.7% --
Random effects model 0.30 [0.13; 0.47] -- 61.6%
Heterogeneity: I^2 = 55%, τ^2 = 0.11, p < 0.01
Fixed effect model 1084 967 0.32 [0.23; 0.41] 100.0% --
Random effects model 0.43 [0.28; 0.59] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.17, p < 0.01
Residual heterogeneity: I^2 = 58%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 11.47, df = 1 (p < 0.01)
Test for subgroup differences (random effects): χ^2_1 = 4.25, df = 1 (p = 0.04)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for incomplete outcome data : High or unclear risk
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Chen D et al., 2014 15 31.00 10.00 7 21.00 11.00 0.93 [-0.01; 1.88] 0.9% 1.5%
Chen, 2018 8 4.50 6.47 8 -0.88 6.82 0.77 [-0.26; 1.79] 0.8% 1.4%
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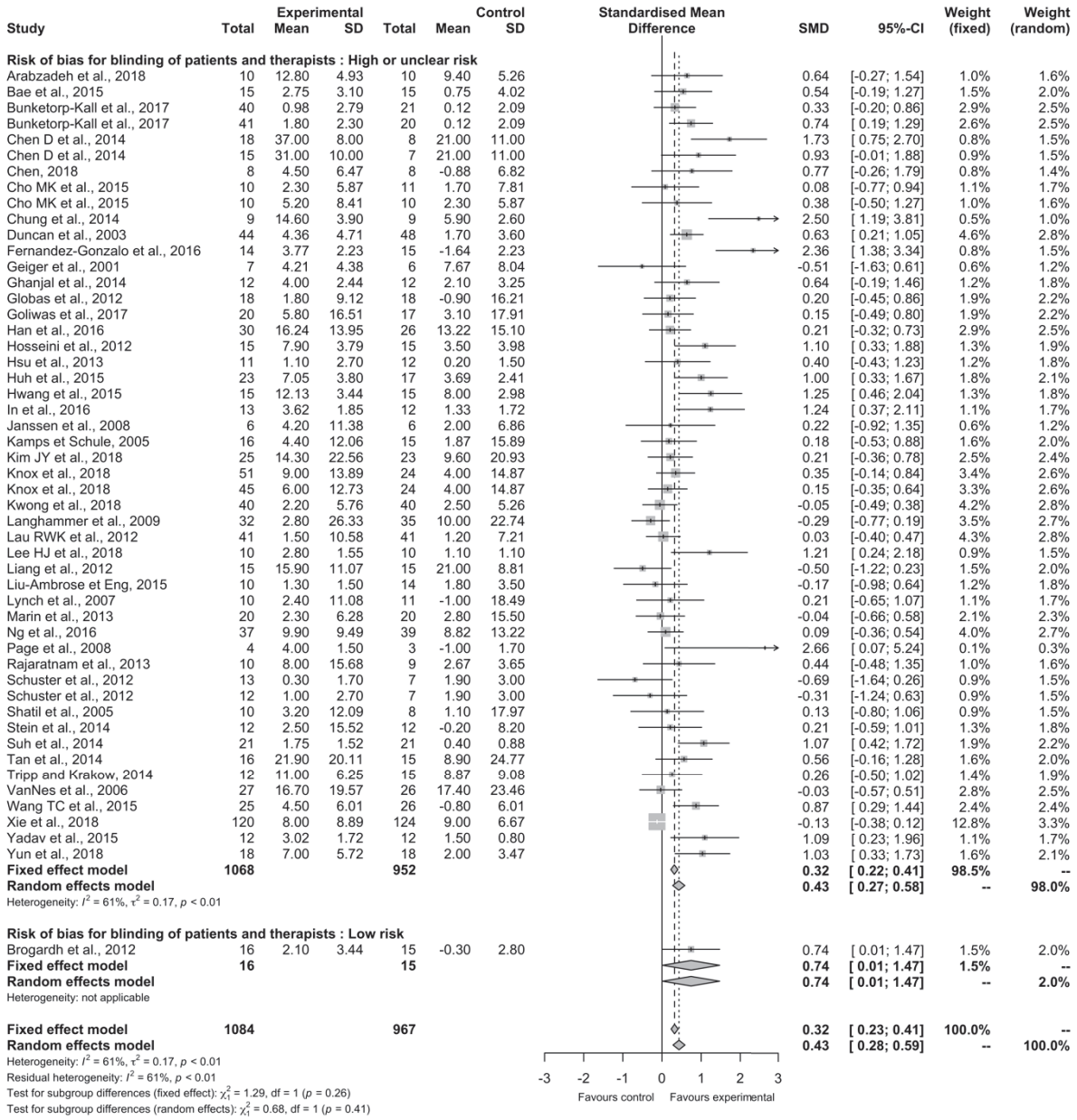
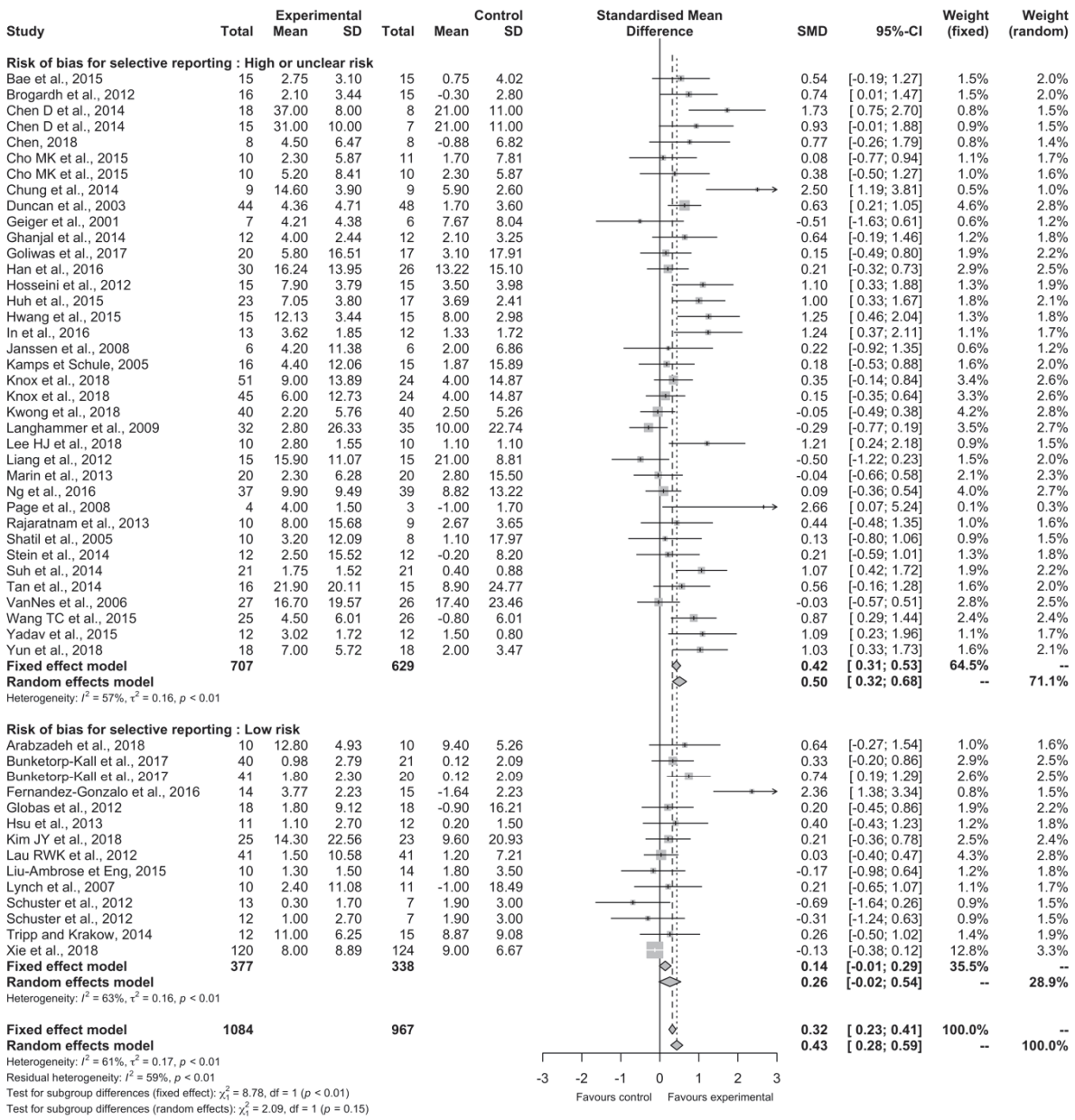
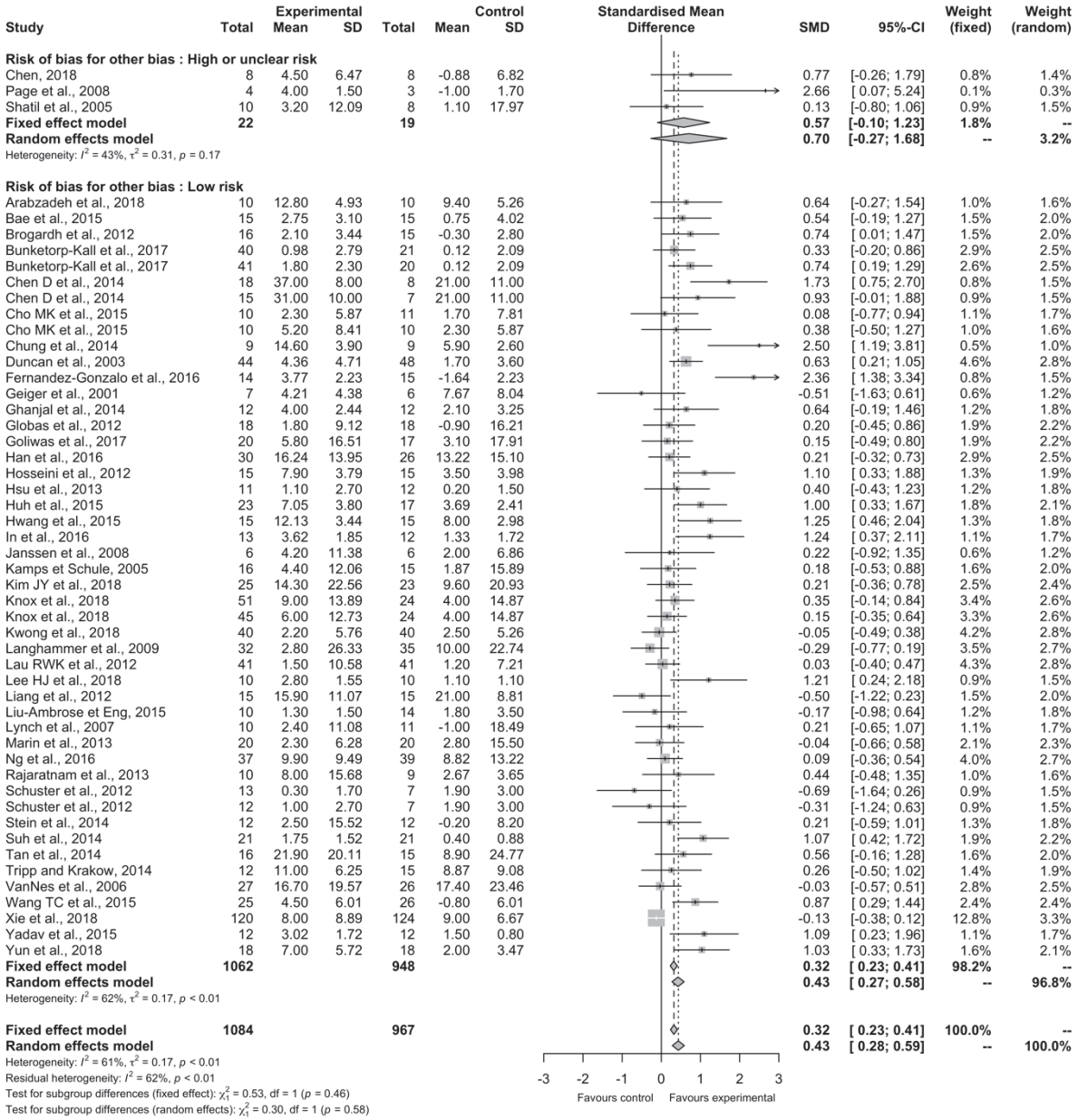
Cho MK et al., 2015 10 5.20 8.41 10 2.30 5.87 0.38 [-0.50; 1.27] 1.0% 1.6%
Chung et al., 2014 9 14.60 3.90 9 5.90 2.60 2.50 [1.19; 3.81] 0.5% 1.0%
Fernandez-Gonzalo et al., 2016 14 3.77 2.23 15 -1.64 2.23 2.36 [1.38; 3.34] 0.8% 1.5%
Geiger et al., 2001 7 4.21 4.38 6 7.67 8.04 -0.51 [-1.63; 0.61] 0.6% 1.2%
Ghanjal et al., 2014 12 4.00 2.44 12 2.10 3.25 0.64 [-0.19; 1.46] 1.2% 1.8%
Globas et al., 2012 18 1.80 9.12 18 -0.90 16.21 0.20 [-0.45; 0.86] 1.9% 2.2%
Goliwas et al., 2017 20 5.80 16.51 17 3.10 17.91 0.15 [-0.49; 0.80] 1.9% 2.2%
Han et al., 2016 30 16.24 13.95 26 13.22 15.10 0.21 [-0.32; 0.73] 2.9% 2.5%
Hosseini et al., 2012 15 7.90 3.79 15 3.50 3.98 1.10 [0.33; 1.88] 1.3% 1.9%
Hsu et al., 2013 11 1.10 2.70 12 0.20 1.50 0.40 [-0.43; 1.23] 1.2% 1.8%
Huh et al., 2015 23 7.05 3.80 17 3.69 2.41 1.00 [0.33; 1.67] 1.8% 2.1%
Hwang et al., 2015 15 12.13 3.44 15 8.00 2.98 1.25 [0.46; 2.04] 1.3% 1.8%
In et al., 2016 13 3.62 1.85 12 1.33 1.72 1.24 [0.37; 2.11] 1.1% 1.7%
Janssen et al., 2008 6 4.20 11.38 6 2.00 6.86 0.22 [-0.92; 1.35] 0.6% 1.2%
Kamps et Schule, 2005 16 4.40 12.06 15 1.87 15.89 0.18 [-0.53; 0.88] 1.6% 2.0%
Kim JY et al., 2018 25 14.30 22.56 23 9.60 20.93 0.21 [-0.36; 0.78] 2.5% 2.4%
Knox et al., 2018 51 9.00 13.89 24 4.00 14.87 0.35 [-0.14; 0.84] 3.4% 2.6%
Knox et al., 2018 45 6.00 12.73 24 4.00 14.87 0.15 [-0.35; 0.64] 3.3% 2.6%
Kwong et al., 2018 40 2.20 5.76 40 2.50 5.26 -0.05 [-0.49; 0.38] 4.2% 2.8%
Langhammer et al., 2009 32 2.80 26.33 35 10.00 22.74 -0.29 [-0.77; 0.19] 3.5% 2.7%
Lee HJ et al., 2018 10 2.80 1.55 10 1.10 1.10 1.21 [0.24; 2.18] 0.9% 1.5%
Liang et al., 2012 15 15.90 11.07 15 21.00 8.81 -0.50 [-1.22; 0.23] 1.5% 2.0%
Liu-Ambrose et Eng, 2015 10 1.30 1.50 14 1.80 3.50 -0.17 [-0.98; 0.64] 1.2% 1.8%
Lynch et al., 2007 10 2.40 11.08 11 -1.00 18.49 0.21 [-0.65; 1.07] 1.1% 1.7%
Ng et al., 2016 37 9.90 9.49 39 8.82 13.22 0.09 [-0.36; 0.54] 4.0% 2.7%
Page et al., 2008 4 4.00 1.50 3 -1.00 1.70 2.66 [0.07; 5.24] 0.1% 0.3%
Schuster et al., 2012 13 0.30 1.70 7 1.90 3.00 -0.69 [-1.64; 0.26] 0.9% 1.5%
Schuster et al., 2012 12 1.00 2.70 7 1.90 3.00 -0.31 [-1.24; 0.63] 0.9% 1.5%
Shatil et al., 2005 10 3.20 12.09 8 1.10 17.97 0.13 [-0.80; 1.06] 0.9% 1.5%
Stein et al., 2014 12 2.50 15.52 12 -0.20 8.20 0.21 [-0.59; 1.01] 1.3% 1.8%
Tan et al., 2014 16 21.90 20.11 15 8.90 24.77 0.56 [-0.16; 1.28] 1.6% 2.0%
Tripp and Krakow, 2014 12 11.00 6.25 15 8.87 9.08 0.26 [-0.50; 1.02] 1.4% 1.9%
VanNes et al., 2006 27 16.70 19.57 26 17.40 23.46 -0.03 [-0.57; 0.51] 2.8% 2.5%
Xie et al., 2018 120 8.00 8.89 124 9.00 6.67 -0.13 [-0.38; 0.12] 12.8% 3.3%
Yadav et al., 2015 12 3.02 1.72 12 1.50 0.80 1.09 [0.23; 1.96] 1.1% 1.7%
Yun et al., 2018 18 7.00 5.72 18 2.00 3.47 1.03 [0.33; 1.73] 1.6% 2.1%
Fixed effect model 907 787 0.29 [0.19; 0.39] 82.2% --
Random effects model 0.42 [0.25; 0.59] -- 84.0%
Heterogeneity: I^2 = 62%, τ^2 = 0.19, p < 0.01
Risk of bias for incomplete outcome data : Low risk
Brogardh et al., 2012 16 2.10 3.44 15 -0.30 2.80 0.74 [0.01; 1.47] 1.5% 2.0%
Duncan et al., 2003 44 4.36 4.71 48 1.70 3.60 0.63 [0.21; 1.05] 4.6% 2.8%
Lau RWK et al., 2012 41 1.50 10.58 41 1.20 7.21 0.03 [-0.40; 0.47] 4.3% 2.8%
Marin et al., 2013 20 2.30 6.28 20 2.80 15.50 -0.04 [-0.66; 0.58] 2.1% 2.3%
Rajaratnam et al., 2013 10 8.00 15.68 9 2.67 3.65 0.44 [-0.48; 1.35] 1.0% 1.6%
Suh et al., 2014 21 1.75 1.52 21 0.40 0.88 1.07 [0.42; 1.72] 1.9% 2.2%
Wang TC et al., 2015 25 4.50 6.01 26 -0.80 6.01 0.87 [0.29; 1.44] 2.4% 2.4%
Fixed effect model 177 180 0.49 [0.27; 0.70] 17.8% --
Random effects model 0.51 [0.19; 0.84] -- 16.0%
Heterogeneity: I^2 = 53%, τ^2 = 0.10, p = 0.05
Fixed effect model 1084 967 0.32 [0.23; 0.41] 100.0% --
Random effects model 0.43 [0.28; 0.59] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.17, p < 0.01
Residual heterogeneity: I^2 = 61%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 2.77, df = 1 (p = 0.10)
Test for subgroup differences (random effects): χ^2_1 = 0.25, df = 1 (p = 0.62)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Study
Experimental
Total
Mean
SD
Control
Total
Mean
SD
Standardised Mean Difference
SMD
95%-CI
Weight (fixed)
Weight (random)
Risk of bias for blinding of patients and therapists : High or unclear risk
Arabzadeh et al., 2018 10 12.80 4.93 10 9.40 5.26 0.64 [-0.27; 1.54] 1.0% 1.6%
Bae et al., 2015 15 2.75 3.10 15 0.75 4.02 0.54 [-0.19; 1.27] 1.5% 2.0%
Bunketorp-Kall et al., 2017 40 0.98 2.79 21 0.12 2.09 0.33 [-0.20; 0.86] 2.9% 2.5%
Bunketorp-Kall et al., 2017 41 1.80 2.30 20 0.12 2.09 0.74 [0.19; 1.29] 2.6% 2.5%
Chen D et al., 2014 18 37.00 8.00 8 21.00 11.00 1.73 [0.75; 2.70] 0.8% 1.5%
Chen D et al., 2014 15 31.00 10.00 7 21.00 11.00 0.93 [-0.01; 1.88] 0.9% 1.5%
Chen, 2018 8 4.50 6.47 8 -0.88 6.82 0.77 [-0.26; 1.79] 0.8% 1.4%
Cho MK et al., 2015 10 2.30 5.87 11 1.70 7.81 0.08 [-0.77; 0.94] 1.1% 1.7%
Cho MK et al., 2015 10 5.20 8.41 10 2.30 5.87 0.38 [-0.50; 1.27] 1.0% 1.6%
Chung et al., 2014 9 14.60 3.90 9 5.90 2.60 2.50 [1.19; 3.81] 0.5% 1.0%
Duncan et al., 2003 44 4.36 4.71 48 1.70 3.60 0.63 [0.21; 1.05] 4.6% 2.8%
Fernandez-Gonzalo et al., 2016 14 3.77 2.23 15 -1.64 2.23 2.36 [1.38; 3.34] 0.8% 1.5%
Geiger et al., 2001 7 4.21 4.38 6 7.67 8.04 -0.51 [-1.63; 0.61] 0.6% 1.2%
Ghanjal et al., 2014 12 4.00 2.44 12 2.10 3.25 0.64 [-0.19; 1.46] 1.2% 1.8%
Globas et al., 2012 18 1.80 9.12 18 -0.90 16.21 0.20 [-0.45; 0.86] 1.9% 2.2%
Goliwas et al., 2017 20 5.80 16.51 17 3.10 17.91 0.15 [-0.49; 0.80] 1.9% 2.2%
Han et al., 2016 30 16.24 13.95 26 13.22 15.10 0.21 [-0.32; 0.73] 2.9% 2.5%
Hosseini et al., 2012 15 7.90 3.79 15 3.50 3.98 1.10 [0.33; 1.88] 1.3% 1.9%
Hsu et al., 2013 11 1.10 2.70 12 0.20 1.50 0.40 [-0.43; 1.23] 1.2% 1.8%
Huh et al., 2015 23 7.05 3.80 17 3.69 2.41 1.00 [0.33; 1.67] 1.8% 2.1%
Hwang et al., 2015 15 12.13 3.44 15 8.00 2.98 1.25 [0.46; 2.04] 1.3% 1.8%
In et al., 2016 13 3.62 1.85 12 1.33 1.72 1.24 [0.37; 2.11] 1.1% 1.7%
Janssen et al., 2008 6 4.20 11.38 6 2.00 6.86 0.22 [-0.92; 1.35] 0.6% 1.2%
Kamps et Schule, 2005 16 4.40 12.06 15 1.87 15.89 0.18 [-0.53; 0.88] 1.6% 2.0%
Kim JY et al., 2018 25 14.30 22.56 23 9.60 20.93 0.21 [-0.36; 0.78] 2.5% 2.4%
Knox et al., 2018 51 9.00 13.89 24 4.00 14.87 0.35 [-0.14; 0.84] 3.4% 2.6%
Knox et al., 2018 45 6.00 12.73 24 4.00 14.87 0.15 [-0.35; 0.64] 3.3% 2.6%
Kwong et al., 2018 40 2.20 5.76 40 2.50 5.26 -0.05 [-0.49; 0.38] 4.2% 2.8%
Langhammer et al., 2009 32 2.80 26.33 35 10.00 22.74 -0.29 [-0.77; 0.19] 3.5% 2.7%
Lau RWK et al., 2012 41 1.50 10.58 41 1.20 7.21 0.03 [-0.40; 0.47] 4.3% 2.8%
Lee HJ et al., 2018 10 2.80 1.55 10 1.10 1.10 1.21 [0.24; 2.18] 0.9% 1.5%
Liang et al., 2012 15 15.90 11.07 15 21.00 8.81 -0.50 [-1.22; 0.23] 1.5% 2.0%
Liu-Ambrose et Eng, 2015 10 1.30 1.50 14 1.80 3.50 -0.17 [-0.98; 0.64] 1.2% 1.8%
Lynch et al., 2007 10 2.40 11.08 11 -1.00 18.49 0.21 [-0.65; 1.07] 1.1% 1.7%
Marin et al., 2013 20 2.30 6.28 20 2.80 15.50 -0.04 [-0.66; 0.58] 2.1% 2.3%
Ng et al., 2016 37 9.90 9.49 39 8.82 13.22 0.09 [-0.36; 0.54] 4.0% 2.7%
Page et al., 2008 4 4.00 1.50 3 -1.00 1.70 2.66 [0.07; 5.24] 0.1% 0.3%
Rajaratnam et al., 2013 10 8.00 15.68 9 2.67 3.65 0.44 [-0.48; 1.35] 1.0% 1.6%
Schuster et al., 2012 13 0.30 1.70 7 1.90 3.00 -0.69 [-1.64; 0.26] 0.9% 1.5%
Schuster et al., 2012 12 1.00 2.70 7 1.90 3.00 -0.31 [-1.24; 0.63] 0.9% 1.5%
Shatil et al., 2005 10 3.20 12.09 8 1.10 17.97 0.13 [-0.80; 1.06] 0.9% 1.5%
Stein et al., 2014 12 2.50 15.52 12 -0.20 8.20 0.21 [-0.59; 1.01] 1.3% 1.8%
Suh et al., 2014 21 1.75 1.52 21 0.40 0.88 1.07 [0.42; 1.72] 1.9% 2.2%
Tan et al., 2014 16 21.90 20.11 15 8.90 24.77 0.56 [-0.16; 1.28] 1.6% 2.0%
Tripp and Krakow, 2014 12 11.00 6.25 15 8.87 9.08 0.26 [-0.50; 1.02] 1.4% 1.9%
VanNes et al., 2006 27 16.70 19.57 26 17.40 23.46 -0.03 [-0.57; 0.51] 2.8% 2.5%
Wang TC et al., 2015 25 4.50 6.01 26 -0.80 6.01 0.87 [0.29; 1.44] 2.4% 2.4%
Xie et al., 2018 120 8.00 8.89 124 9.00 6.67 -0.13 [-0.38; 0.12] 12.8% 3.3%
Yadav et al., 2015 12 3.02 1.72 12 1.50 0.80 1.09 [0.23; 1.96] 1.1% 1.7%
Yun et al., 2018 18 7.00 5.72 18 2.00 3.47 1.03 [0.33; 1.73] 1.6% 2.1%
Fixed effect model 1068 952 0.32 [0.22; 0.41] 98.5% --
Random effects model 0.43 [0.27; 0.58] -- 98.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.17, p < 0.01
Risk of bias for blinding of patients and therapists : Low risk
Brogardh et al., 2012 16 2.10 3.44 15 -0.30 2.80 0.74 [0.01; 1.47] 1.5% 2.0%
Fixed effect model 16 15 0.74 [0.01; 1.47] 1.5% --
Random effects model 0.74 [0.01; 1.47] -- 2.0%
Heterogeneity: not applicable
Fixed effect model 1084 967 0.32 [0.23; 0.41] 100.0% --
Random effects model 0.43 [0.28; 0.59] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.17, p < 0.01
Residual heterogeneity: I^2 = 61%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 1.29, df = 1 (p = 0.26)
Test for subgroup differences (random effects): χ^2_1 = 0.68, df = 1 (p = 0.41)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

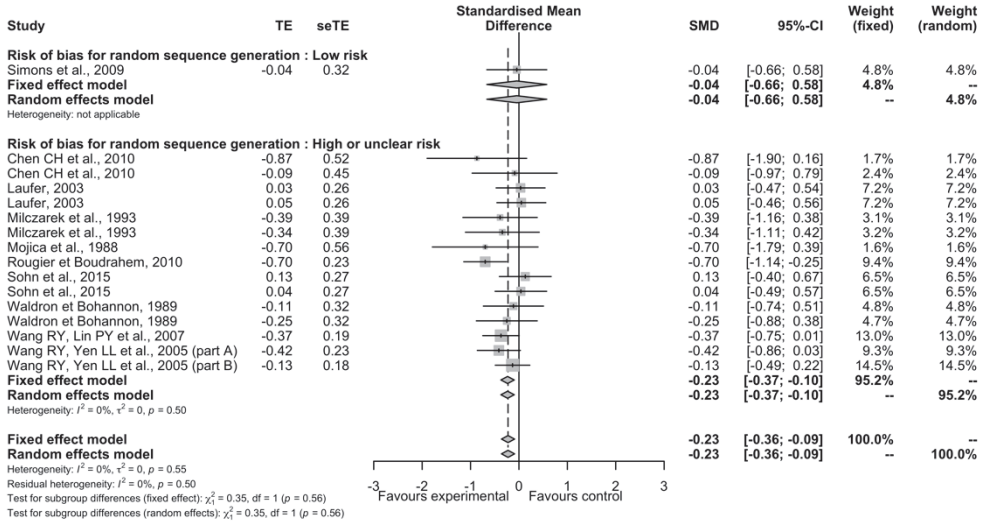

Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for selective reporting : High or unclear risk
Bae et al., 2015 15 2.75 3.10 15 0.75 4.02 0.54 [-0.19; 1.27] 1.5% 2.0%
Brogardh et al., 2012 16 2.10 3.44 15 -0.30 2.80 0.74 [0.01; 1.47] 1.5% 2.0%
Chen D et al., 2014 18 37.00 8.00 8 21.00 11.00 1.73 [0.75; 2.70] 0.8% 1.5%
Chen D et al., 2014 15 31.00 10.00 7 21.00 11.00 0.93 [-0.01; 1.88] 0.9% 1.5%
Chen, 2018 8 4.50 6.47 8 -0.88 6.82 0.77 [-0.26; 1.79] 0.8% 1.4%
Cho MK et al., 2015 10 2.30 5.87 11 1.70 7.81 0.08 [-0.77; 0.94] 1.1% 1.7%
Cho MK et al., 2015 10 5.20 8.41 10 2.30 5.87 0.38 [-0.50; 1.27] 1.0% 1.6%
Chung et al., 2014 9 14.60 3.90 9 5.90 2.60 2.50 [1.19; 3.81] 0.5% 1.0%
Duncan et al., 2003 44 4.36 4.71 48 1.70 3.60 0.63 [0.21; 1.05] 4.6% 2.8%
Geiger et al., 2001 7 4.21 4.38 6 7.67 8.04 -0.51 [-1.63; 0.61] 0.6% 1.2%
Ghanjal et al., 2014 12 4.00 2.44 12 2.10 3.25 0.64 [-0.19; 1.46] 1.2% 1.8%
Goliwas et al., 2017 20 5.80 16.51 17 3.10 17.91 0.15 [-0.49; 0.80] 1.9% 2.2%
Han et al., 2016 30 16.24 13.95 26 13.22 15.10 0.21 [-0.32; 0.73] 2.9% 2.5%
Hosseini et al., 2012 15 7.90 3.79 15 3.50 3.98 1.10 [0.33; 1.88] 1.3% 1.9%
Huh et al., 2015 23 7.05 3.80 17 3.69 2.41 1.00 [0.33; 1.67] 1.8% 2.1%
Hwang et al., 2015 15 12.13 3.44 15 8.00 2.98 1.25 [0.46; 2.04] 1.3% 1.8%
In et al., 2016 13 3.62 1.85 12 1.33 1.72 1.24 [0.37; 2.11] 1.1% 1.7%
Janssen et al., 2008 6 4.20 11.38 6 2.00 6.86 0.22 [-0.92; 1.35] 0.6% 1.2%
Kamps et Schule, 2005 16 4.40 12.06 15 1.87 15.89 0.18 [-0.53; 0.88] 1.6% 2.0%
Knox et al., 2018 51 9.00 13.89 24 4.00 14.87 0.35 [-0.14; 0.84] 3.4% 2.6%
Knox et al., 2018 45 6.00 12.73 24 4.00 14.87 0.15 [-0.35; 0.64] 3.3% 2.6%
Kwong et al., 2018 40 2.20 5.76 40 2.50 5.26 -0.05 [-0.49; 0.38] 4.2% 2.8%
Langhammer et al., 2009 32 2.80 26.33 35 10.00 22.74 -0.29 [-0.77; 0.19] 3.5% 2.7%
Lee HJ et al., 2018 10 2.80 1.55 10 1.10 1.10 1.21 [0.24; 2.18] 0.9% 1.5%
Liang et al., 2012 15 15.90 11.07 15 21.00 8.81 -0.50 [-1.22; 0.23] 1.5% 2.0%
Marin et al., 2013 20 2.30 6.28 20 2.80 15.50 -0.04 [-0.66; 0.58] 2.1% 2.3%
Ng et al., 2016 37 9.90 9.49 39 8.82 13.22 0.09 [-0.36; 0.54] 4.0% 2.7%
Page et al., 2008 4 4.00 1.50 3 -1.00 1.70 2.66 [0.07; 5.24] 0.1% 0.3%
Rajaratnam et al., 2013 10 8.00 15.68 9 2.67 3.65 0.44 [-0.48; 1.35] 1.0% 1.6%
Shatil et al., 2005 10 3.20 12.09 8 1.10 17.97 0.13 [-0.80; 1.06] 0.9% 1.5%
Stein et al., 2014 12 2.50 15.52 12 -0.20 8.20 0.21 [-0.59; 1.01] 1.3% 1.8%
Suh et al., 2014 21 1.75 1.52 21 0.40 0.88 1.07 [0.42; 1.72] 1.9% 2.2%
Tan et al., 2014 16 21.90 20.11 15 8.90 24.77 0.56 [-0.16; 1.28] 1.6% 2.0%
VanNes et al., 2006 27 16.70 19.57 26 17.40 23.46 -0.03 [-0.57; 0.51] 2.8% 2.5%
Wang TC et al., 2015 25 4.50 6.01 26 -0.80 6.01 0.87 [0.29; 1.44] 2.4% 2.4%
Yadav et al., 2015 12 3.02 1.72 12 1.50 0.80 1.09 [0.23; 1.96] 1.1% 1.7%
Yun et al., 2018 18 7.00 5.72 18 2.00 3.47 1.03 [0.33; 1.73] 1.6% 2.1%
Fixed effect model 707 629 0.42 [0.31; 0.53] 64.5% --
Random effects model 0.50 [0.32; 0.68] -- 71.1%
Heterogeneity: I^2 = 57%, τ^2 = 0.16, p < 0.01
Risk of bias for selective reporting : Low risk
Arabzadeh et al., 2018 10 12.80 4.93 10 9.40 5.26 0.64 [-0.27; 1.54] 1.0% 1.6%
Bunketorp-Kall et al., 2017 40 0.98 2.79 21 0.12 2.09 0.33 [-0.20; 0.86] 2.9% 2.5%
Bunketorp-Kall et al., 2017 41 1.80 2.30 20 0.12 2.09 0.74 [0.19; 1.29] 2.6% 2.5%
Fernandez-Gonzalo et al., 2016 14 3.77 2.23 15 -1.64 2.23 2.36 [1.38; 3.34] 0.8% 1.5%
Globas et al., 2012 18 1.80 9.12 18 -0.90 16.21 0.20 [-0.45; 0.86] 1.9% 2.2%
Hsu et al., 2013 11 1.10 2.70 12 0.20 1.50 0.40 [-0.43; 1.23] 1.2% 1.8%
Kim JY et al., 2018 25 14.30 22.56 23 9.60 20.93 0.21 [-0.36; 0.78] 2.5% 2.4%
Lau RWK et al., 2012 41 1.50 10.58 41 1.20 7.21 0.03 [-0.40; 0.47] 4.3% 2.8%
Liu-Ambrose et Eng, 2015 10 1.30 1.50 14 1.80 3.50 -0.17 [-0.98; 0.64] 1.2% 1.8%
Lynch et al., 2007 10 2.40 11.08 11 -1.00 18.49 0.21 [-0.65; 1.07] 1.1% 1.7%
Schuster et al., 2012 13 0.30 1.70 7 1.90 3.00 -0.69 [-1.64; 0.26] 0.9% 1.5%
Schuster et al., 2012 12 1.00 2.70 7 1.90 3.00 -0.31 [-1.24; 0.63] 0.9% 1.5%
Tripp and Krakow, 2014 12 11.00 6.25 15 8.87 9.08 0.26 [-0.50; 1.02] 1.4% 1.9%
Xie et al., 2018 120 8.00 8.89 124 9.00 6.67 -0.13 [-0.38; 0.12] 12.8% 3.3%
Fixed effect model 377 338 0.14 [-0.01; 0.29] 35.5% --
Random effects model 0.26 [-0.02; 0.54] -- 28.9%
Heterogeneity: I^2 = 63%, τ^2 = 0.16, p < 0.01
Fixed effect model 1084 967 0.32 [0.23; 0.41] 100.0% --
Random effects model 0.43 [0.28; 0.59] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.17, p < 0.01
Residual heterogeneity: I^2 = 59%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 8.78, df = 1 (p < 0.01)
Test for subgroup differences (random effects): χ^2_1 = 2.09, df = 1 (p = 0.15)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

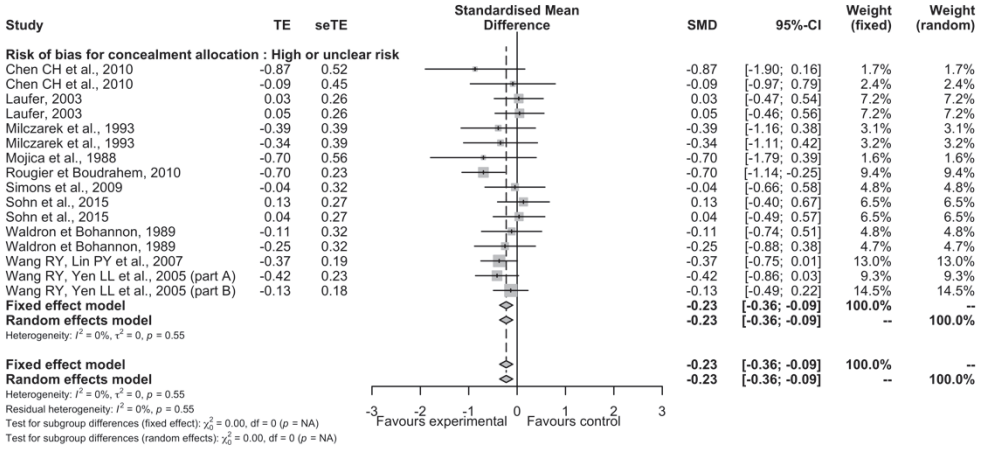


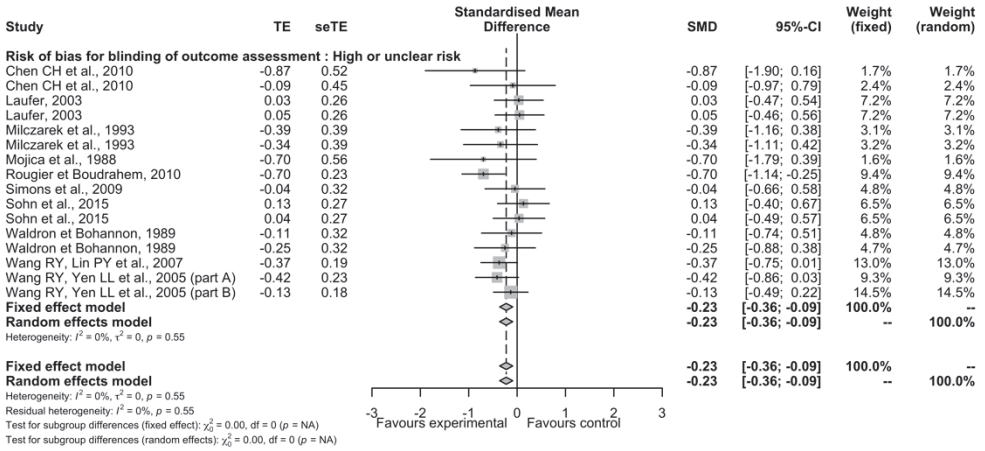
Study	Total	Experimental Mean	Experimental SD	Total	Control Mean	Control SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for other bias : High or unclear risk										
Chen, 2018	8	4.50	6.47	8	-0.88	6.82	0.77	[-0.26; 1.79]	0.8%	1.4%
Page et al., 2008	4	4.00	1.50	3	-1.00	1.70	2.66	[0.07; 5.24]	0.1%	0.3%
Shatil et al., 2005	10	3.20	12.09	8	1.10	17.97	0.13	[-0.80; 1.06]	0.9%	1.5%
Fixed effect model	**22**			**19**			**0.57**	**[-0.10; 1.23]**	**1.8%**	**--**
Random effects model							**0.70**	**[-0.27; 1.68]**	**--**	**3.2%**
Heterogeneity: I^2 = 43%, τ^2 = 0.31, p = 0.17										
Risk of bias for other bias : Low risk										
Arabzadeh et al., 2018	10	12.80	4.93	10	9.40	5.26	0.64	[-0.27; 1.54]	1.0%	1.6%
Bae et al., 2015	15	2.75	3.10	15	0.75	4.02	0.54	[-0.19; 1.27]	1.5%	2.0%
Brogardh et al., 2012	16	2.10	3.44	15	-0.30	2.80	0.74	[0.01; 1.47]	1.5%	2.0%
Bunketorp-Kall et al., 2017	40	0.98	2.79	21	0.12	2.09	0.33	[-0.20; 0.86]	2.9%	2.5%
Bunketorp-Kall et al., 2017	41	1.80	2.30	20	0.12	2.09	0.74	[0.19; 1.29]	2.6%	2.5%
Chen D et al., 2014	18	37.00	8.00	8	21.00	11.00	1.73	[0.75; 2.70]	0.8%	1.5%
Chen D et al., 2014	15	31.00	10.00	7	21.00	11.00	0.93	[-0.01; 1.88]	0.9%	1.5%
Cho MK et al., 2015	10	2.30	5.87	11	1.70	7.81	0.08	[-0.77; 0.94]	1.1%	1.7%
Cho MK et al., 2015	10	5.20	8.41	10	2.30	5.87	0.38	[-0.50; 1.27]	1.0%	1.6%
Chung et al., 2014	9	14.60	3.90	9	5.90	2.60	2.50	[1.19; 3.81]	0.5%	1.0%
Duncan et al., 2003	44	4.36	4.71	48	1.70	3.60	0.63	[0.21; 1.05]	4.6%	2.8%
Fernandez-Gonzalo et al., 2016	14	3.77	2.23	15	-1.64	2.23	2.36	[1.38; 3.34]	0.8%	1.5%
Geiger et al., 2001	7	4.21	4.38	6	7.67	8.04	-0.51	[-1.63; 0.61]	0.6%	1.2%
Ghanjal et al., 2014	12	4.00	2.44	12	2.10	3.25	0.64	[-0.19; 1.46]	1.2%	1.8%
Globas et al., 2012	18	1.80	9.12	18	-0.90	16.21	0.20	[-0.45; 0.86]	1.9%	2.2%
Goliwas et al., 2017	20	5.80	16.51	17	3.10	17.91	0.15	[-0.49; 0.80]	1.9%	2.2%
Han et al., 2016	30	16.24	13.95	26	13.22	15.10	0.21	[-0.32; 0.73]	2.9%	2.5%
Hosseini et al., 2012	15	7.90	3.79	15	3.50	3.98	1.10	[0.33; 1.88]	1.3%	1.9%
Hsu et al., 2013	11	1.10	2.70	12	0.20	1.50	0.40	[-0.43; 1.23]	1.2%	1.8%
Huh et al., 2015	23	7.05	3.80	17	3.69	2.41	1.00	[0.33; 1.67]	1.8%	2.1%
Hwang et al., 2015	15	12.13	3.44	15	8.00	2.98	1.25	[0.46; 2.04]	1.3%	1.8%
In et al., 2016	13	3.62	1.85	12	1.33	1.72	1.24	[0.37; 2.11]	1.1%	1.7%
Janssen et al., 2008	6	4.20	11.38	6	2.00	6.86	0.22	[-0.92; 1.35]	0.6%	1.2%
Kamps et Schule, 2005	16	4.40	12.06	15	1.87	15.89	0.18	[-0.53; 0.88]	1.6%	2.0%
Kim JY et al., 2018	25	14.30	22.56	23	9.60	20.93	0.21	[-0.36; 0.78]	2.5%	2.4%
Knox et al., 2018	51	9.00	13.89	24	4.00	14.87	0.35	[-0.14; 0.84]	3.4%	2.6%
Knox et al., 2018	45	6.00	12.73	24	4.00	14.87	0.15	[-0.35; 0.64]	3.3%	2.6%
Kwong et al., 2018	40	2.20	5.76	40	2.50	5.26	-0.05	[-0.49; 0.38]	4.2%	2.8%
Langhammer et al., 2009	32	2.80	26.33	35	10.00	22.74	-0.29	[-0.77; 0.19]	3.5%	2.7%
Lau RWK et al., 2012	41	1.50	10.58	41	1.20	7.21	0.03	[-0.40; 0.47]	4.3%	2.8%
Lee HJ et al., 2018	10	2.80	1.55	10	1.10	1.10	1.21	[0.24; 2.18]	0.9%	1.5%
Liang et al., 2012	15	15.90	11.07	15	21.00	8.81	-0.50	[-1.22; 0.23]	1.5%	2.0%
Liu-Ambrose et Eng, 2015	10	1.30	1.50	14	1.80	3.50	-0.17	[-0.98; 0.64]	1.2%	1.8%
Lynch et al., 2007	10	2.40	11.08	11	-1.00	18.49	0.21	[-0.65; 1.07]	1.1%	1.7%
Marin et al., 2013	20	2.30	6.28	20	2.80	15.50	-0.04	[-0.66; 0.58]	2.1%	2.3%
Ng et al., 2016	37	9.90	9.49	39	8.82	13.22	0.09	[-0.36; 0.54]	4.0%	2.7%
Rajaratnam et al., 2013	10	8.00	15.68	9	2.67	3.65	0.44	[-0.48; 1.35]	1.0%	1.6%
Schuster et al., 2012	13	0.30	1.70	7	1.90	3.00	-0.69	[-1.64; 0.26]	0.9%	1.5%
Schuster et al., 2012	12	1.00	2.70	7	1.90	3.00	-0.31	[-1.24; 0.63]	0.9%	1.5%
Stein et al., 2014	12	2.50	15.52	12	-0.20	8.20	0.21	[-0.59; 1.01]	1.3%	1.8%
Suh et al., 2014	21	1.75	1.52	21	0.40	0.88	1.07	[0.42; 1.72]	1.9%	2.2%
Tan et al., 2014	16	21.90	20.11	15	8.90	24.77	0.56	[-0.16; 1.28]	1.6%	2.0%
Tripp and Krakow, 2014	12	11.00	6.25	15	8.87	9.08	0.26	[-0.50; 1.02]	1.4%	1.9%
VanNes et al., 2006	27	16.70	19.57	26	17.40	23.46	-0.03	[-0.57; 0.51]	2.8%	2.5%
Wang TC et al., 2015	25	4.50	6.01	26	-0.80	6.01	0.87	[0.29; 1.44]	2.4%	2.4%
Xie et al., 2018	120	8.00	8.89	124	9.00	6.67	-0.13	[-0.38; 0.12]	12.8%	3.3%
Yadav et al., 2015	12	3.02	1.72	12	1.50	0.80	1.09	[0.23; 1.96]	1.1%	1.7%
Yun et al., 2018	18	7.00	5.72	18	2.00	3.47	1.03	[0.33; 1.73]	1.6%	2.1%
Fixed effect model	**1062**			**948**			**0.32**	**[0.23; 0.41]**	**98.2%**	**--**
Random effects model							**0.43**	**[0.27; 0.58]**	**--**	**96.8%**
Heterogeneity: I^2 = 62%, τ^2 = 0.17, p < 0.01										
Fixed effect model	**1084**			**967**			**0.32**	**[0.23; 0.41]**	**100.0%**	**--**
Random effects model							**0.43**	**[0.28; 0.59]**	**--**	**100.0%**

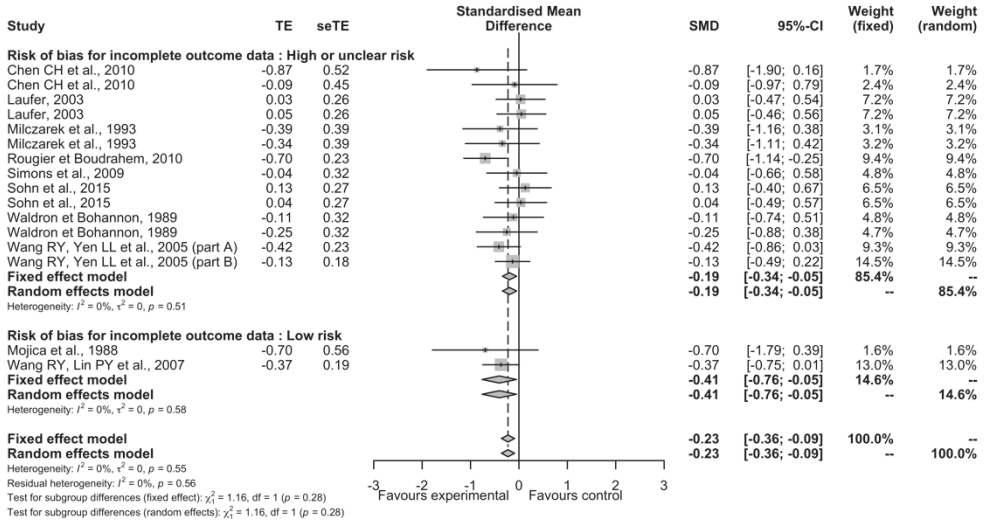
Heterogeneity: I^2 = 61%, τ^2 = 0.17, p < 0.01
Residual heterogeneity: I^2 = 62%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 0.53, df = 1 (p = 0.46)
Test for subgroup differences (random effects): χ^2_1 = 0.30, df = 1 (p = 0.58)

S6 Fig. Forest plot of physical therapy versus no treatment. Outcome: Mediolateral postural deviation EO, post-intervention effects. Subgroup: risk of bias

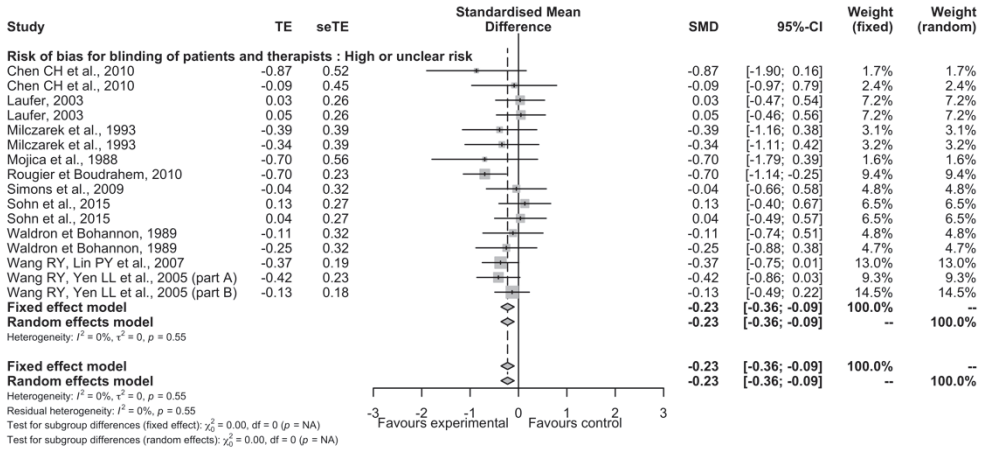




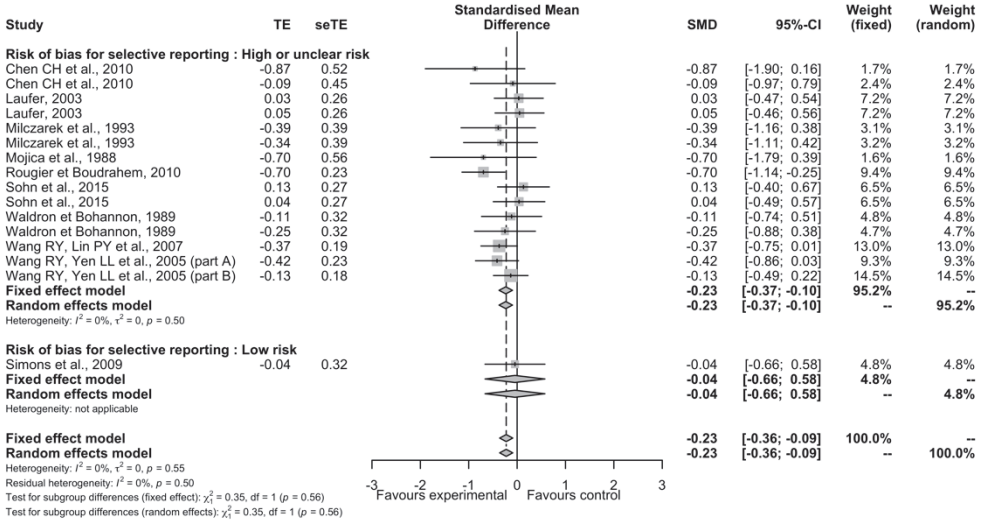




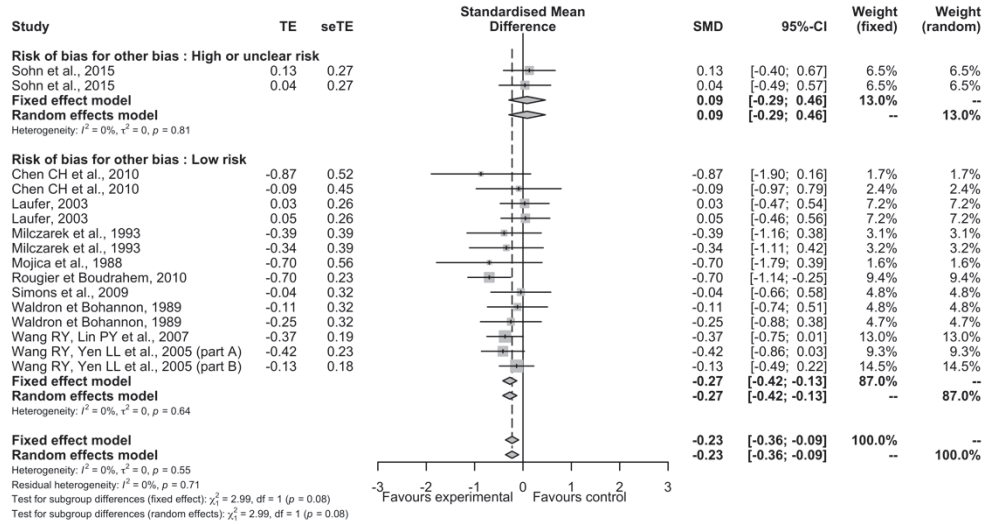
Study	TE	seTE	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for incomplete outcome data : High or unclear risk						
Chen CH et al., 2010	-0.87	0.52	-0.87	[-1.90; 0.16]	1.7%	1.7%
Chen CH et al., 2010	-0.09	0.45	-0.09	[-0.97; 0.79]	2.4%	2.4%
Laufer, 2003	0.03	0.26	0.03	[-0.47; 0.54]	7.2%	7.2%
Laufer, 2003	0.05	0.26	0.05	[-0.46; 0.56]	7.2%	7.2%
Milczarek et al., 1993	-0.39	0.39	-0.39	[-1.16; 0.38]	3.1%	3.1%
Milczarek et al., 1993	-0.34	0.39	-0.34	[-1.11; 0.42]	3.2%	3.2%
Rougier et Boudrahem, 2010	-0.70	0.23	-0.70	[-1.14; -0.25]	9.4%	9.4%
Simons et al., 2009	-0.04	0.32	-0.04	[-0.66; 0.58]	4.8%	4.8%
Sohn et al., 2015	0.13	0.27	0.13	[-0.40; 0.67]	6.5%	6.5%
Sohn et al., 2015	0.04	0.27	0.04	[-0.49; 0.57]	6.5%	6.5%
Waldron et Bohannon, 1989	-0.11	0.32	-0.11	[-0.74; 0.51]	4.8%	4.8%
Waldron et Bohannon, 1989	-0.25	0.32	-0.25	[-0.88; 0.38]	4.7%	4.7%
Wang RY, Yen LL et al., 2005 (part A)	-0.42	0.23	-0.42	[-0.86; 0.03]	9.3%	9.3%
Wang RY, Yen LL et al., 2005 (part B)	-0.13	0.18	-0.13	[-0.49; 0.22]	14.5%	14.5%
Fixed effect model			**-0.19**	**[-0.34; -0.05]**	**85.4%**	--
Random effects model			**-0.19**	**[-0.34; -0.05]**	--	**85.4%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.51						
Risk of bias for incomplete outcome data : Low risk						
Mojica et al., 1988	-0.70	0.56	-0.70	[-1.79; 0.39]	1.6%	1.6%
Wang RY, Lin PY et al., 2007	-0.37	0.19	-0.37	[-0.75; 0.01]	13.0%	13.0%
Fixed effect model			**-0.41**	**[-0.76; -0.05]**	**14.6%**	--
Random effects model			**-0.41**	**[-0.76; -0.05]**	--	**14.6%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.58						
Fixed effect model			**-0.23**	**[-0.36; -0.09]**	**100.0%**	--
Random effects model			**-0.23**	**[-0.36; -0.09]**	--	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.55						
Residual heterogeneity: I^2 = 0%, p = 0.56						
Test for subgroup differences (fixed effect): χ^2_1 = 1.16, df = 1 (p = 0.28)						
Test for subgroup differences (random effects): χ^2_1 = 1.16, df = 1 (p = 0.28)						



Study	TE	seTE	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for blinding of patients and therapists : High or unclear risk						
Chen CH et al., 2010	-0.87	0.52	-0.87	[-1.90; 0.16]	1.7%	1.7%
Chen CH et al., 2010	-0.09	0.45	-0.09	[-0.97; 0.79]	2.4%	2.4%
Laufer, 2003	0.03	0.26	0.03	[-0.47; 0.54]	7.2%	7.2%
Laufer, 2003	0.05	0.26	0.05	[-0.46; 0.56]	7.2%	7.2%
Milczarek et al., 1993	-0.39	0.39	-0.39	[-1.16; 0.38]	3.1%	3.1%
Milczarek et al., 1993	-0.34	0.39	-0.34	[-1.11; 0.42]	3.2%	3.2%
Mojica et al., 1988	-0.70	0.56	-0.70	[-1.79; 0.39]	1.6%	1.6%
Rougier et Boudrahem, 2010	-0.70	0.23	-0.70	[-1.14; -0.25]	9.4%	9.4%
Simons et al., 2009	-0.04	0.32	-0.04	[-0.66; 0.58]	4.8%	4.8%
Sohn et al., 2015	0.13	0.27	0.13	[-0.40; 0.67]	6.5%	6.5%
Sohn et al., 2015	0.04	0.27	0.04	[-0.49; 0.57]	6.5%	6.5%
Waldron et Bohannon, 1989	-0.11	0.32	-0.11	[-0.74; 0.51]	4.8%	4.8%
Waldron et Bohannon, 1989	-0.25	0.32	-0.25	[-0.88; 0.38]	4.7%	4.7%
Wang RY, Lin PY et al., 2007	-0.37	0.19	-0.37	[-0.75; 0.01]	13.0%	13.0%
Wang RY, Yen LL et al., 2005 (part A)	-0.42	0.23	-0.42	[-0.86; 0.03]	9.3%	9.3%
Wang RY, Yen LL et al., 2005 (part B)	-0.13	0.18	-0.13	[-0.49; 0.22]	14.5%	14.5%
Fixed effect model			**-0.23**	**[-0.36; -0.09]**	**100.0%**	--
Random effects model			**-0.23**	**[-0.36; -0.09]**	--	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.55						
Fixed effect model			**-0.23**	**[-0.36; -0.09]**	**100.0%**	--
Random effects model			**-0.23**	**[-0.36; -0.09]**	--	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.55						
Residual heterogeneity: I^2 = 0%, p = 0.55						
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)						
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)						

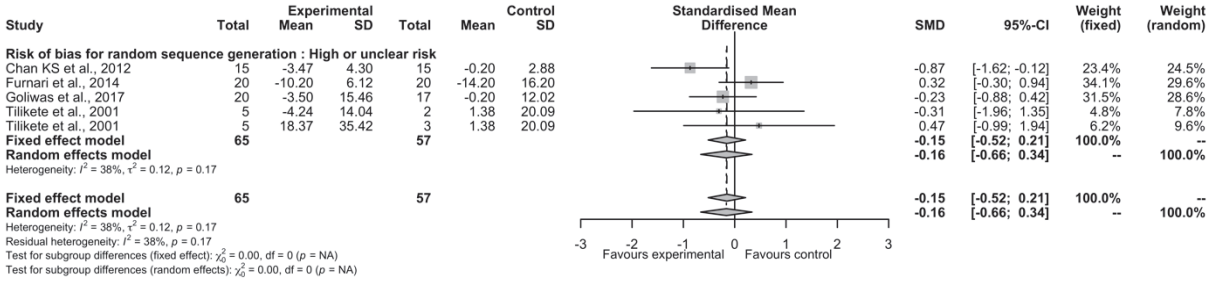


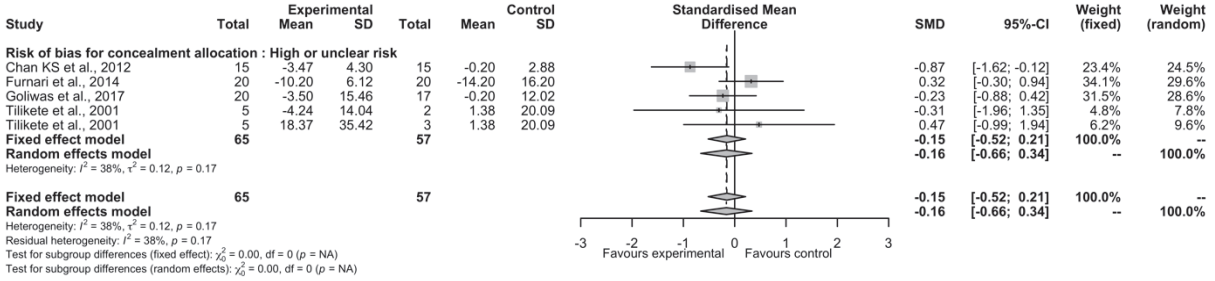
Study	TE	seTE	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for selective reporting : High or unclear risk						
Chen CH et al., 2010	-0.87	0.52	-0.87	[-1.90; 0.16]	1.7%	1.7%
Chen CH et al., 2010	-0.09	0.45	-0.09	[-0.97; 0.79]	2.4%	2.4%
Laufer, 2003	0.03	0.26	0.03	[-0.47; 0.54]	7.2%	7.2%
Laufer, 2003	0.05	0.26	0.05	[-0.46; 0.56]	7.2%	7.2%
Milczarek et al., 1993	-0.39	0.39	-0.39	[-1.16; 0.38]	3.1%	3.1%
Milczarek et al., 1993	-0.34	0.39	-0.34	[-1.11; 0.42]	3.2%	3.2%
Mojica et al., 1988	-0.70	0.56	-0.70	[-1.79; 0.39]	1.6%	1.6%
Rougier et Boudrahem, 2010	-0.70	0.23	-0.70	[-1.14; -0.25]	9.4%	9.4%
Sohn et al., 2015	0.13	0.27	0.13	[-0.40; 0.67]	6.5%	6.5%
Sohn et al., 2015	0.04	0.27	0.04	[-0.49; 0.57]	6.5%	6.5%
Waldron et Bohannon, 1989	-0.11	0.32	-0.11	[-0.74; 0.51]	4.8%	4.8%
Waldron et Bohannon, 1989	-0.25	0.32	-0.25	[-0.88; 0.38]	4.7%	4.7%
Wang RY, Lin PY et al., 2007	-0.37	0.19	-0.37	[-0.75; 0.01]	13.0%	13.0%
Wang RY, Yen LL et al., 2005 (part A)	-0.42	0.23	-0.42	[-0.86; 0.03]	9.3%	9.3%
Wang RY, Yen LL et al., 2005 (part B)	-0.13	0.18	-0.13	[-0.49; 0.22]	14.5%	14.5%
Fixed effect model			**-0.23**	**[-0.37; -0.10]**	**95.2%**	--
Random effects model			**-0.23**	**[-0.37; -0.10]**	--	**95.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.50						
Risk of bias for selective reporting : Low risk						
Simons et al., 2009	-0.04	0.32	-0.04	[-0.66; 0.58]	4.8%	4.8%
Fixed effect model			**-0.04**	**[-0.66; 0.58]**	**4.8%**	--
Random effects model			**-0.04**	**[-0.66; 0.58]**	--	**4.8%**
Heterogeneity: not applicable						
Fixed effect model			**-0.23**	**[-0.36; -0.09]**	**100.0%**	--
Random effects model			**-0.23**	**[-0.36; -0.09]**	--	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.55						
Residual heterogeneity: I^2 = 0%, p = 0.50						
Test for subgroup differences (fixed effect): χ^2_1 = 0.35, df = 1 (p = 0.56)						
Test for subgroup differences (random effects): χ^2_1 = 0.35, df = 1 (p = 0.56)						

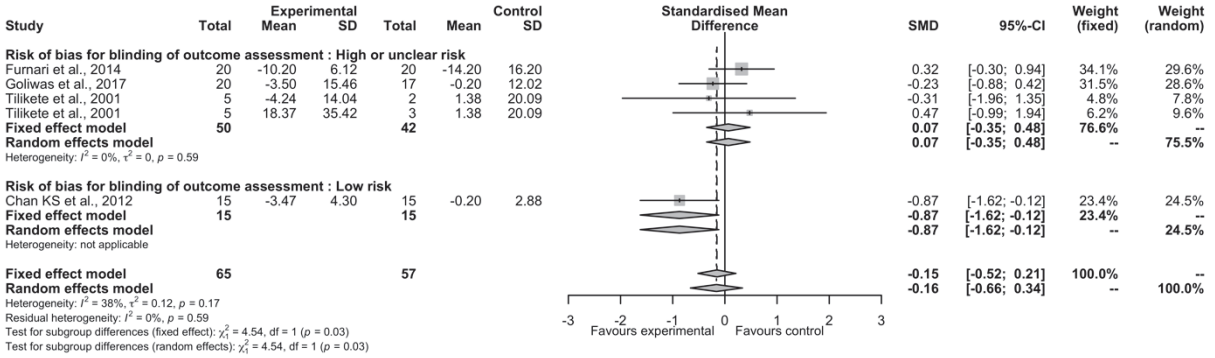


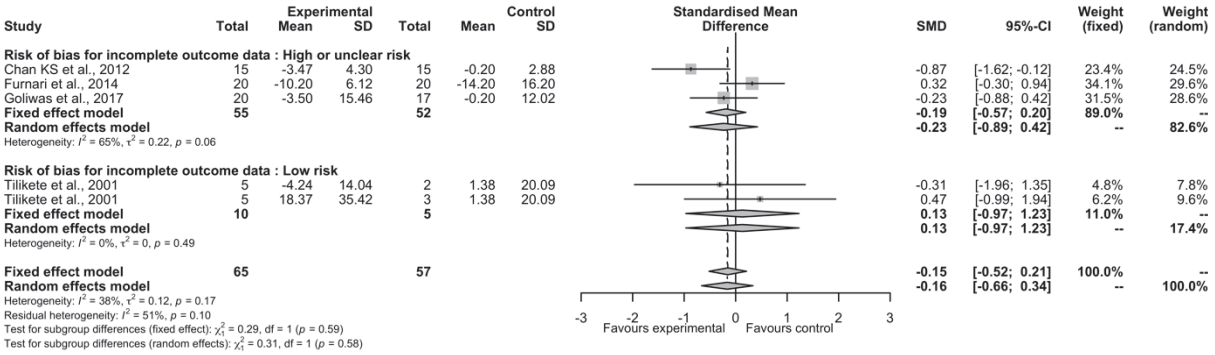
Study	TE	seTE	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for other bias : High or unclear risk						
Sohn et al., 2015	0.13	0.27	0.13	[-0.40; 0.67]	6.5%	6.5%
Sohn et al., 2015	0.04	0.27	0.04	[-0.49; 0.57]	6.5%	6.5%
Fixed effect model			**0.09**	**[-0.29; 0.46]**	**13.0%**	**--**
Random effects model			**0.09**	**[-0.29; 0.46]**	**--**	**13.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.81						
Risk of bias for other bias : Low risk						
Chen CH et al., 2010	-0.87	0.52	-0.87	[-1.90; 0.16]	1.7%	1.7%
Chen CH et al., 2010	-0.09	0.45	-0.09	[-0.97; 0.79]	2.4%	2.4%
Laufer, 2003	0.03	0.26	0.03	[-0.47; 0.54]	7.2%	7.2%
Laufer, 2003	0.05	0.26	0.05	[-0.46; 0.56]	7.2%	7.2%
Milczarek et al., 1993	-0.39	0.39	-0.39	[-1.16; 0.38]	3.1%	3.1%
Milczarek et al., 1993	-0.34	0.39	-0.34	[-1.11; 0.42]	3.2%	3.2%
Mojica et al., 1988	-0.70	0.56	-0.70	[-1.79; 0.39]	1.6%	1.6%
Rougier et Boudrahem, 2010	-0.70	0.23	-0.70	[-1.14; -0.25]	9.4%	9.4%
Simons et al., 2009	-0.04	0.32	-0.04	[-0.66; 0.58]	4.8%	4.8%
Waldron et Bohannon, 1989	-0.11	0.32	-0.11	[-0.74; 0.51]	4.8%	4.8%
Waldron et Bohannon, 1989	-0.25	0.32	-0.25	[-0.88; 0.38]	4.7%	4.7%
Wang RY, Lin PY et al., 2007	-0.37	0.19	-0.37	[-0.75; 0.01]	13.0%	13.0%
Wang RY, Yen LL et al., 2005 (part A)	-0.42	0.23	-0.42	[-0.86; 0.03]	9.3%	9.3%
Wang RY, Yen LL et al., 2005 (part B)	-0.13	0.18	-0.13	[-0.49; 0.22]	14.5%	14.5%
Fixed effect model			**-0.27**	**[-0.42; -0.13]**	**87.0%**	**--**
Random effects model			**-0.27**	**[-0.42; -0.13]**	**--**	**87.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.64						
Fixed effect model			**-0.23**	**[-0.36; -0.09]**	**100.0%**	**--**
Random effects model			**-0.23**	**[-0.36; -0.09]**	**--**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.55						
Residual heterogeneity: I^2 = 0%, p = 0.71						
Test for subgroup differences (fixed effect): χ^2_1 = 2.99, df = 1 (p = 0.08)						
Test for subgroup differences (random effects): χ^2_1 = 2.99, df = 1 (p = 0.08)						

S7 Fig. Forest plot of physical therapy versus sham treatment/usual care. Outcome: Mediolateral postural deviation EO, post-intervention effects. Subgroup: risk of bias



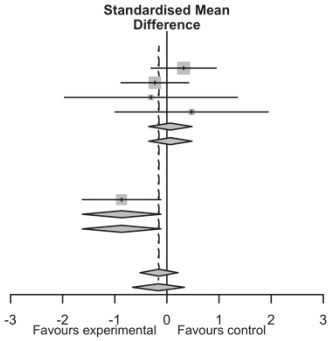






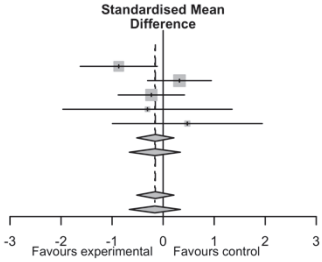
Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for blinding of patients and therapists : High or unclear risk										
Furnari et al., 2014	20	-10.20	6.12	20	-14.20	16.20	0.32	[-0.30; 0.94]	34.1%	29.6%
Goliwas et al., 2017	20	-3.50	15.46	17	-0.20	12.02	-0.23	[-0.88; 0.42]	31.5%	28.6%
Tilikete et al., 2001	5	-4.24	14.04	2	1.38	20.09	-0.31	[-1.96; 1.35]	4.8%	7.8%
Tilikete et al., 2001	5	18.37	35.42	3	1.38	20.09	0.47	[-0.99; 1.94]	6.2%	9.6%
Fixed effect model	**50**			**42**			**0.07**	**[-0.35; 0.48]**	**76.6%**	**--**
Random effects model							**0.07**	**[-0.35; 0.48]**	**--**	**75.5%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.59										
Risk of bias for blinding of patients and therapists : Low risk										
Chan KS et al., 2012	15	-3.47	4.30	15	-0.20	2.88	-0.87	[-1.62; -0.12]	23.4%	24.5%
Fixed effect model	**15**			**15**			**-0.87**	**[-1.62; -0.12]**	**23.4%**	**--**
Random effects model							**-0.87**	**[-1.62; -0.12]**	**--**	**24.5%**
Heterogeneity: not applicable										
Fixed effect model	**65**			**57**			**-0.15**	**[-0.52; 0.21]**	**100.0%**	**--**
Random effects model							**-0.16**	**[-0.66; 0.34]**	**--**	**100.0%**

Heterogeneity: I^2 = 38%, τ^2 = 0.12, p = 0.17
Residual heterogeneity: I^2 = 0%, p = 0.59
Test for subgroup differences (fixed effect): χ^2_1 = 4.54, df = 1 (p = 0.03)
Test for subgroup differences (random effects): χ^2_1 = 4.54, df = 1 (p = 0.03)



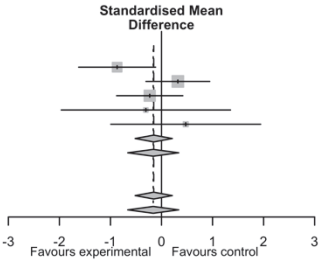
Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for selective reporting : High or unclear risk										
Chan KS et al., 2012	15	-3.47	4.30	15	-0.20	2.88	-0.87	[-1.62; -0.12]	23.4%	24.5%
Furnari et al., 2014	20	-10.20	6.12	20	-14.20	16.20	0.32	[-0.30; 0.94]	34.1%	29.6%
Goliwas et al., 2017	20	-3.50	15.46	17	-0.20	12.02	-0.23	[-0.88; 0.42]	31.5%	28.6%
Tilikete et al., 2001	5	-4.24	14.04	2	1.38	20.09	-0.31	[-1.96; 1.35]	4.8%	7.8%
Tilikete et al., 2001	5	18.37	35.42	3	1.38	20.09	0.47	[-0.99; 1.94]	6.2%	9.6%
Fixed effect model	**65**			**57**			**-0.15**	**[-0.52; 0.21]**	**100.0%**	**--**
Random effects model							**-0.16**	**[-0.66; 0.34]**	**--**	**100.0%**
Heterogeneity: I^2 = 38%, τ^2 = 0.12, p = 0.17										
Fixed effect model	**65**			**57**			**-0.15**	**[-0.52; 0.21]**	**100.0%**	**--**
Random effects model							**-0.16**	**[-0.66; 0.34]**	**--**	**100.0%**

Heterogeneity: I^2 = 38%, τ^2 = 0.12, p = 0.17
Residual heterogeneity: I^2 = 38%, p = 0.17
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)

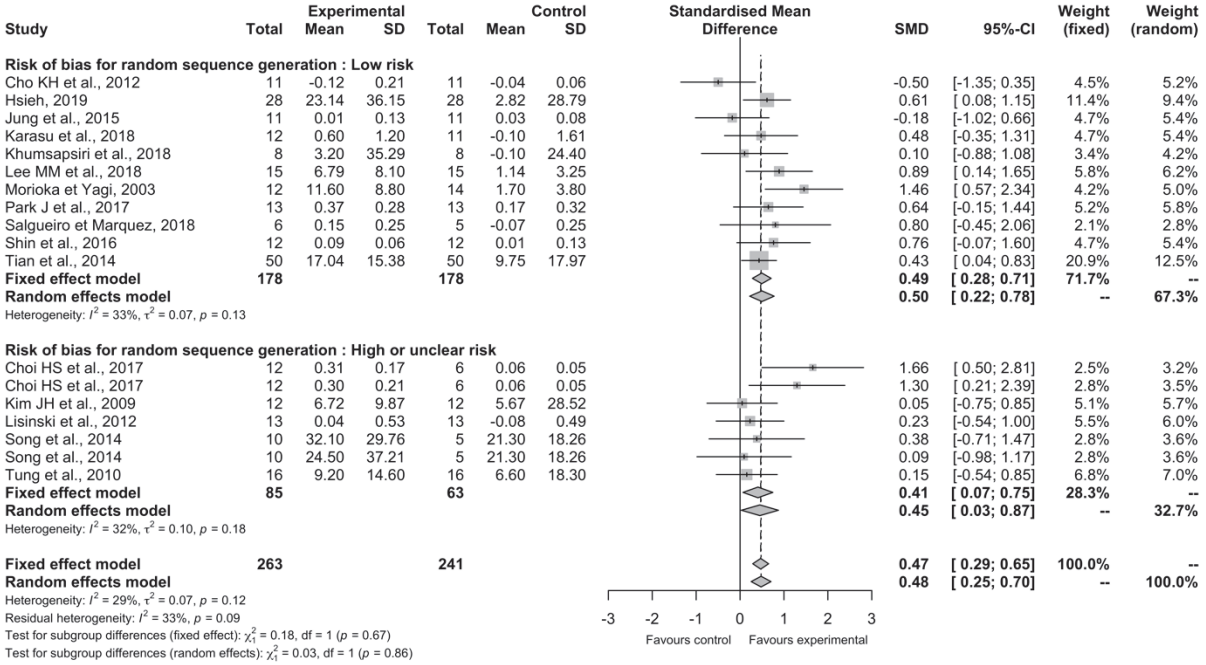


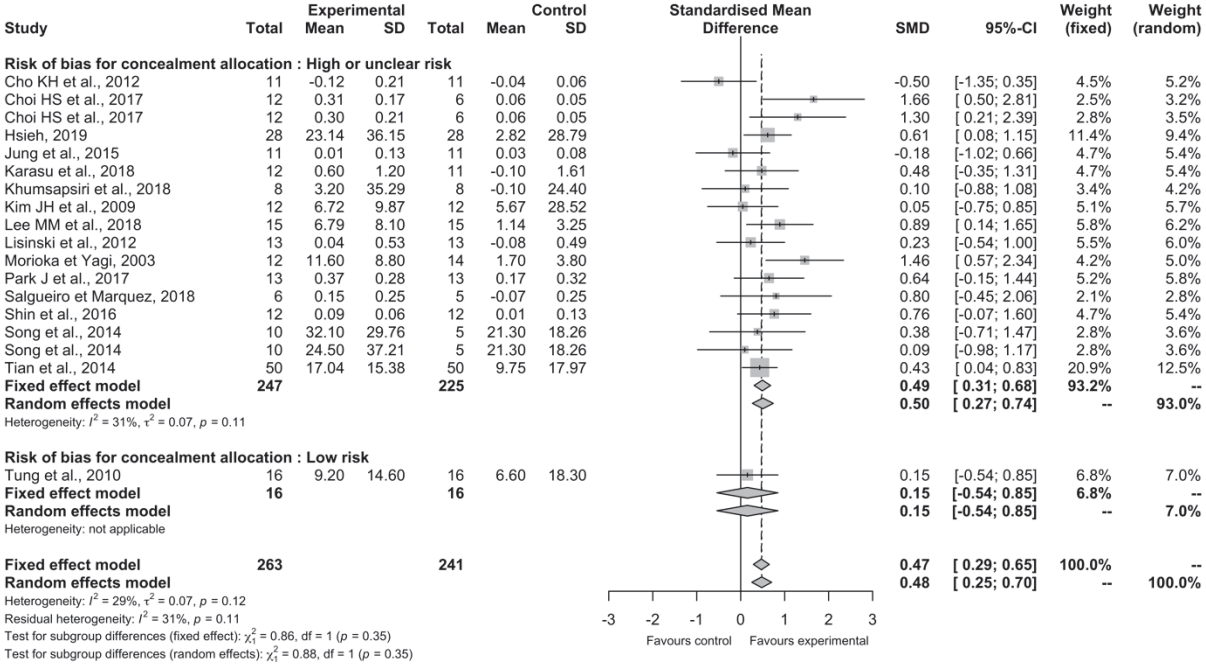
Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for other bias : Low risk										
Chan KS et al., 2012	15	-3.47	4.30	15	-0.20	2.88	-0.87	[-1.62; -0.12]	23.4%	24.5%
Furnari et al., 2014	20	-10.20	6.12	20	-14.20	16.20	0.32	[-0.30; 0.94]	34.1%	29.6%
Goliwas et al., 2017	20	-3.50	15.46	17	-0.20	12.02	-0.23	[-0.88; 0.42]	31.5%	28.6%
Tilikete et al., 2001	5	-4.24	14.04	2	1.38	20.09	-0.31	[-1.96; 1.35]	4.8%	7.8%
Tilikete et al., 2001	5	18.37	35.42	3	1.38	20.09	0.47	[-0.99; 1.94]	6.2%	9.6%
Fixed effect model	**65**			**57**			**-0.15**	**[-0.52; 0.21]**	**100.0%**	**--**
Random effects model							**-0.16**	**[-0.66; 0.34]**	**--**	**100.0%**
Heterogeneity: I^2 = 38%, τ^2 = 0.12, p = 0.17										
Fixed effect model	**65**			**57**			**-0.15**	**[-0.52; 0.21]**	**100.0%**	**--**
Random effects model							**-0.16**	**[-0.66; 0.34]**	**--**	**100.0%**

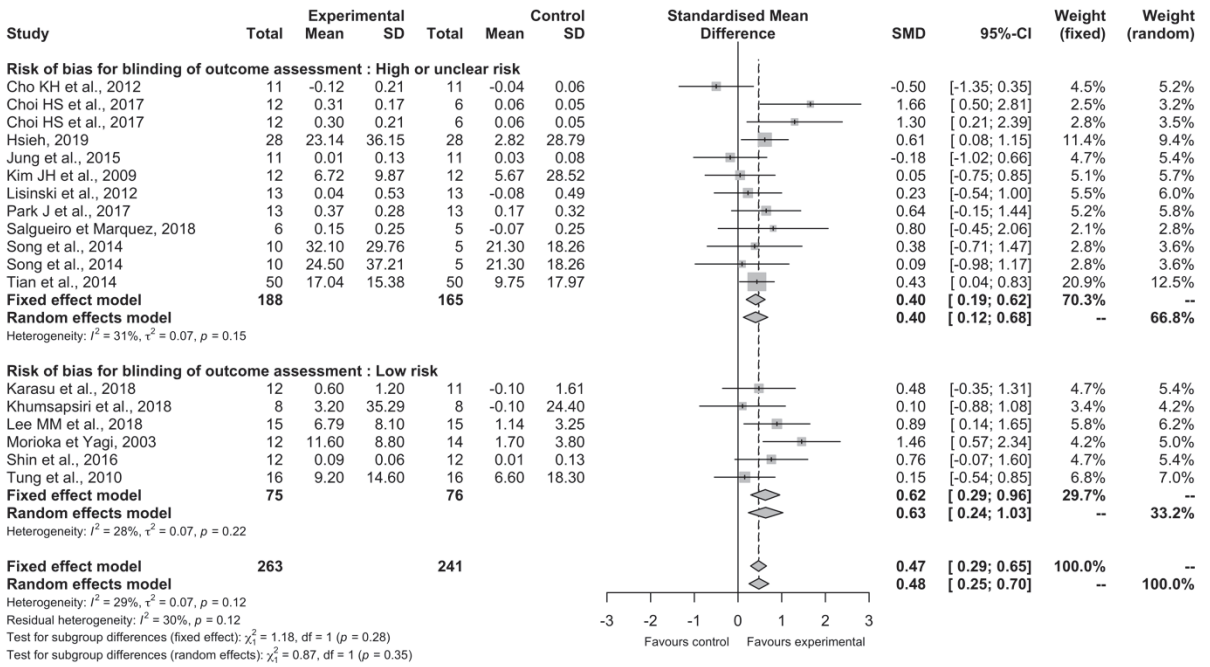
Heterogeneity: I^2 = 38%, τ^2 = 0.12, p = 0.17
Residual heterogeneity: I^2 = 38%, p = 0.17
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)

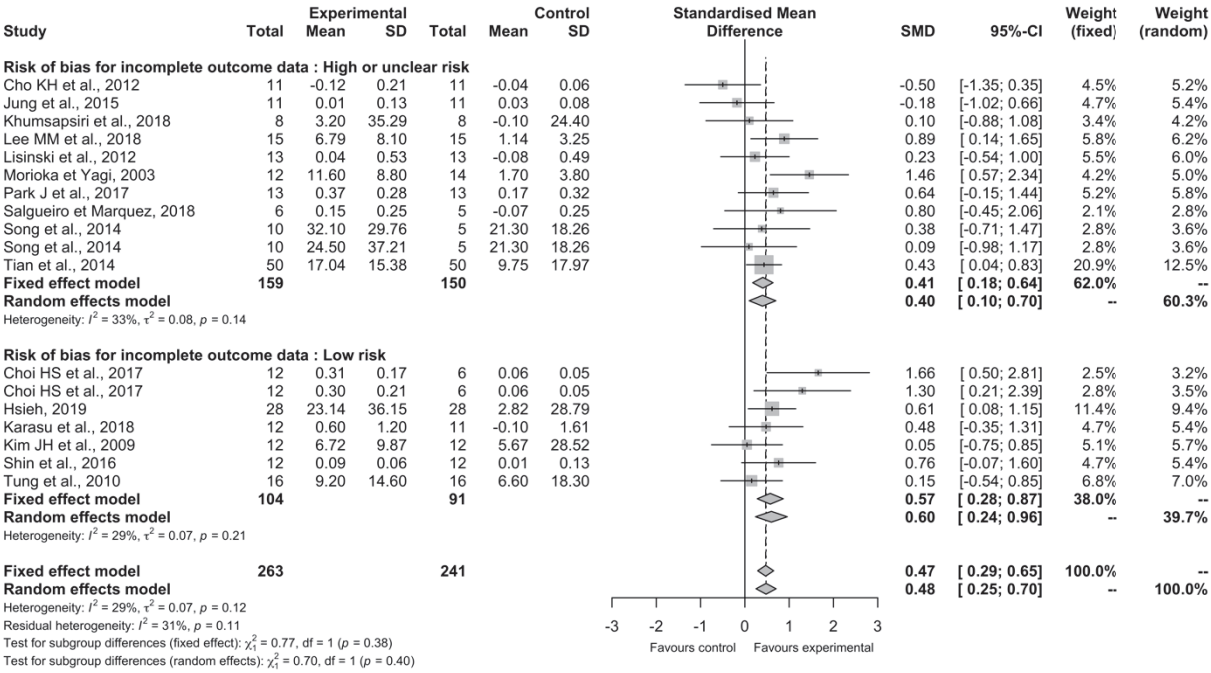


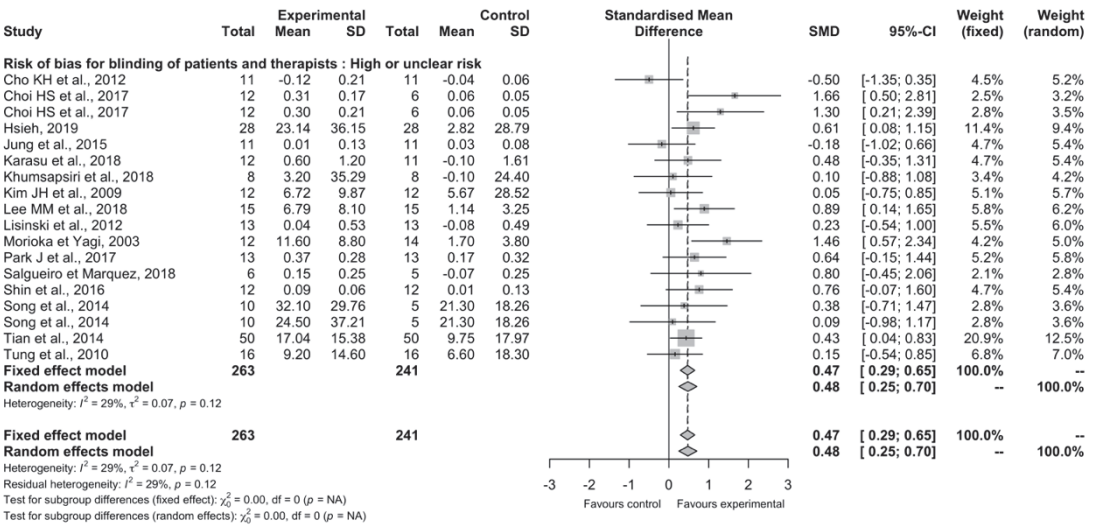
S8 Fig. Forest plot of physical therapy versus no treatment. Outcome: Postural stability EO, post-intervention effects. Subgroup: risk of bias



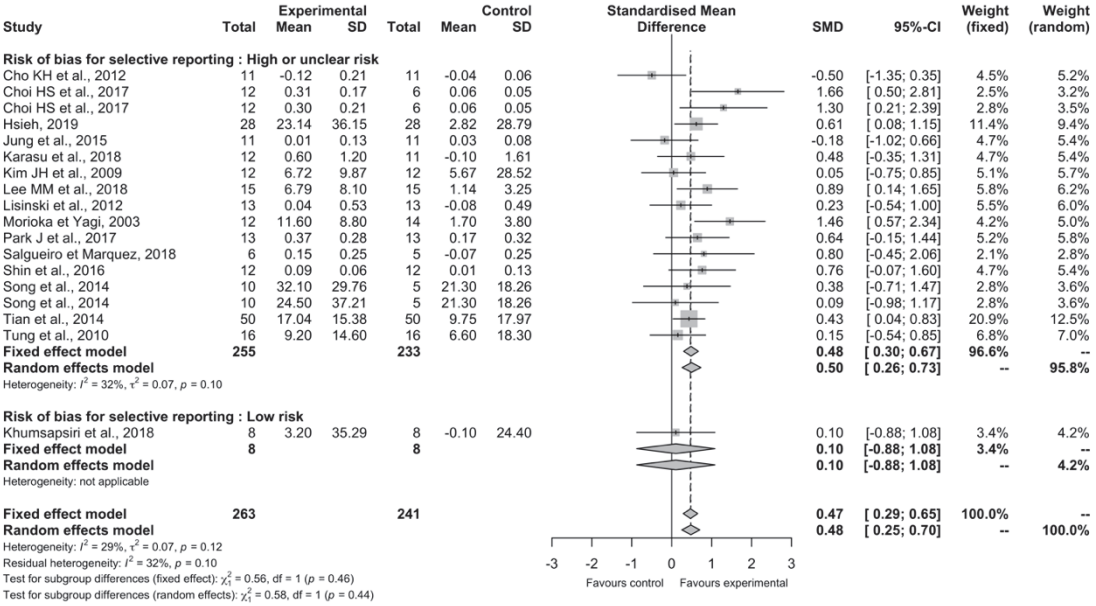



Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for blinding of outcome assessment : High or unclear risk
Cho KH et al., 2012 11 -0.12 0.21 11 -0.04 0.06 -0.50 [-1.35; 0.35] 4.5% 5.2%
Choi HS et al., 2017 12 0.31 0.17 6 0.06 0.05 1.66 [0.50; 2.81] 2.5% 3.2%
Choi HS et al., 2017 12 0.30 0.21 6 0.06 0.05 1.30 [0.21; 2.39] 2.8% 3.5%
Hsieh, 2019 28 23.14 36.15 28 2.82 28.79 0.61 [0.08; 1.15] 11.4% 9.4%
Jung et al., 2015 11 0.01 0.13 11 0.03 0.08 -0.18 [-1.02; 0.66] 4.7% 5.4%
Kim JH et al., 2009 12 6.72 9.87 12 5.67 28.52 0.05 [-0.75; 0.85] 5.1% 5.7%
Lisinski et al., 2012 13 0.04 0.53 13 -0.08 0.49 0.23 [-0.54; 1.00] 5.5% 6.0%
Park J et al., 2017 13 0.37 0.28 13 0.17 0.32 0.64 [-0.15; 1.44] 5.2% 5.8%
Salgueiro et Marquez, 2018 6 0.15 0.25 5 -0.07 0.25 0.80 [-0.45; 2.06] 2.1% 2.8%
Song et al., 2014 10 32.10 29.76 5 21.30 18.26 0.38 [-0.71; 1.47] 2.8% 3.6%
Song et al., 2014 10 24.50 37.21 5 21.30 18.26 0.09 [-0.98; 1.17] 2.8% 3.6%
Tian et al., 2014 50 17.04 15.38 50 9.75 17.97 0.43 [0.04; 0.83] 20.9% 12.5%
Fixed effect model 188 165 0.40 [0.19; 0.62] 70.3% --
Random effects model 0.40 [0.12; 0.68] -- 66.8%
Heterogeneity: I^2 = 31%, τ^2 = 0.07, p = 0.15
Risk of bias for blinding of outcome assessment : Low risk
Karasu et al., 2018 12 0.60 1.20 11 -0.10 1.61 0.48 [-0.35; 1.31] 4.7% 5.4%
Khumsapsiri et al., 2018 8 3.20 35.29 8 -0.10 24.40 0.10 [-0.88; 1.08] 3.4% 4.2%
Lee MM et al., 2018 15 6.79 8.10 15 1.14 3.25 0.89 [0.14; 1.65] 5.8% 6.2%
Morioka et Yagi, 2003 12 11.60 8.80 14 1.70 3.80 1.46 [0.57; 2.34] 4.2% 5.0%
Shin et al., 2016 12 0.09 0.06 12 0.01 0.13 0.76 [-0.07; 1.60] 4.7% 5.4%
Tung et al., 2010 16 9.20 14.60 16 6.60 18.30 0.15 [-0.54; 0.85] 6.8% 7.0%
Fixed effect model 75 76 0.62 [0.29; 0.96] 29.7% --
Random effects model 0.63 [0.24; 1.03] -- 33.2%
Heterogeneity: I^2 = 28%, τ^2 = 0.07, p = 0.22
Fixed effect model 263 241 0.47 [0.29; 0.65] 100.0% --
Random effects model 0.48 [0.25; 0.70] -- 100.0%
Heterogeneity: I^2 = 29%, τ^2 = 0.07, p = 0.12
Residual heterogeneity: I^2 = 30%, p = 0.12
Test for subgroup differences (fixed effect): χ^2_1 = 1.18, df = 1 (p = 0.28)
Test for subgroup differences (random effects): χ^2_1 = 0.87, df = 1 (p = 0.35)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

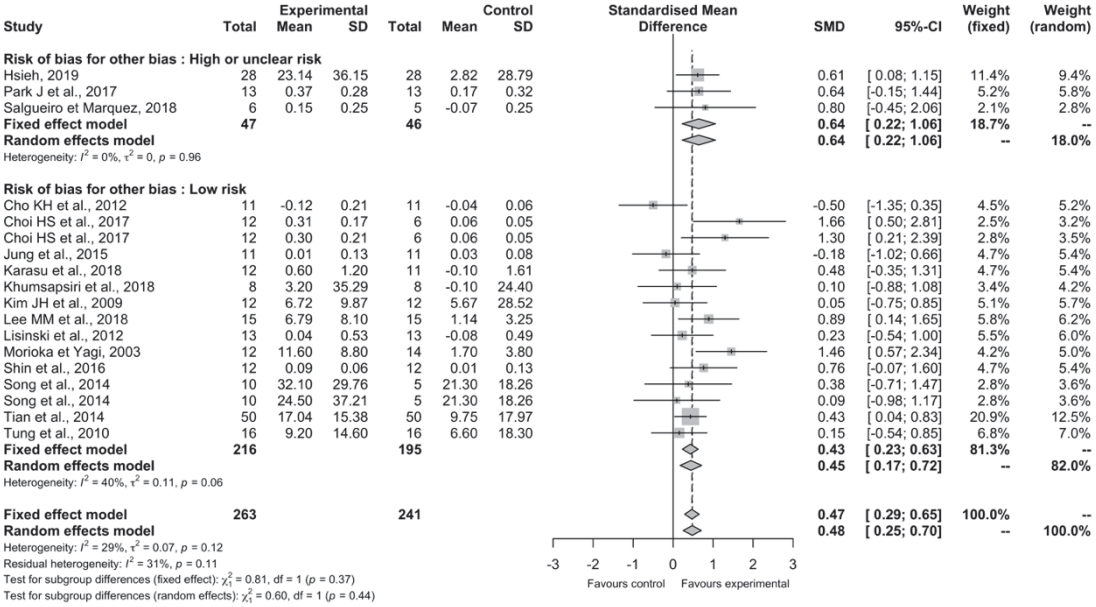

Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for incomplete outcome data : High or unclear risk
Cho KH et al., 2012 11 -0.12 0.21 11 -0.04 0.06 -0.50 [-1.35; 0.35] 4.5% 5.2%
Jung et al., 2015 11 0.01 0.13 11 0.03 0.08 -0.18 [-1.02; 0.66] 4.7% 5.4%
Khumsapsiri et al., 2018 8 3.20 35.29 8 -0.10 24.40 0.10 [-0.88; 1.08] 3.4% 4.2%
Lee MM et al., 2018 15 6.79 8.10 15 1.14 3.25 0.89 [0.14; 1.65] 5.8% 6.2%
Lisinski et al., 2012 13 0.04 0.53 13 -0.08 0.49 0.23 [-0.54; 1.00] 5.5% 6.0%
Morioka et Yagi, 2003 12 11.60 8.80 14 1.70 3.80 1.46 [0.57; 2.34] 4.2% 5.0%
Park J et al., 2017 13 0.37 0.28 13 0.17 0.32 0.64 [-0.15; 1.44] 5.2% 5.8%
Salgueiro et Marquez, 2018 6 0.15 0.25 5 -0.07 0.25 0.80 [-0.45; 2.06] 2.1% 2.8%
Song et al., 2014 10 32.10 29.76 5 21.30 18.26 0.38 [-0.71; 1.47] 2.8% 3.6%
Song et al., 2014 10 24.50 37.21 5 21.30 18.26 0.09 [-0.98; 1.17] 2.8% 3.6%
Tian et al., 2014 50 17.04 15.38 50 9.75 17.97 0.43 [0.04; 0.83] 20.9% 12.5%
Fixed effect model 159 150 0.41 [0.18; 0.64] 62.0% --
Random effects model 0.40 [0.10; 0.70] -- 60.3%
Heterogeneity: I^2 = 33%, τ^2 = 0.08, p = 0.14
Risk of bias for incomplete outcome data : Low risk
Choi HS et al., 2017 12 0.31 0.17 6 0.06 0.05 1.66 [0.50; 2.81] 2.5% 3.2%
Choi HS et al., 2017 12 0.30 0.21 6 0.06 0.05 1.30 [0.21; 2.39] 2.8% 3.5%
Hsieh, 2019 28 23.14 36.15 28 2.82 28.79 0.61 [0.08; 1.15] 11.4% 9.4%
Karasu et al., 2018 12 0.60 1.20 11 -0.10 1.61 0.48 [-0.35; 1.31] 4.7% 5.4%
Kim JH et al., 2009 12 6.72 9.87 12 5.67 28.52 0.05 [-0.75; 0.85] 5.1% 5.7%
Shin et al., 2016 12 0.09 0.06 12 0.01 0.13 0.76 [-0.07; 1.60] 4.7% 5.4%
Tung et al., 2010 16 9.20 14.60 16 6.60 18.30 0.15 [-0.54; 0.85] 6.8% 7.0%
Fixed effect model 104 91 0.57 [0.28; 0.87] 38.0% --
Random effects model 0.60 [0.24; 0.96] -- 39.7%
Heterogeneity: I^2 = 29%, τ^2 = 0.07, p = 0.21
Fixed effect model 263 241 0.47 [0.29; 0.65] 100.0% --
Random effects model 0.48 [0.25; 0.70] -- 100.0%
Heterogeneity: I^2 = 29%, τ^2 = 0.07, p = 0.12
Residual heterogeneity: I^2 = 31%, p = 0.11
Test for subgroup differences (fixed effect): χ^2_1 = 0.77, df = 1 (p = 0.38)
Test for subgroup differences (random effects): χ^2_1 = 0.70, df = 1 (p = 0.40)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental



Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for blinding of patients and therapists : High or unclear risk										
Cho KH et al., 2012	11	-0.12	0.21	11	-0.04	0.06	-0.50	[-1.35; 0.35]	4.5%	5.2%
Choi HS et al., 2017	12	0.31	0.17	6	0.06	0.05	1.66	[0.50; 2.81]	2.5%	3.2%
Choi HS et al., 2017	12	0.30	0.21	6	0.06	0.05	1.30	[0.21; 2.39]	2.8%	3.5%
Hsieh, 2019	28	23.14	36.15	28	2.82	28.79	0.61	[0.08; 1.15]	11.4%	9.4%
Jung et al., 2015	11	0.01	0.13	11	0.03	0.08	-0.18	[-1.02; 0.66]	4.7%	5.4%
Karasu et al., 2018	12	0.60	1.20	11	-0.10	1.61	0.48	[-0.35; 1.31]	4.7%	5.4%
Khumsapsiri et al., 2018	8	3.20	35.29	8	-0.10	24.40	0.10	[-0.88; 1.08]	3.4%	4.2%
Kim JH et al., 2009	12	6.72	9.87	12	5.67	28.52	0.05	[-0.75; 0.85]	5.1%	5.7%
Lee MM et al., 2018	15	6.79	8.10	15	1.14	3.25	0.89	[0.14; 1.65]	5.8%	6.2%
Lisinski et al., 2012	13	0.04	0.53	13	-0.08	0.49	0.23	[-0.54; 1.00]	5.5%	6.0%
Morioka et Yagi, 2003	12	11.60	8.80	14	1.70	3.80	1.46	[0.57; 2.34]	4.2%	5.0%
Park J et al., 2017	13	0.37	0.28	13	0.17	0.32	0.64	[-0.15; 1.44]	5.2%	5.8%
Salgueiro et Marquez, 2018	6	0.15	0.25	5	-0.07	0.25	0.80	[-0.45; 2.06]	2.1%	2.8%
Shin et al., 2016	12	0.09	0.06	12	0.01	0.13	0.76	[-0.07; 1.60]	4.7%	5.4%
Song et al., 2014	10	32.10	29.76	5	21.30	18.26	0.38	[-0.71; 1.47]	2.8%	3.6%
Song et al., 2014	10	24.50	37.21	5	21.30	18.26	0.09	[-0.98; 1.17]	2.8%	3.6%
Tian et al., 2014	50	17.04	15.38	50	9.75	17.97	0.43	[0.04; 0.83]	20.9%	12.5%
Tung et al., 2010	16	9.20	14.60	16	6.60	18.30	0.15	[-0.54; 0.85]	6.8%	7.0%
Fixed effect model	**263**			**241**			**0.47**	**[0.29; 0.65]**	**100.0%**	**--**
Random effects model							**0.48**	**[0.25; 0.70]**	**--**	**100.0%**
Heterogeneity: I^2 = 29%, τ^2 = 0.07, p = 0.12										
Fixed effect model	**263**			**241**			**0.47**	**[0.29; 0.65]**	**100.0%**	**--**
Random effects model							**0.48**	**[0.25; 0.70]**	**--**	**100.0%**
Heterogeneity: I^2 = 29%, τ^2 = 0.07, p = 0.12										
Residual heterogeneity: I^2 = 29%, p = 0.12										
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)										
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)										



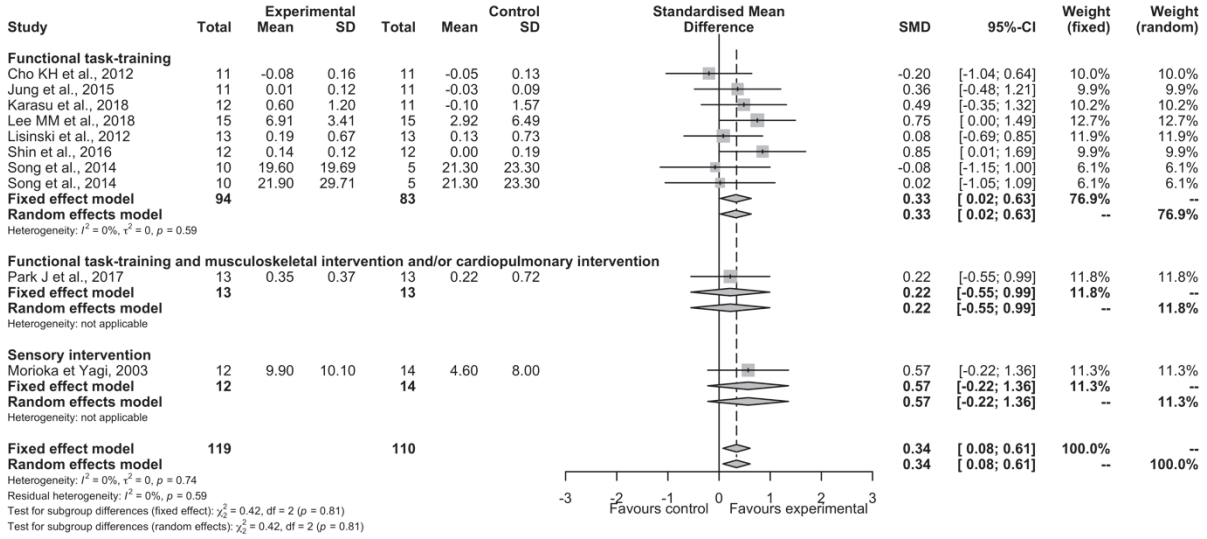
Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for selective reporting : High or unclear risk										
Cho KH et al., 2012	11	-0.12	0.21	11	-0.04	0.06	-0.50	[-1.35; 0.35]	4.5%	5.2%
Choi HS et al., 2017	12	0.31	0.17	6	0.06	0.05	1.66	[0.50; 2.81]	2.5%	3.2%
Choi HS et al., 2017	12	0.30	0.21	6	0.06	0.05	1.30	[0.21; 2.39]	2.8%	3.5%
Hsieh, 2019	28	23.14	36.15	28	2.82	28.79	0.61	[0.08; 1.15]	11.4%	9.4%
Jung et al., 2015	11	0.01	0.13	11	0.03	0.08	-0.18	[-1.02; 0.66]	4.7%	5.4%
Karasu et al., 2018	12	0.60	1.20	11	-0.10	1.61	0.48	[-0.35; 1.31]	4.7%	5.4%
Kim JH et al., 2009	12	6.72	9.87	12	5.67	28.52	0.05	[-0.75; 0.85]	5.1%	5.7%
Lee MM et al., 2018	15	6.79	8.10	15	1.14	3.25	0.89	[0.14; 1.65]	5.8%	6.2%
Lisinski et al., 2012	13	0.04	0.53	13	-0.08	0.49	0.23	[-0.54; 1.00]	5.5%	6.0%
Morioka et Yagi, 2003	12	11.60	8.80	14	1.70	3.80	1.46	[0.57; 2.34]	4.2%	5.0%
Park J et al., 2017	13	0.37	0.28	13	0.17	0.32	0.64	[-0.15; 1.44]	5.2%	5.8%
Salgueiro et Marquez, 2018	6	0.15	0.25	5	-0.07	0.25	0.80	[-0.45; 2.06]	2.1%	2.8%
Shin et al., 2016	12	0.09	0.06	12	0.01	0.13	0.76	[-0.07; 1.60]	4.7%	5.4%
Song et al., 2014	10	32.10	29.76	5	21.30	18.26	0.38	[-0.71; 1.47]	2.8%	3.6%
Song et al., 2014	10	24.50	37.21	5	21.30	18.26	0.09	[-0.98; 1.17]	2.8%	3.6%
Tian et al., 2014	50	17.04	15.38	50	9.75	17.97	0.43	[0.04; 0.83]	20.9%	12.5%
Tung et al., 2010	16	9.20	14.60	16	6.60	18.30	0.15	[-0.54; 0.85]	6.8%	7.0%
Fixed effect model	**255**			**233**			**0.48**	**[0.30; 0.67]**	**96.6%**	**--**
Random effects model							**0.50**	**[0.26; 0.73]**	**--**	**95.8%**
Heterogeneity: I^2 = 32%, τ^2 = 0.07, p = 0.10										
Risk of bias for selective reporting : Low risk										
Khumsapsiri et al., 2018	8	3.20	35.29	8	-0.10	24.40	0.10	[-0.88; 1.08]	3.4%	4.2%
Fixed effect model	**8**			**8**			**0.10**	**[-0.88; 1.08]**	**3.4%**	**--**
Random effects model							**0.10**	**[-0.88; 1.08]**	**--**	**4.2%**
Heterogeneity: not applicable										
Fixed effect model	**263**			**241**			**0.47**	**[0.29; 0.65]**	**100.0%**	**--**
Random effects model							**0.48**	**[0.25; 0.70]**	**--**	**100.0%**
Heterogeneity: I^2 = 29%, τ^2 = 0.07, p = 0.12										
Residual heterogeneity: I^2 = 32%, p = 0.10										
Test for subgroup differences (fixed effect): χ^2_1 = 0.56, df = 1 (p = 0.46)										
Test for subgroup differences (random effects): χ^2_1 = 0.58, df = 1 (p = 0.44)										



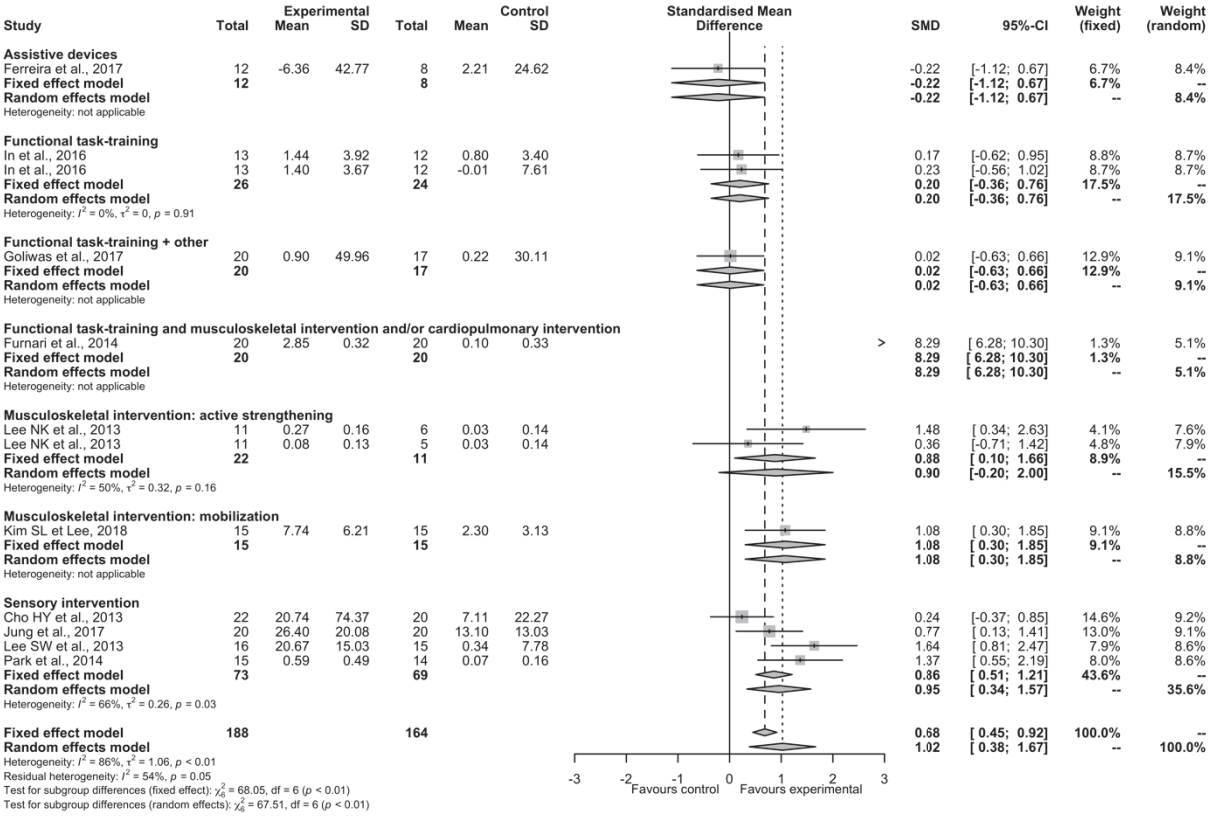
Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for other bias : High or unclear risk										
Hsieh, 2019	28	23.14	36.15	28	2.82	28.79	0.61	[0.08; 1.15]	11.4%	9.4%
Park J et al., 2017	13	0.37	0.28	13	0.17	0.32	0.64	[-0.15; 1.44]	5.2%	5.8%
Salgueiro et Marquez, 2018	6	0.15	0.25	5	-0.07	0.25	0.80	[-0.45; 2.06]	2.1%	2.8%
Fixed effect model	**47**			**46**			**0.64**	**[0.22; 1.06]**	**18.7%**	**--**
Random effects model							**0.64**	**[0.22; 1.06]**	**--**	**18.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.96										
Risk of bias for other bias : Low risk										
Cho KH et al., 2012	11	-0.12	0.21	11	-0.04	0.06	-0.50	[-1.35; 0.35]	4.5%	5.2%
Choi HS et al., 2017	12	0.31	0.17	6	0.06	0.05	1.66	[0.50; 2.81]	2.5%	3.2%
Choi HS et al., 2017	12	0.30	0.21	6	0.06	0.05	1.30	[0.21; 2.39]	2.8%	3.5%
Jung et al., 2015	11	0.01	0.13	11	0.03	0.08	-0.18	[-1.02; 0.66]	4.7%	5.4%
Karasu et al., 2018	12	0.60	1.20	11	-0.10	1.61	0.48	[-0.35; 1.31]	4.7%	5.4%
Khumsapsiri et al., 2018	8	3.20	35.29	8	-0.10	24.40	0.10	[-0.88; 1.08]	3.4%	4.2%
Kim JH et al., 2009	12	6.72	9.87	12	5.67	28.52	0.05	[-0.75; 0.85]	5.1%	5.7%
Lee MM et al., 2018	15	6.79	8.10	15	1.14	3.25	0.89	[0.14; 1.65]	5.8%	6.2%
Lisinski et al., 2012	13	0.04	0.53	13	-0.08	0.49	0.23	[-0.54; 1.00]	5.5%	6.0%
Morioka et Yagi, 2003	12	11.60	8.80	14	1.70	3.80	1.46	[0.57; 2.34]	4.2%	5.0%
Shin et al., 2016	12	0.09	0.06	12	0.01	0.13	0.76	[-0.07; 1.60]	4.7%	5.4%
Song et al., 2014	10	32.10	29.76	5	21.30	18.26	0.38	[-0.71; 1.47]	2.8%	3.6%
Song et al., 2014	10	24.50	37.21	5	21.30	18.26	0.09	[-0.98; 1.17]	2.8%	3.6%
Tian et al., 2014	50	17.04	15.38	50	9.75	17.97	0.43	[0.04; 0.83]	20.9%	12.5%
Tung et al., 2010	16	9.20	14.60	16	6.60	18.30	0.15	[-0.54; 0.85]	6.8%	7.0%
Fixed effect model	**216**			**195**			**0.43**	**[0.23; 0.63]**	**81.3%**	**--**
Random effects model							**0.45**	**[0.17; 0.72]**	**--**	**82.0%**
Heterogeneity: I^2 = 40%, τ^2 = 0.11, p = 0.06										
Fixed effect model	**263**			**241**			**0.47**	**[0.29; 0.65]**	**100.0%**	**--**
Random effects model							**0.48**	**[0.25; 0.70]**	**--**	**100.0%**
Heterogeneity: I^2 = 29%, τ^2 = 0.07, p = 0.12										
Residual heterogeneity: I^2 = 31%, p = 0.11										
Test for subgroup differences (fixed effect): χ^2_1 = 0.81, df = 1 (p = 0.37)										
Test for subgroup differences (random effects): χ^2_1 = 0.60, df = 1 (p = 0.44)										

S9 Fig. Forest plot of physical therapy. Outcome: Postural stability EC, post-intervention effects.

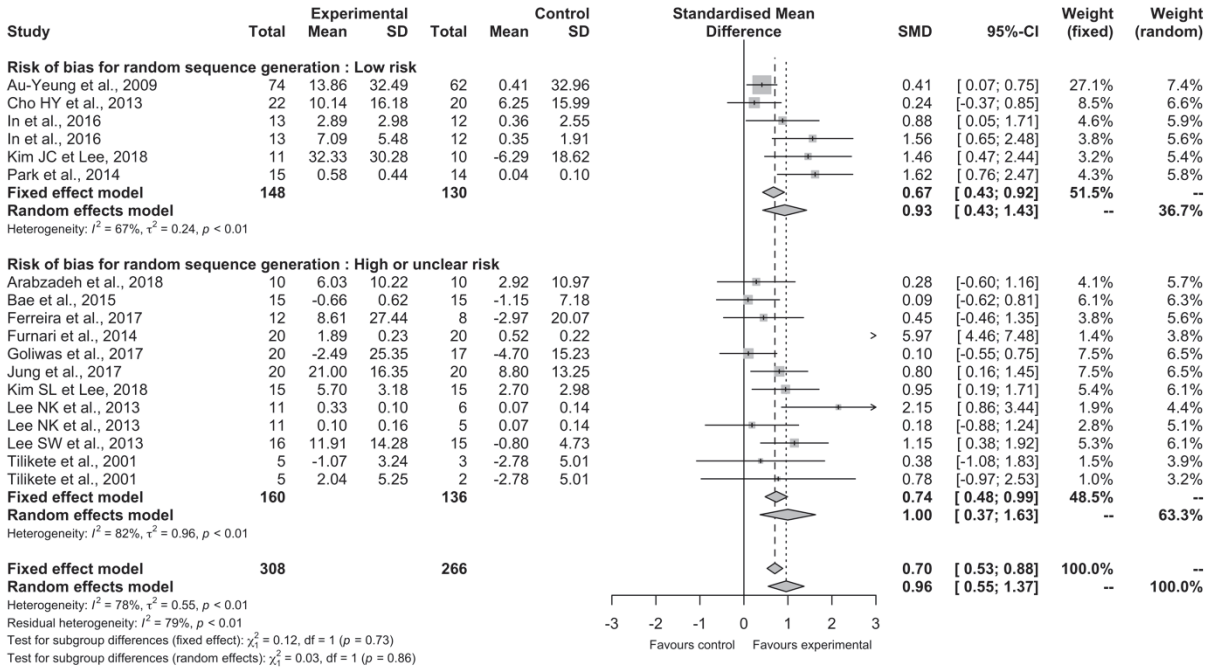
S9A Fig. Forest plot of physical therapy versus no treatment.

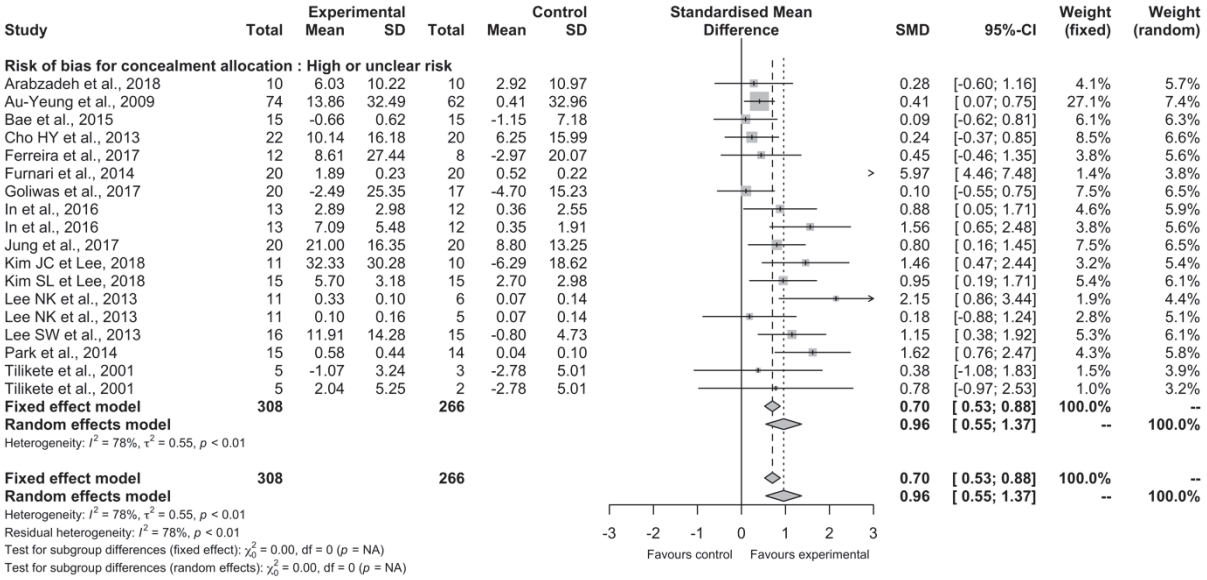


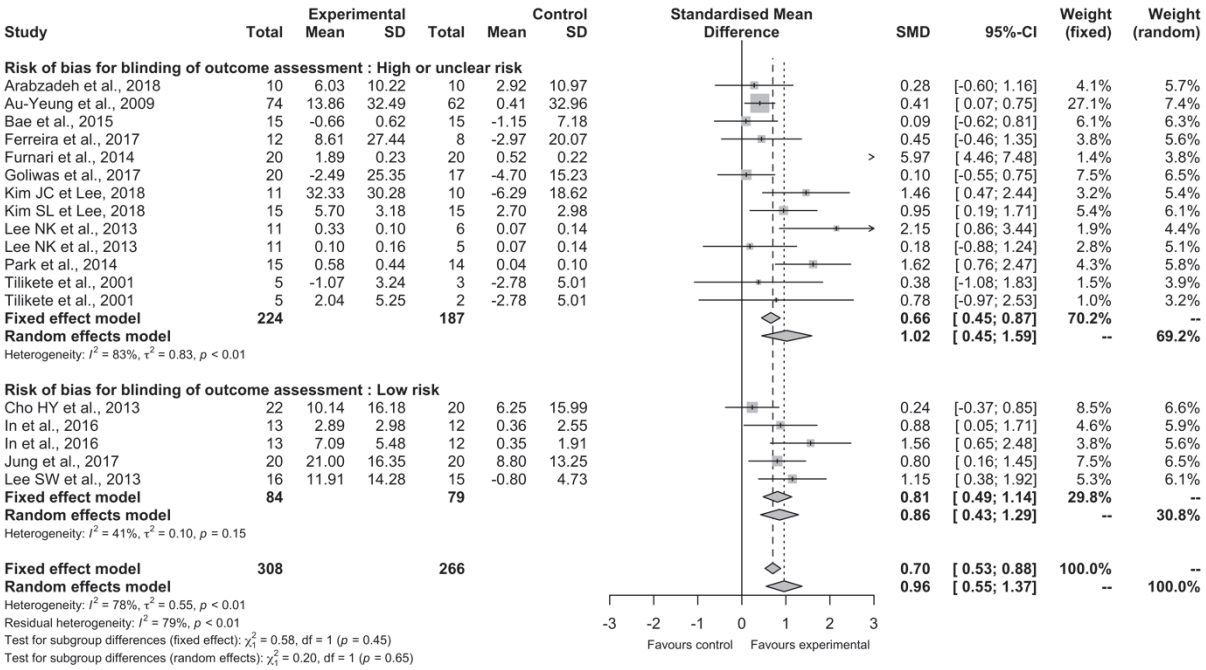
S9B Fig. Forest plot of physical therapy versus sham treatment/usual care.

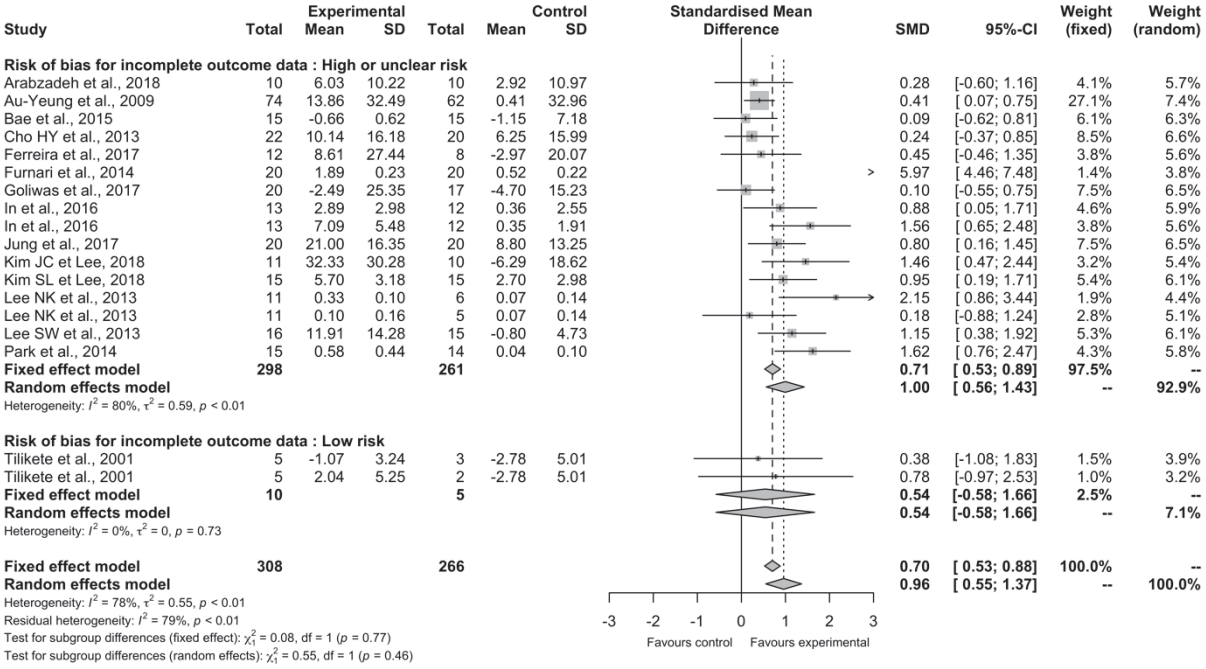


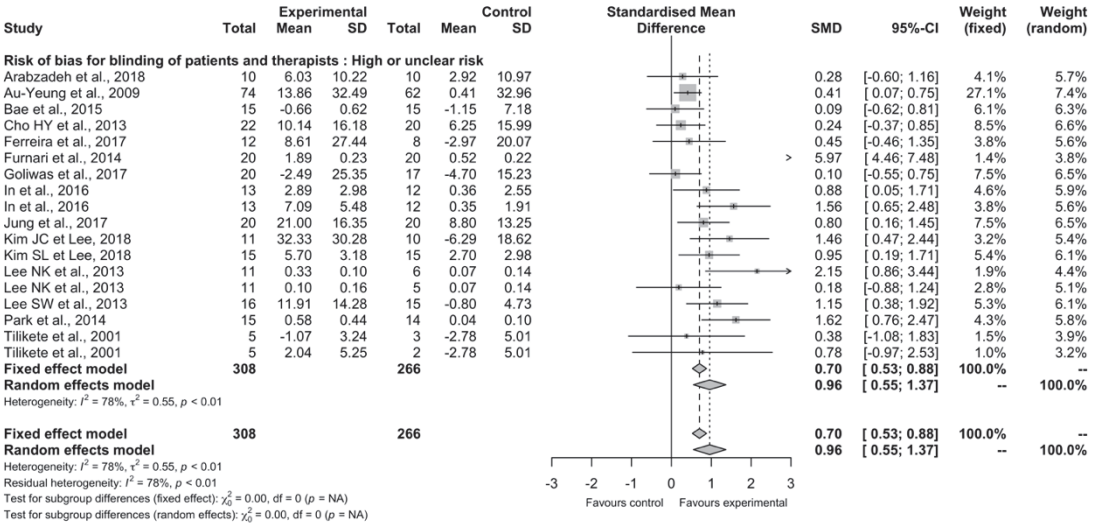
S10 Fig. Forest plot of physical therapy versus sham treatment/usual care. Outcome: Postural stability EO, post-intervention effects. Subgroup: risk of bias

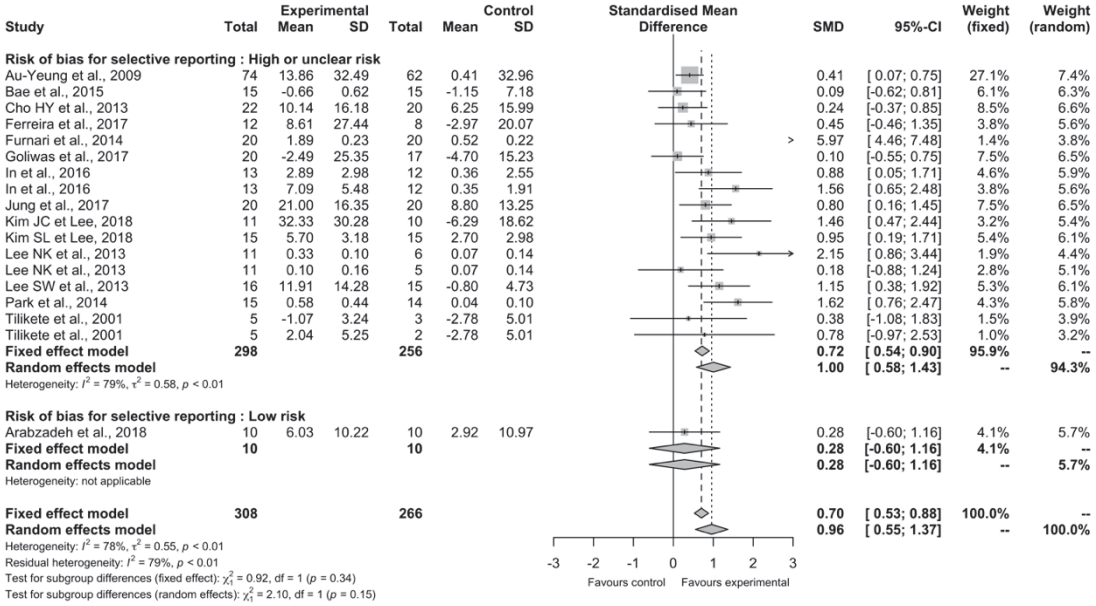


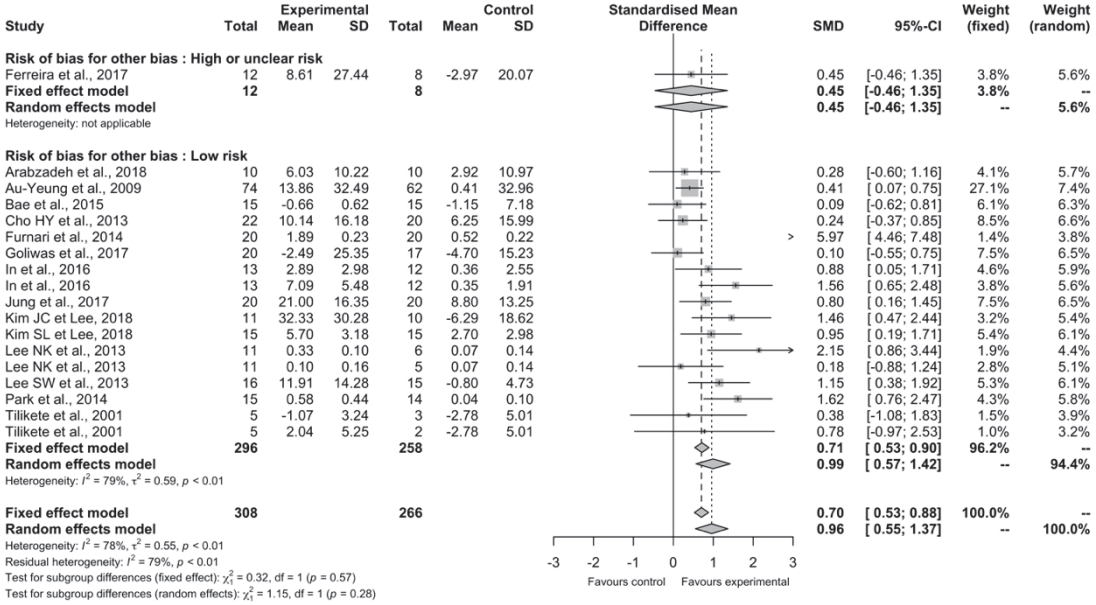



Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for blinding of outcome assessment : High or unclear risk
Arabzadeh et al., 2018 10 6.03 10.22 10 2.92 10.97 0.28 [-0.60; 1.16] 4.1% 5.7%
Au-Yeung et al., 2009 74 13.86 32.49 62 0.41 32.96 0.41 [0.07; 0.75] 27.1% 7.4%
Bae et al., 2015 15 -0.66 0.62 15 -1.15 7.18 0.09 [-0.62; 0.81] 6.1% 6.3%
Ferreira et al., 2017 12 8.61 27.44 8 -2.97 20.07 0.45 [-0.46; 1.35] 3.8% 5.6%
Furnari et al., 2014 20 1.89 0.23 20 0.52 0.22 > 5.97 [4.46; 7.48] 1.4% 3.8%
Goliwas et al., 2017 20 -2.49 25.35 17 -4.70 15.23 0.10 [-0.55; 0.75] 7.5% 6.5%
Kim JC et Lee, 2018 11 32.33 30.28 10 -6.29 18.62 1.46 [0.47; 2.44] 3.2% 5.4%
Kim SL et Lee, 2018 15 5.70 3.18 15 2.70 2.98 0.95 [0.19; 1.71] 5.4% 6.1%
Lee NK et al., 2013 11 0.33 0.10 6 0.07 0.14 2.15 [0.86; 3.44] 1.9% 4.4%
Lee NK et al., 2013 11 0.10 0.16 5 0.07 0.14 0.18 [-0.88; 1.24] 2.8% 5.1%
Park et al., 2014 15 0.58 0.44 14 0.04 0.10 1.62 [0.76; 2.47] 4.3% 5.8%
Tilikete et al., 2001 5 -1.07 3.24 3 -2.78 5.01 0.38 [-1.08; 1.83] 1.5% 3.9%
Tilikete et al., 2001 5 2.04 5.25 2 -2.78 5.01 0.78 [-0.97; 2.53] 1.0% 3.2%
Fixed effect model 224 187 0.66 [0.45; 0.87] 70.2% --
Random effects model 1.02 [0.45; 1.59] -- 69.2%
Heterogeneity: I^2 = 83%, τ^2 = 0.83, p < 0.01
Risk of bias for blinding of outcome assessment : Low risk
Cho HY et al., 2013 22 10.14 16.18 20 6.25 15.99 0.24 [-0.37; 0.85] 8.5% 6.6%
In et al., 2016 13 2.89 2.98 12 0.36 2.55 0.88 [0.05; 1.71] 4.6% 5.9%
In et al., 2016 13 7.09 5.48 12 0.35 1.91 1.56 [0.65; 2.48] 3.8% 5.6%
Jung et al., 2017 20 21.00 16.35 20 8.80 13.25 0.80 [0.16; 1.45] 7.5% 6.5%
Lee SW et al., 2013 16 11.91 14.28 15 -0.80 4.73 1.15 [0.38; 1.92] 5.3% 6.1%
Fixed effect model 84 79 0.81 [0.49; 1.14] 29.8% --
Random effects model 0.86 [0.43; 1.29] -- 30.8%
Heterogeneity: I^2 = 41%, τ^2 = 0.10, p = 0.15
Fixed effect model 308 266 0.70 [0.53; 0.88] 100.0% --
Random effects model 0.96 [0.55; 1.37] -- 100.0%
Heterogeneity: I^2 = 78%, τ^2 = 0.55, p < 0.01
Residual heterogeneity: I^2 = 79%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 0.58, df = 1 (p = 0.45)
Test for subgroup differences (random effects): χ^2_1 = 0.20, df = 1 (p = 0.65)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for incomplete outcome data : High or unclear risk
Arabzadeh et al., 2018 10 6.03 10.22 10 2.92 10.97 0.28 [-0.60; 1.16] 4.1% 5.7%
Au-Yeung et al., 2009 74 13.86 32.49 62 0.41 32.96 0.41 [0.07; 0.75] 27.1% 7.4%
Bae et al., 2015 15 -0.66 0.62 15 -1.15 7.18 0.09 [-0.62; 0.81] 6.1% 6.3%
Cho HY et al., 2013 22 10.14 16.18 20 6.25 15.99 0.24 [-0.37; 0.85] 8.5% 6.6%
Ferreira et al., 2017 12 8.61 27.44 8 -2.97 20.07 0.45 [-0.46; 1.35] 3.8% 5.6%
Furnari et al., 2014 20 1.89 0.23 20 0.52 0.22 > 5.97 [4.46; 7.48] 1.4% 3.8%
Goliwas et al., 2017 20 -2.49 25.35 17 -4.70 15.23 0.10 [-0.55; 0.75] 7.5% 6.5%
In et al., 2016 13 2.89 2.98 12 0.36 2.55 0.88 [0.05; 1.71] 4.6% 5.9%
In et al., 2016 13 7.09 5.48 12 0.35 1.91 1.56 [0.65; 2.48] 3.8% 5.6%
Jung et al., 2017 20 21.00 16.35 20 8.80 13.25 0.80 [0.16; 1.45] 7.5% 6.5%
Kim JC et Lee, 2018 11 32.33 30.28 10 -6.29 18.62 1.46 [0.47; 2.44] 3.2% 5.4%
Kim SL et Lee, 2018 15 5.70 3.18 15 2.70 2.98 0.95 [0.19; 1.71] 5.4% 6.1%
Lee NK et al., 2013 11 0.33 0.10 6 0.07 0.14 2.15 [0.86; 3.44] 1.9% 4.4%
Lee NK et al., 2013 11 0.10 0.16 5 0.07 0.14 0.18 [-0.88; 1.24] 2.8% 5.1%
Lee SW et al., 2013 16 11.91 14.28 15 -0.80 4.73 1.15 [0.38; 1.92] 5.3% 6.1%
Park et al., 2014 15 0.58 0.44 14 0.04 0.10 1.62 [0.76; 2.47] 4.3% 5.8%
Fixed effect model 298 261 0.71 [0.53; 0.89] 97.5% --
Random effects model 1.00 [0.56; 1.43] -- 92.9%
Heterogeneity: I^2 = 80%, τ^2 = 0.59, p < 0.01
Risk of bias for incomplete outcome data : Low risk
Tilikete et al., 2001 5 -1.07 3.24 3 -2.78 5.01 0.38 [-1.08; 1.83] 1.5% 3.9%
Tilikete et al., 2001 5 2.04 5.25 2 -2.78 5.01 0.78 [-0.97; 2.53] 1.0% 3.2%
Fixed effect model 10 5 0.54 [-0.58; 1.66] 2.5% --
Random effects model 0.54 [-0.58; 1.66] -- 7.1%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.73
Fixed effect model 308 266 0.70 [0.53; 0.88] 100.0% --
Random effects model 0.96 [0.55; 1.37] -- 100.0%
Heterogeneity: I^2 = 78%, τ^2 = 0.55, p < 0.01
Residual heterogeneity: I^2 = 79%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 0.08, df = 1 (p = 0.77)
Test for subgroup differences (random effects): χ^2_1 = 0.55, df = 1 (p = 0.46)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

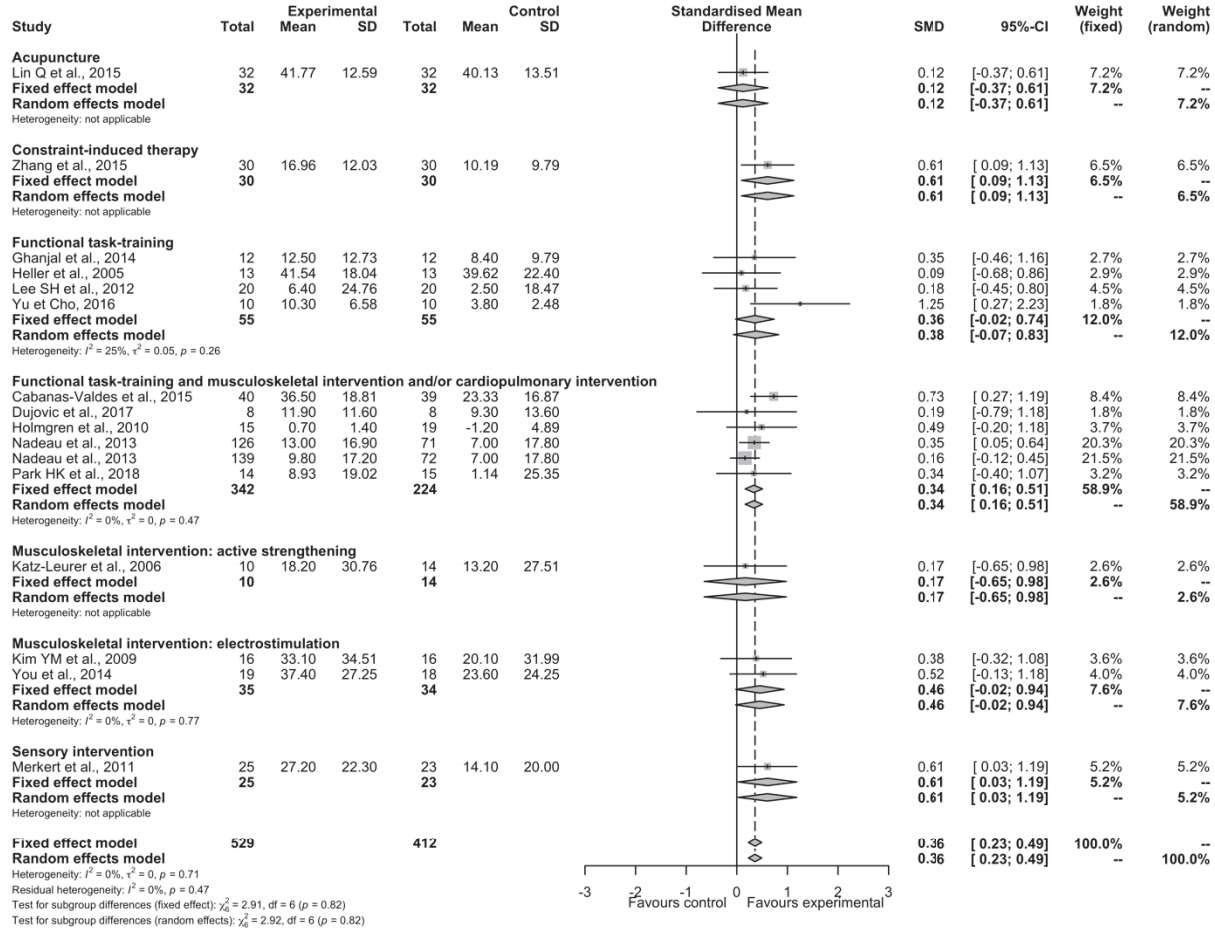

Study
Experimental Total Mean SD
Control Total Mean SD
Standardised Mean Difference
SMD 95%-CI
Weight (fixed) Weight (random)
Risk of bias for blinding of patients and therapists : High or unclear risk
Arabzadeh et al., 2018 10 6.03 10.22 10 2.92 10.97 0.28 [-0.60; 1.16] 4.1% 5.7%
Au-Yeung et al., 2009 74 13.86 32.49 62 0.41 32.96 0.41 [0.07; 0.75] 27.1% 7.4%
Bae et al., 2015 15 -0.66 0.62 15 -1.15 7.18 0.09 [-0.62; 0.81] 6.1% 6.3%
Cho HY et al., 2013 22 10.14 16.18 20 6.25 15.99 0.24 [-0.37; 0.85] 8.5% 6.6%
Ferreira et al., 2017 12 8.61 27.44 8 -2.97 20.07 0.45 [-0.46; 1.35] 3.8% 5.6%
Furnari et al., 2014 20 1.89 0.23 20 0.52 0.22 5.97 [4.46; 7.48] 1.4% 3.8%
Goliwas et al., 2017 20 -2.49 25.35 17 -4.70 15.23 0.10 [-0.55; 0.75] 7.5% 6.5%
In et al., 2016 13 2.89 2.98 12 0.36 2.55 0.88 [0.05; 1.71] 4.6% 5.9%
In et al., 2016 13 7.09 5.48 12 0.35 1.91 1.56 [0.65; 2.48] 3.8% 5.6%
Jung et al., 2017 20 21.00 16.35 20 8.80 13.25 0.80 [0.16; 1.45] 7.5% 6.5%
Kim JC et Lee, 2018 11 32.33 30.28 10 -6.29 18.62 1.46 [0.47; 2.44] 3.2% 5.4%
Kim SL et Lee, 2018 15 5.70 3.18 15 2.70 2.98 0.95 [0.19; 1.71] 5.4% 6.1%
Lee NK et al., 2013 11 0.33 0.10 6 0.07 0.14 2.15 [0.86; 3.44] 1.9% 4.4%
Lee NK et al., 2013 11 0.10 0.16 5 0.07 0.14 0.18 [-0.88; 1.24] 2.8% 5.1%
Lee SW et al., 2013 16 11.91 14.28 15 -0.80 4.73 1.15 [0.38; 1.92] 5.3% 6.1%
Park et al., 2014 15 0.58 0.44 14 0.04 0.10 1.62 [0.76; 2.47] 4.3% 5.8%
Tilikete et al., 2001 5 -1.07 3.24 3 -2.78 5.01 0.38 [-1.08; 1.83] 1.5% 3.9%
Tilikete et al., 2001 5 2.04 5.25 2 -2.78 5.01 0.78 [-0.97; 2.53] 1.0% 3.2%
Fixed effect model 308 266 0.70 [0.53; 0.88] 100.0% --
Random effects model 0.96 [0.55; 1.37] -- 100.0%
Heterogeneity: I^2 = 78%, τ^2 = 0.55, p < 0.01
Fixed effect model 308 266 0.70 [0.53; 0.88] 100.0% --
Random effects model 0.96 [0.55; 1.37] -- 100.0%
Heterogeneity: I^2 = 78%, τ^2 = 0.55, p < 0.01
Residual heterogeneity: I^2 = 78%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Study
Experimental Total Mean SD
Control Total Mean SD
Standardised Mean Difference
SMD 95%-CI
Weight (fixed) Weight (random)
Risk of bias for selective reporting : High or unclear risk
Au-Yeung et al., 2009 74 13.86 32.49 62 0.41 32.96 0.41 [0.07; 0.75] 27.1% 7.4%
Bae et al., 2015 15 -0.66 0.62 15 -1.15 7.18 0.09 [-0.62; 0.81] 6.1% 6.3%
Cho HY et al., 2013 22 10.14 16.18 20 6.25 15.99 0.24 [-0.37; 0.85] 8.5% 6.6%
Ferreira et al., 2017 12 8.61 27.44 8 -2.97 20.07 0.45 [-0.46; 1.35] 3.8% 5.6%
Furnari et al., 2014 20 1.89 0.23 20 0.52 0.22 5.97 [4.46; 7.48] 1.4% 3.8%
Goliwas et al., 2017 20 -2.49 25.35 17 -4.70 15.23 0.10 [-0.55; 0.75] 7.5% 6.5%
In et al., 2016 13 2.89 2.98 12 0.36 2.55 0.88 [0.05; 1.71] 4.6% 5.9%
In et al., 2016 13 7.09 5.48 12 0.35 1.91 1.56 [0.65; 2.48] 3.8% 5.6%
Jung et al., 2017 20 21.00 16.35 20 8.80 13.25 0.80 [0.16; 1.45] 7.5% 6.5%
Kim JC et Lee, 2018 11 32.33 30.28 10 -6.29 18.62 1.46 [0.47; 2.44] 3.2% 5.4%
Kim SL et Lee, 2018 15 5.70 3.18 15 2.70 2.98 0.95 [0.19; 1.71] 5.4% 6.1%
Lee NK et al., 2013 11 0.33 0.10 6 0.07 0.14 2.15 [0.86; 3.44] 1.9% 4.4%
Lee NK et al., 2013 11 0.10 0.16 5 0.07 0.14 0.18 [-0.88; 1.24] 2.8% 5.1%
Lee SW et al., 2013 16 11.91 14.28 15 -0.80 4.73 1.15 [0.38; 1.92] 5.3% 6.1%
Park et al., 2014 15 0.58 0.44 14 0.04 0.10 1.62 [0.76; 2.47] 4.3% 5.8%
Tilikete et al., 2001 5 -1.07 3.24 3 -2.78 5.01 0.38 [-1.08; 1.83] 1.5% 3.9%
Tilikete et al., 2001 5 2.04 5.25 2 -2.78 5.01 0.78 [-0.97; 2.53] 1.0% 3.2%
Fixed effect model 298 256 0.72 [0.54; 0.90] 95.9% --
Random effects model 1.00 [0.58; 1.43] -- 94.3%
Heterogeneity: I^2 = 79%, τ^2 = 0.58, p < 0.01
Risk of bias for selective reporting : Low risk
Arabzadeh et al., 2018 10 6.03 10.22 10 2.92 10.97 0.28 [-0.60; 1.16] 4.1% 5.7%
Fixed effect model 10 10 0.28 [-0.60; 1.16] 4.1% --
Random effects model 0.28 [-0.60; 1.16] -- 5.7%
Heterogeneity: not applicable
Fixed effect model 308 266 0.70 [0.53; 0.88] 100.0% --
Random effects model 0.96 [0.55; 1.37] -- 100.0%
Heterogeneity: I^2 = 78%, τ^2 = 0.55, p < 0.01
Residual heterogeneity: I^2 = 79%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 0.92, df = 1 (p = 0.34)
Test for subgroup differences (random effects): χ^2_1 = 2.10, df = 1 (p = 0.15)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

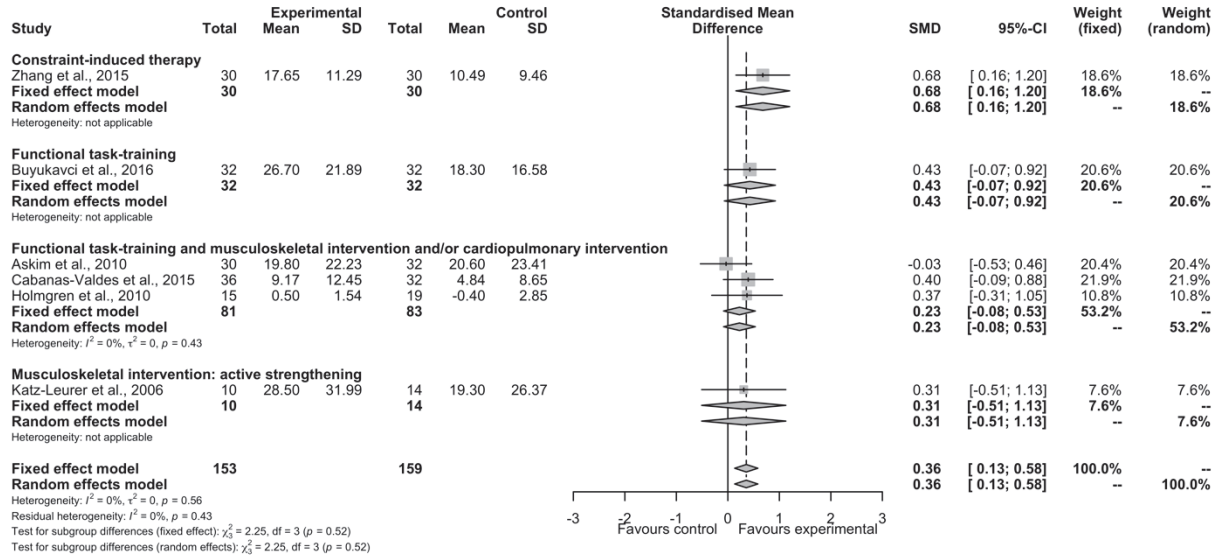

Study
Experimental Total Mean SD
Control Total Mean SD
Standardised Mean Difference
SMD 95%-CI
Weight (fixed) Weight (random)
Risk of bias for other bias : High or unclear risk
Ferreira et al., 2017 12 8.61 27.44 8 -2.97 20.07 0.45 [-0.46; 1.35] 3.8% 5.6%
Fixed effect model 12 8 0.45 [-0.46; 1.35] 3.8% --
Random effects model 0.45 [-0.46; 1.35] -- 5.6%
Heterogeneity: not applicable
Risk of bias for other bias : Low risk
Arabzadeh et al., 2018 10 6.03 10.22 10 2.92 10.97 0.28 [-0.60; 1.16] 4.1% 5.7%
Au-Yeung et al., 2009 74 13.86 32.49 62 0.41 32.96 0.41 [0.07; 0.75] 27.1% 7.4%
Bae et al., 2015 15 -0.66 0.62 15 -1.15 7.18 0.09 [-0.62; 0.81] 6.1% 6.3%
Cho HY et al., 2013 22 10.14 16.18 20 6.25 15.99 0.24 [-0.37; 0.85] 8.5% 6.6%
Furnari et al., 2014 20 1.89 0.23 20 0.52 0.22 5.97 [4.46; 7.48] 1.4% 3.8%
Goliwas et al., 2017 20 -2.49 25.35 17 -4.70 15.23 0.10 [-0.55; 0.75] 7.5% 6.5%
In et al., 2016 13 2.89 2.98 12 0.36 2.55 0.88 [0.05; 1.71] 4.6% 5.9%
In et al., 2016 13 7.09 5.48 12 0.35 1.91 1.56 [0.65; 2.48] 3.8% 5.6%
Jung et al., 2017 20 21.00 16.35 20 8.80 13.25 0.80 [0.16; 1.45] 7.5% 6.5%
Kim JC et Lee, 2018 11 32.33 30.28 10 -6.29 18.62 1.46 [0.47; 2.44] 3.2% 5.4%
Kim SL et Lee, 2018 15 5.70 3.18 15 2.70 2.98 0.95 [0.19; 1.71] 5.4% 6.1%
Lee NK et al., 2013 11 0.33 0.10 6 0.07 0.14 2.15 [0.86; 3.44] 1.9% 4.4%
Lee NK et al., 2013 11 0.10 0.16 5 0.07 0.14 0.18 [-0.88; 1.24] 2.8% 5.1%
Lee SW et al., 2013 16 11.91 14.28 15 -0.80 4.73 1.15 [0.38; 1.92] 5.3% 6.1%
Park et al., 2014 15 0.58 0.44 14 0.04 0.10 1.62 [0.76; 2.47] 4.3% 5.8%
Tilikete et al., 2001 5 -1.07 3.24 3 -2.78 5.01 0.38 [-1.08; 1.83] 1.5% 3.9%
Tilikete et al., 2001 5 2.04 5.25 2 -2.78 5.01 0.78 [-0.97; 2.53] 1.0% 3.2%
Fixed effect model 296 258 0.71 [0.53; 0.90] 96.2% --
Random effects model 0.99 [0.57; 1.42] -- 94.4%
Heterogeneity: I^2 = 79%, τ^2 = 0.59, p < 0.01
Fixed effect model 308 266 0.70 [0.53; 0.88] 100.0% --
Random effects model 0.96 [0.55; 1.37] -- 100.0%
Heterogeneity: I^2 = 78%, τ^2 = 0.55, p < 0.01
Residual heterogeneity: I^2 = 79%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 0.32, df = 1 (p = 0.57)
Test for subgroup differences (random effects): χ^2_1 = 1.15, df = 1 (p = 0.28)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

S11 Fig. Forest plot of physical therapy. Outcome: Autonomy. Subgroup: Categories of PT

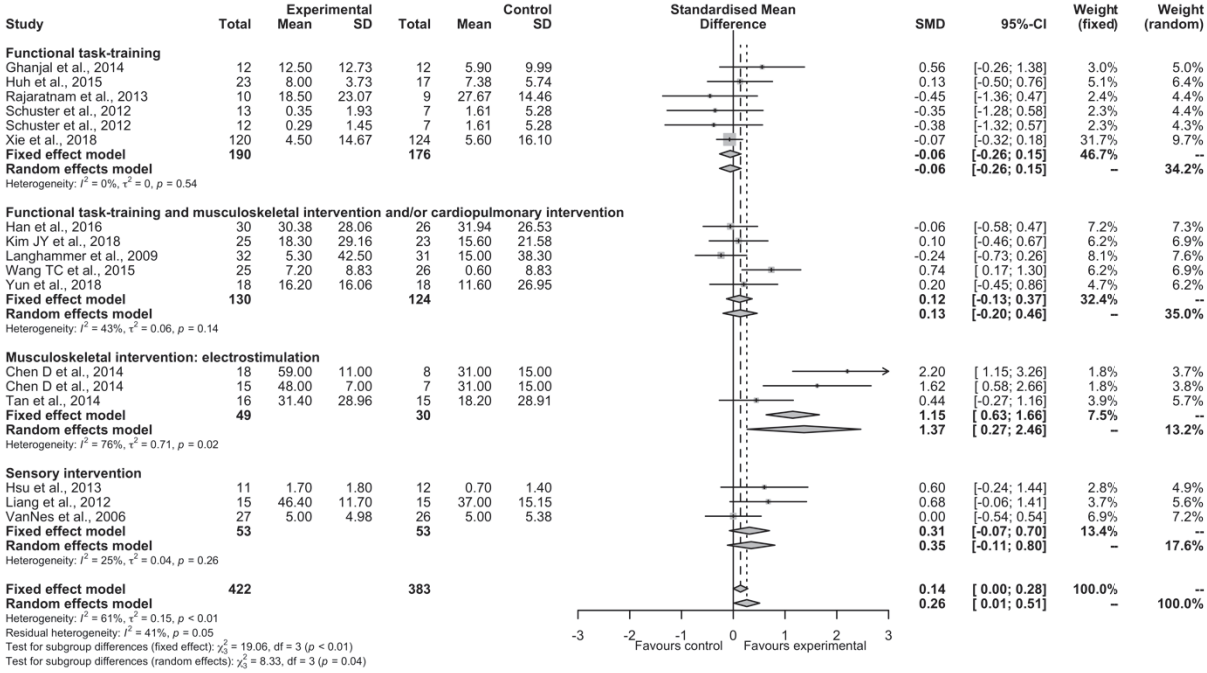
S11A Fig. Forest plot of physical therapy versus no treatment. Outcome: Autonomy, post-intervention effects. Subgroup: Categories of PT



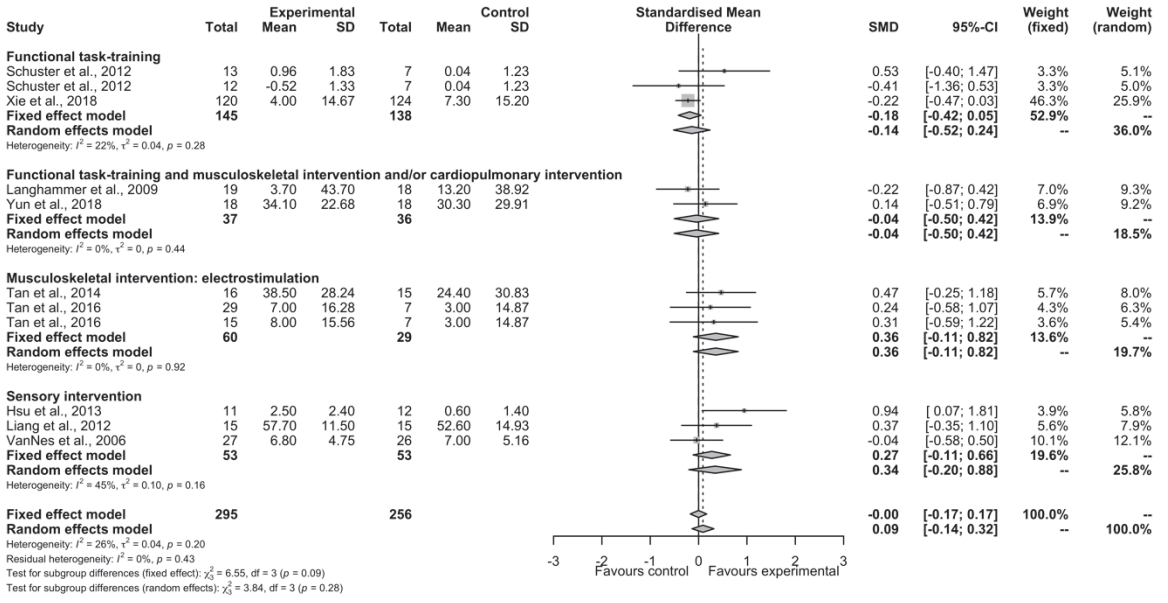
S11B Fig. Forest plot of physical therapy versus no treatment. Outcome: Autonomy, persisting effects. Subgroup: Categories of PT



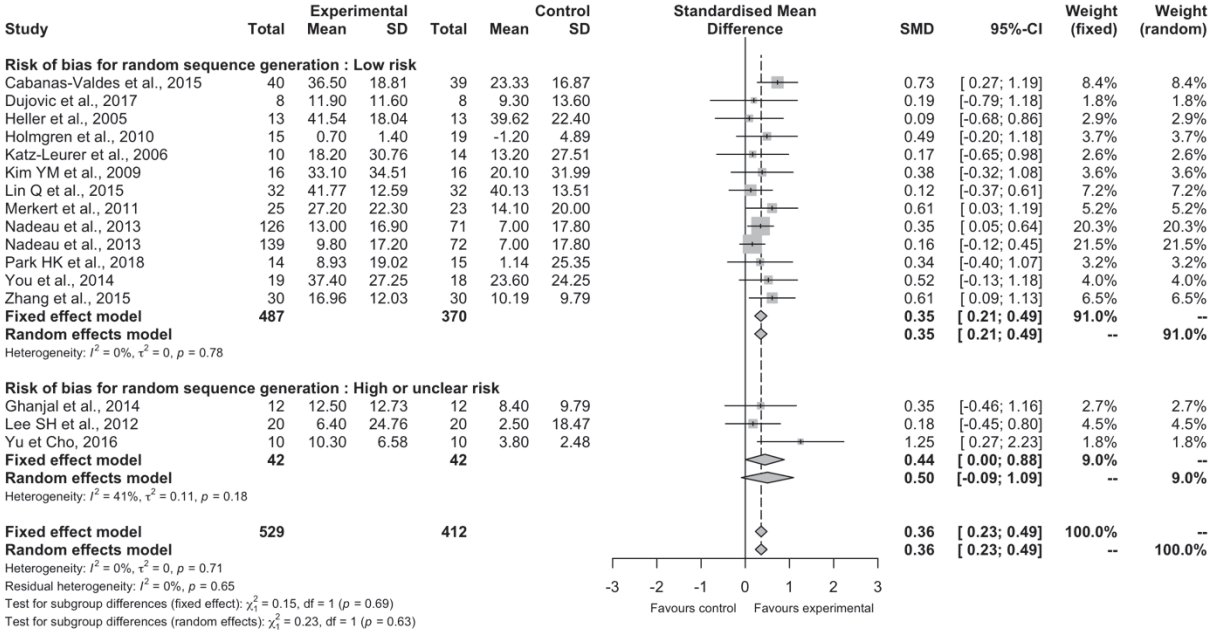
S11C Fig. Forest plot of physical therapy versus sham treatment/usual care. Outcome: Autonomy, post-intervention effects. Subgroup: Categories of PT

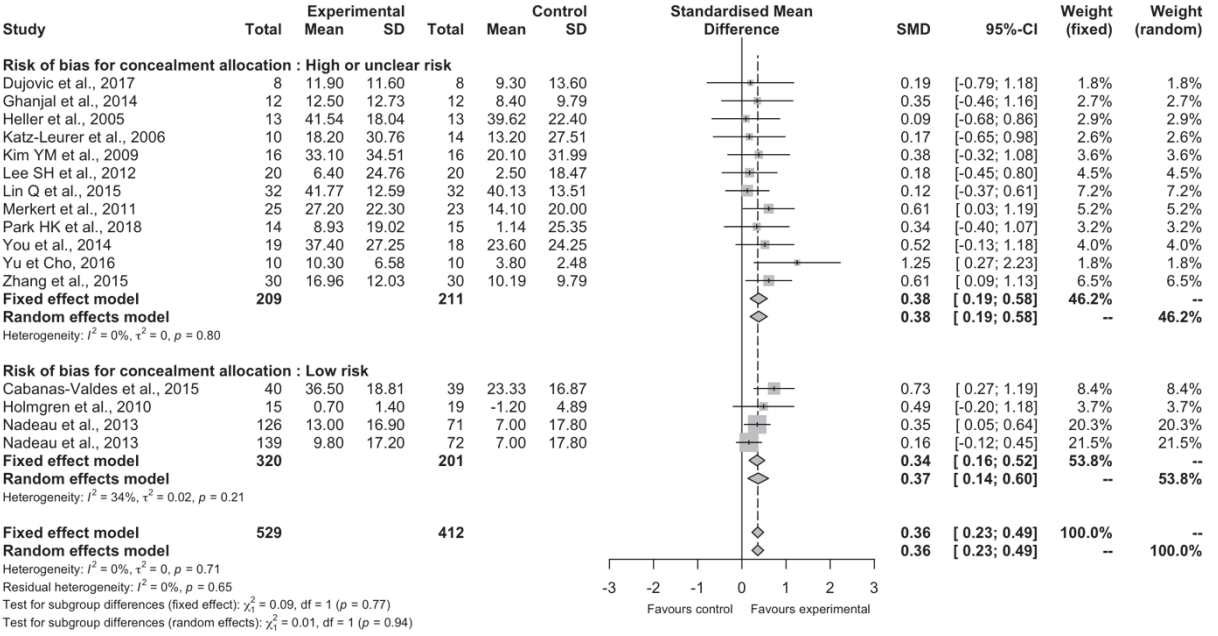


S11A Fig. Forest plot of physical therapy versus sham treatment/usual care. Outcome: Autonomy, persisting effects. Subgroup: Categories of PT

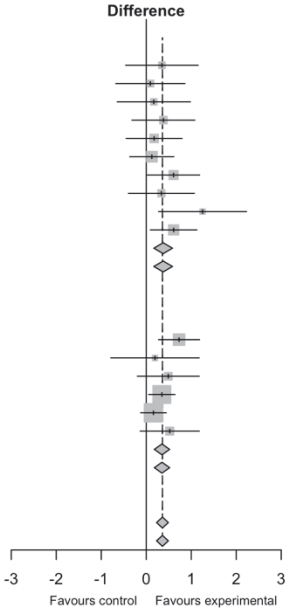


S12 Fig. Forest plot of physical therapy versus no treatment. Outcome: Autonomy, post-intervention effects. Subgroup: risk of bias

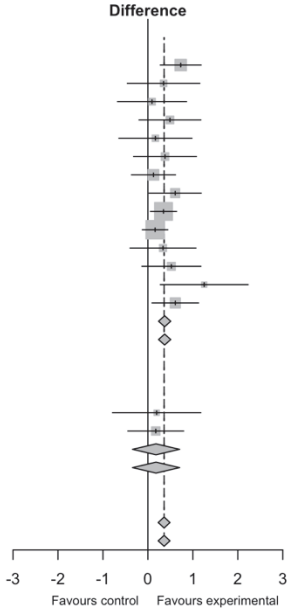


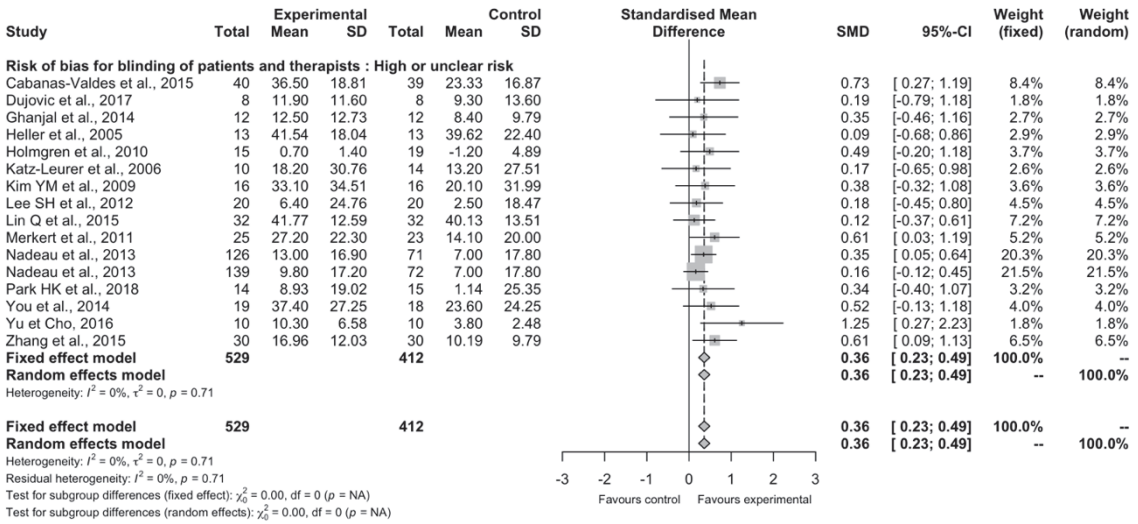


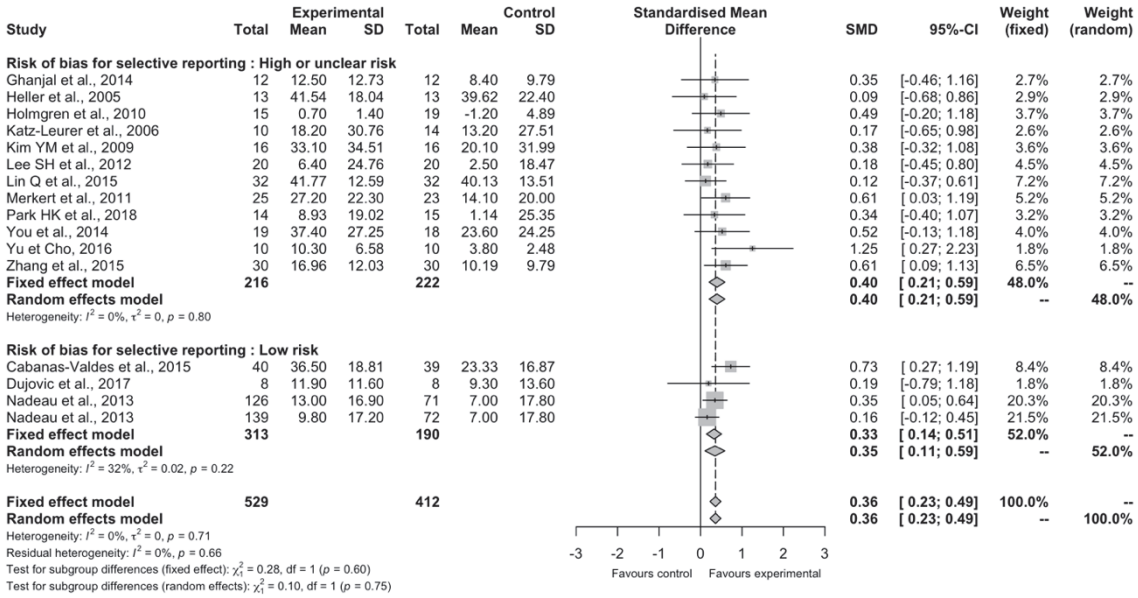
Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for blinding of outcome assessment : High or unclear risk										
Ghanjal et al., 2014	12	12.50	12.73	12	8.40	9.79	0.35	[-0.46; 1.16]	2.7%	2.7%
Heller et al., 2005	13	41.54	18.04	13	39.62	22.40	0.09	[-0.68; 0.86]	2.9%	2.9%
Katz-Leurer et al., 2006	10	18.20	30.76	14	13.20	27.51	0.17	[-0.65; 0.98]	2.6%	2.6%
Kim YM et al., 2009	16	33.10	34.51	16	20.10	31.99	0.38	[-0.32; 1.08]	3.6%	3.6%
Lee SH et al., 2012	20	6.40	24.76	20	2.50	18.47	0.18	[-0.45; 0.80]	4.5%	4.5%
Lin Q et al., 2015	32	41.77	12.59	32	40.13	13.51	0.12	[-0.37; 0.61]	7.2%	7.2%
Merkert et al., 2011	25	27.20	22.30	23	14.10	20.00	0.61	[0.03; 1.19]	5.2%	5.2%
Park HK et al., 2018	14	8.93	19.02	15	1.14	25.35	0.34	[-0.40; 1.07]	3.2%	3.2%
Yu et Cho, 2016	10	10.30	6.58	10	3.80	2.48	1.25	[0.27; 2.23]	1.8%	1.8%
Zhang et al., 2015	30	16.96	12.03	30	10.19	9.79	0.61	[0.09; 1.13]	6.5%	6.5%
Fixed effect model	**182**			**185**			**0.38**	**[0.17; 0.58]**	**40.3%**	**--**
Random effects model							**0.38**	**[0.17; 0.58]**	**--**	**40.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.67										
Risk of bias for blinding of outcome assessment : Low risk										
Cabanas-Valdes et al., 2015	40	36.50	18.81	39	23.33	16.87	0.73	[0.27; 1.19]	8.4%	8.4%
Dujovic et al., 2017	8	11.90	11.60	8	9.30	13.60	0.19	[-0.79; 1.18]	1.8%	1.8%
Holmgren et al., 2010	15	0.70	1.40	19	-1.20	4.89	0.49	[-0.20; 1.18]	3.7%	3.7%
Nadeau et al., 2013	126	13.00	16.90	71	7.00	17.80	0.35	[0.05; 0.64]	20.3%	20.3%
Nadeau et al., 2013	139	9.80	17.20	72	7.00	17.80	0.16	[-0.12; 0.45]	21.5%	21.5%
You et al., 2014	19	37.40	27.25	18	23.60	24.25	0.52	[-0.13; 1.18]	4.0%	4.0%
Fixed effect model	**347**			**227**			**0.35**	**[0.18; 0.52]**	**59.7%**	**--**
Random effects model							**0.35**	**[0.18; 0.52]**	**--**	**59.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.43										
Fixed effect model	**529**			**412**			**0.36**	**[0.23; 0.49]**	**100.0%**	**--**
Random effects model							**0.36**	**[0.23; 0.49]**	**--**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.71										
Residual heterogeneity: I^2 = 0%, p = 0.64										
Test for subgroup differences (fixed effect): χ^2_1 = 0.04, df = 1 (p = 0.85)										
Test for subgroup differences (random effects): χ^2_1 = 0.04, df = 1 (p = 0.85)										

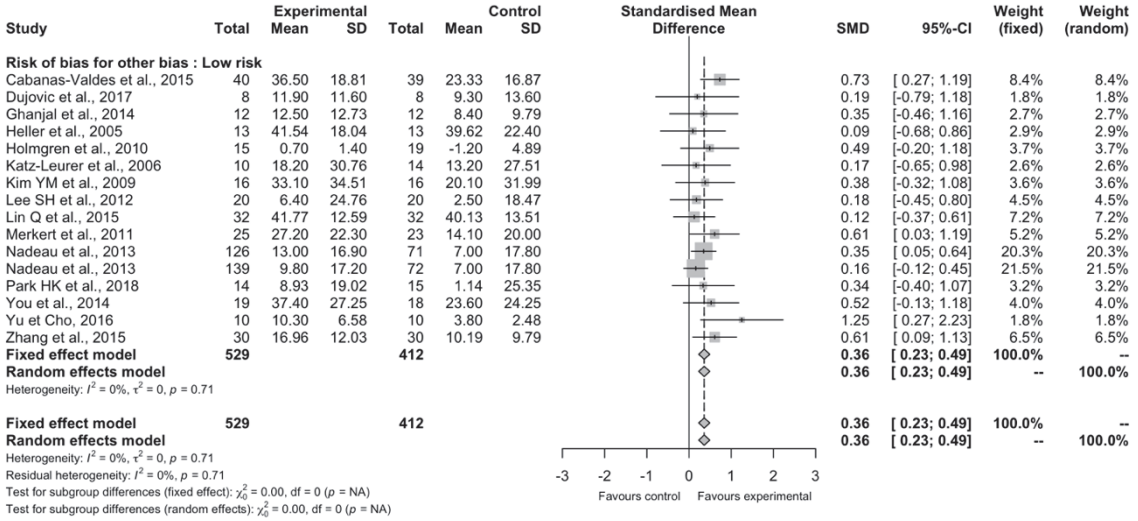


Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Risk of bias for incomplete outcome data : High or unclear risk										
Cabanas-Valdes et al., 2015	40	36.50	18.81	39	23.33	16.87	0.73	[0.27; 1.19]	8.4%	8.4%
Ghanjal et al., 2014	12	12.50	12.73	12	8.40	9.79	0.35	[-0.46; 1.16]	2.7%	2.7%
Heller et al., 2005	13	41.54	18.04	13	39.62	22.40	0.09	[-0.68; 0.86]	2.9%	2.9%
Holmgren et al., 2010	15	0.70	1.40	19	-1.20	4.89	0.49	[-0.20; 1.18]	3.7%	3.7%
Katz-Leurer et al., 2006	10	18.20	30.76	14	13.20	27.51	0.17	[-0.65; 0.98]	2.6%	2.6%
Kim YM et al., 2009	16	33.10	34.51	16	20.10	31.99	0.38	[-0.32; 1.08]	3.6%	3.6%
Lin Q et al., 2015	32	41.77	12.59	32	40.13	13.51	0.12	[-0.37; 0.61]	7.2%	7.2%
Merkert et al., 2011	25	27.20	22.30	23	14.10	20.00	0.61	[0.03; 1.19]	5.2%	5.2%
Nadeau et al., 2013	126	13.00	16.90	71	7.00	17.80	0.35	[0.05; 0.64]	20.3%	20.3%
Nadeau et al., 2013	139	9.80	17.20	72	7.00	17.80	0.16	[-0.12; 0.45]	21.5%	21.5%
Park HK et al., 2018	14	8.93	19.02	15	1.14	25.35	0.34	[-0.40; 1.07]	3.2%	3.2%
You et al., 2014	19	37.40	27.25	18	23.60	24.25	0.52	[-0.13; 1.18]	4.0%	4.0%
Yu et Cho, 2016	10	10.30	6.58	10	3.80	2.48	1.25	[0.27; 2.23]	1.8%	1.8%
Zhang et al., 2015	30	16.96	12.03	30	10.19	9.79	0.61	[0.09; 1.13]	6.5%	6.5%
Fixed effect model	**501**			**384**			**0.37**	**[0.24; 0.51]**	**93.7%**	**--**
Random effects model							**0.37**	**[0.24; 0.51]**	**--**	**93.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.60										
Risk of bias for incomplete outcome data : Low risk										
Dujovic et al., 2017	8	11.90	11.60	8	9.30	13.60	0.19	[-0.79; 1.18]	1.8%	1.8%
Lee SH et al., 2012	20	6.40	24.76	20	2.50	18.47	0.18	[-0.45; 0.80]	4.5%	4.5%
Fixed effect model	**28**			**28**			**0.18**	**[-0.34; 0.71]**	**6.3%**	**--**
Random effects model							**0.18**	**[-0.34; 0.71]**	**--**	**6.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.97										
Fixed effect model	**529**			**412**			**0.36**	**[0.23; 0.49]**	**100.0%**	**--**
Random effects model							**0.36**	**[0.23; 0.49]**	**--**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.71										
Residual heterogeneity: I^2 = 0%, p = 0.68										
Test for subgroup differences (fixed effect): χ^2_1 = 0.48, df = 1 (p = 0.49)										
Test for subgroup differences (random effects): χ^2_1 = 0.48, df = 1 (p = 0.49)										

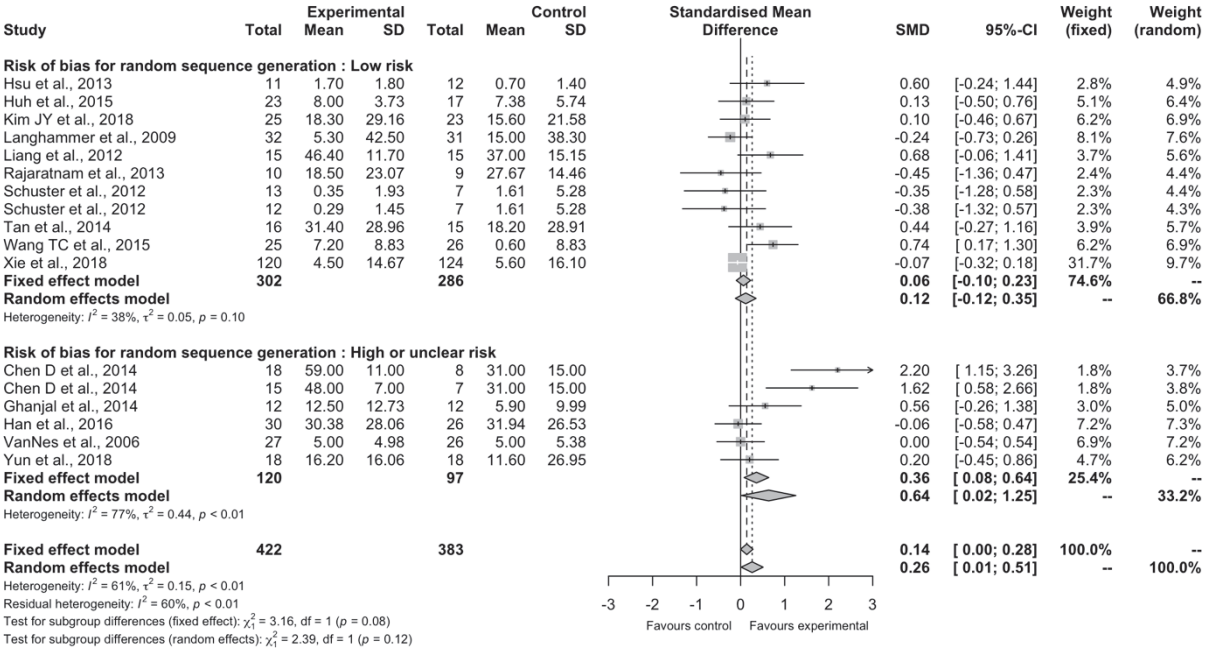


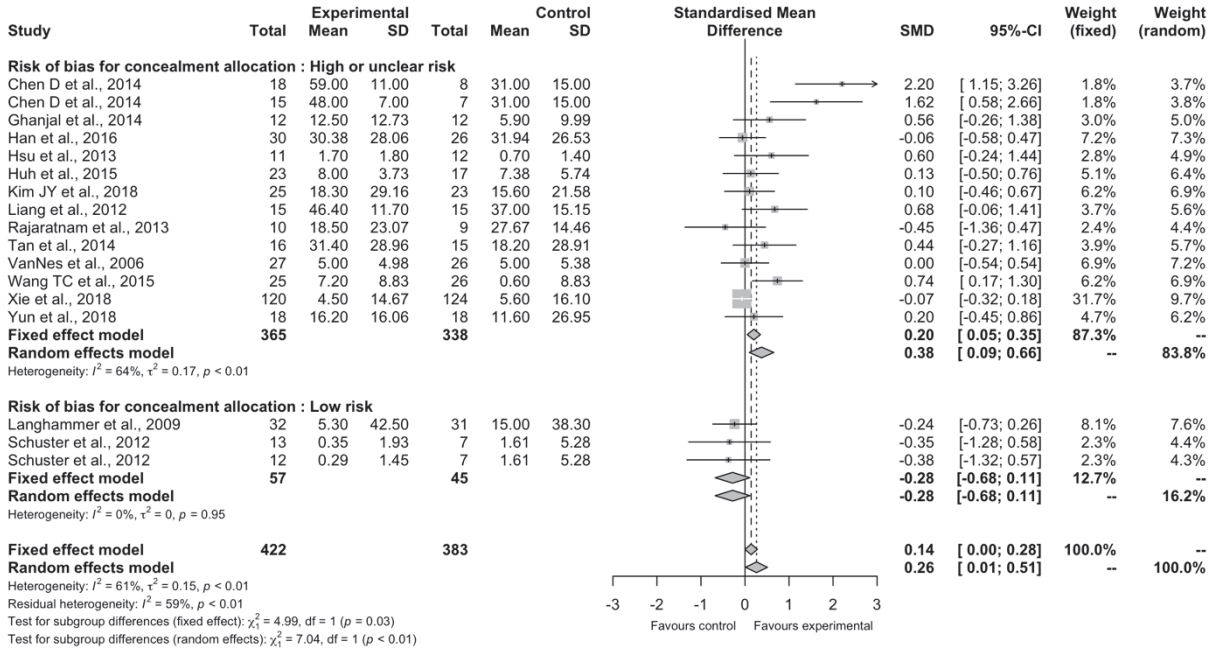

Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for blinding of patients and therapists : High or unclear risk
Cabanas-Valdes et al., 2015 40 36.50 18.81 39 23.33 16.87 0.73 [0.27; 1.19] 8.4% 8.4%
Dujovic et al., 2017 8 11.90 11.60 8 9.30 13.60 0.19 [-0.79; 1.18] 1.8% 1.8%
Ghanjal et al., 2014 12 12.50 12.73 12 8.40 9.79 0.35 [-0.46; 1.16] 2.7% 2.7%
Heller et al., 2005 13 41.54 18.04 13 39.62 22.40 0.09 [-0.68; 0.86] 2.9% 2.9%
Holmgren et al., 2010 15 0.70 1.40 19 -1.20 4.89 0.49 [-0.20; 1.18] 3.7% 3.7%
Katz-Leurer et al., 2006 10 18.20 30.76 14 13.20 27.51 0.17 [-0.65; 0.98] 2.6% 2.6%
Kim YM et al., 2009 16 33.10 34.51 16 20.10 31.99 0.38 [-0.32; 1.08] 3.6% 3.6%
Lee SH et al., 2012 20 6.40 24.76 20 2.50 18.47 0.18 [-0.45; 0.80] 4.5% 4.5%
Lin Q et al., 2015 32 41.77 12.59 32 40.13 13.51 0.12 [-0.37; 0.61] 7.2% 7.2%
Merkert et al., 2011 25 27.20 22.30 23 14.10 20.00 0.61 [0.03; 1.19] 5.2% 5.2%
Nadeau et al., 2013 126 13.00 16.90 71 7.00 17.80 0.35 [0.05; 0.64] 20.3% 20.3%
Nadeau et al., 2013 139 9.80 17.20 72 7.00 17.80 0.16 [-0.12; 0.45] 21.5% 21.5%
Park HK et al., 2018 14 8.93 19.02 15 1.14 25.35 0.34 [-0.40; 1.07] 3.2% 3.2%
You et al., 2014 19 37.40 27.25 18 23.60 24.25 0.52 [-0.13; 1.18] 4.0% 4.0%
Yu et Cho, 2016 10 10.30 6.58 10 3.80 2.48 1.25 [0.27; 2.23] 1.8% 1.8%
Zhang et al., 2015 30 16.96 12.03 30 10.19 9.79 0.61 [0.09; 1.13] 6.5% 6.5%
Fixed effect model 529 412 0.36 [0.23; 0.49] 100.0% --
Random effects model 0.36 [0.23; 0.49] -- 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.71
Fixed effect model 529 412 0.36 [0.23; 0.49] 100.0% --
Random effects model 0.36 [0.23; 0.49] -- 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.71
Residual heterogeneity: I^2 = 0%, p = 0.71
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

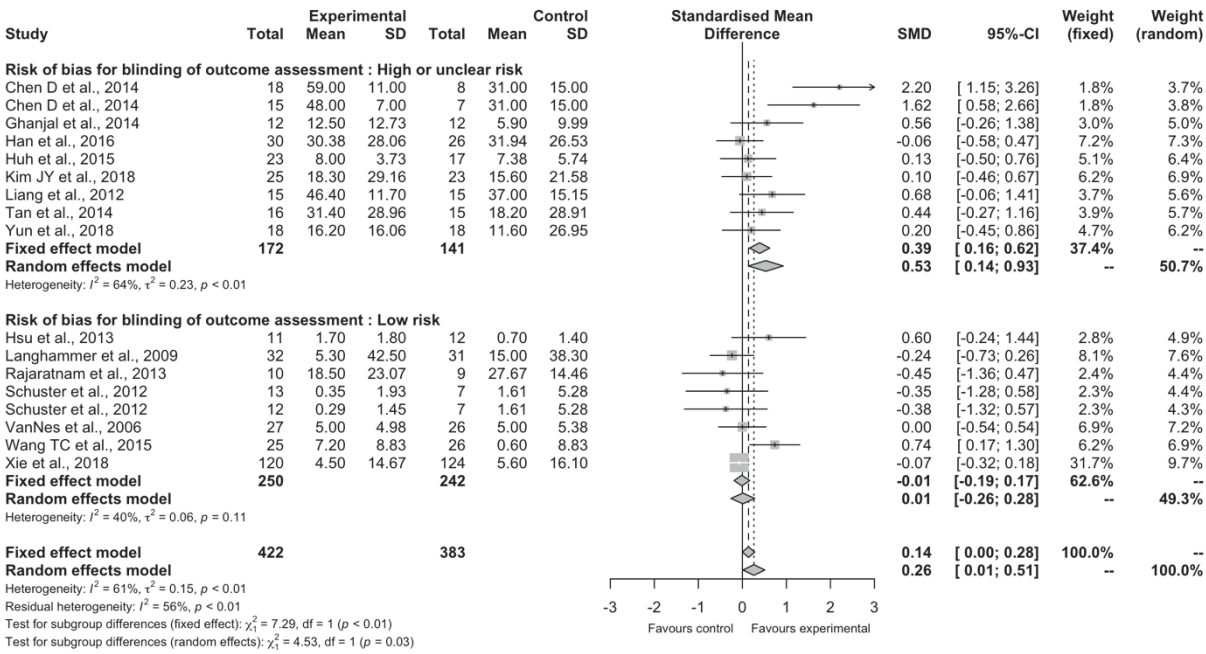

Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for selective reporting : High or unclear risk
Ghanjal et al., 2014 12 12.50 12.73 12 8.40 9.79 0.35 [-0.46; 1.16] 2.7% 2.7%
Heller et al., 2005 13 41.54 18.04 13 39.62 22.40 0.09 [-0.68; 0.86] 2.9% 2.9%
Holmgren et al., 2010 15 0.70 1.40 19 -1.20 4.89 0.49 [-0.20; 1.18] 3.7% 3.7%
Katz-Leurer et al., 2006 10 18.20 30.76 14 13.20 27.51 0.17 [-0.65; 0.98] 2.6% 2.6%
Kim YM et al., 2009 16 33.10 34.51 16 20.10 31.99 0.38 [-0.32; 1.08] 3.6% 3.6%
Lee SH et al., 2012 20 6.40 24.76 20 2.50 18.47 0.18 [-0.45; 0.80] 4.5% 4.5%
Lin Q et al., 2015 32 41.77 12.59 32 40.13 13.51 0.12 [-0.37; 0.61] 7.2% 7.2%
Merkert et al., 2011 25 27.20 22.30 23 14.10 20.00 0.61 [0.03; 1.19] 5.2% 5.2%
Park HK et al., 2018 14 8.93 19.02 15 1.14 25.35 0.34 [-0.40; 1.07] 3.2% 3.2%
You et al., 2014 19 37.40 27.25 18 23.60 24.25 0.52 [-0.13; 1.18] 4.0% 4.0%
Yu et Cho, 2016 10 10.30 6.58 10 3.80 2.48 1.25 [0.27; 2.23] 1.8% 1.8%
Zhang et al., 2015 30 16.96 12.03 30 10.19 9.79 0.61 [0.09; 1.13] 6.5% 6.5%
Fixed effect model 216 222 0.40 [0.21; 0.59] 48.0% --
Random effects model 0.40 [0.21; 0.59] -- 48.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.80
Risk of bias for selective reporting : Low risk
Cabanas-Valdes et al., 2015 40 36.50 18.81 39 23.33 16.87 0.73 [0.27; 1.19] 8.4% 8.4%
Dujovic et al., 2017 8 11.90 11.60 8 9.30 13.60 0.19 [-0.79; 1.18] 1.8% 1.8%
Nadeau et al., 2013 126 13.00 16.90 71 7.00 17.80 0.35 [0.05; 0.64] 20.3% 20.3%
Nadeau et al., 2013 139 9.80 17.20 72 7.00 17.80 0.16 [-0.12; 0.45] 21.5% 21.5%
Fixed effect model 313 190 0.33 [0.14; 0.51] 52.0% --
Random effects model 0.35 [0.11; 0.59] -- 52.0%
Heterogeneity: I^2 = 32%, τ^2 = 0.02, p = 0.22
Fixed effect model 529 412 0.36 [0.23; 0.49] 100.0% --
Random effects model 0.36 [0.23; 0.49] -- 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.71
Residual heterogeneity: I^2 = 0%, p = 0.66
Test for subgroup differences (fixed effect): χ^2_1 = 0.28, df = 1 (p = 0.60)
Test for subgroup differences (random effects): χ^2_1 = 0.10, df = 1 (p = 0.75)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

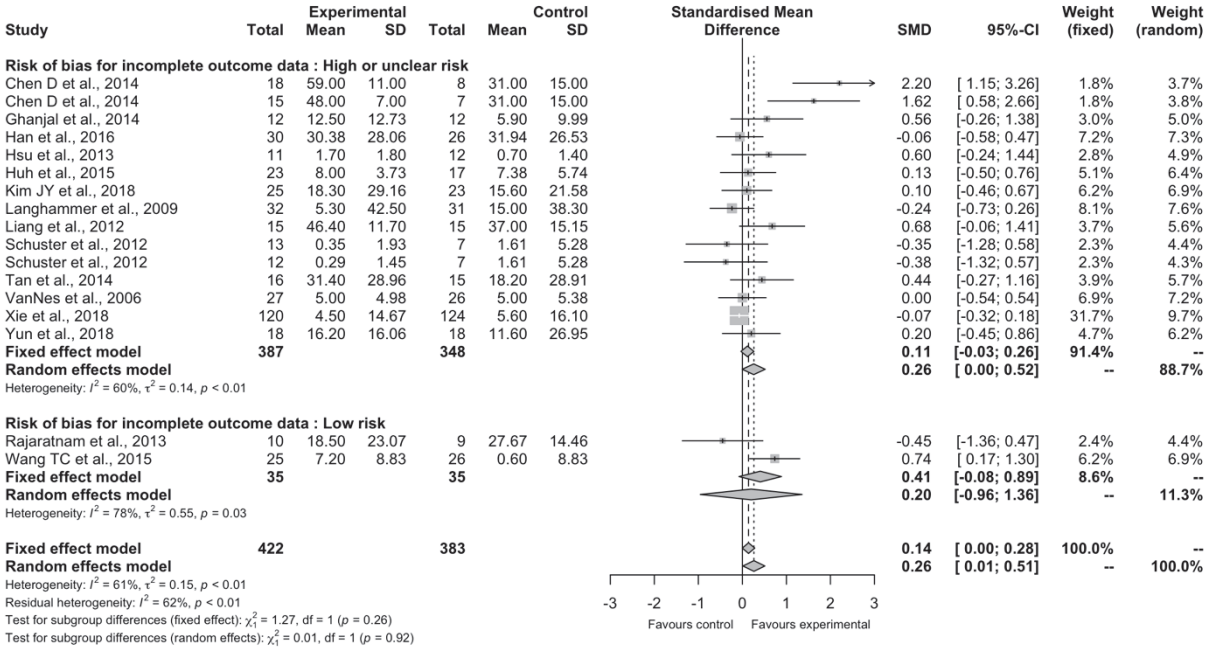

Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for other bias : Low risk
Cabanas-Valdes et al., 2015 40 36.50 18.81 39 23.33 16.87 0.73 [0.27; 1.19] 8.4% 8.4%
Dujovic et al., 2017 8 11.90 11.60 8 9.30 13.60 0.19 [-0.79; 1.18] 1.8% 1.8%
Ghanjal et al., 2014 12 12.50 12.73 12 8.40 9.79 0.35 [-0.46; 1.16] 2.7% 2.7%
Heller et al., 2005 13 41.54 18.04 13 39.62 22.40 0.09 [-0.68; 0.86] 2.9% 2.9%
Holmgren et al., 2010 15 0.70 1.40 19 -1.20 4.89 0.49 [-0.20; 1.18] 3.7% 3.7%
Katz-Leurer et al., 2006 10 18.20 30.76 14 13.20 27.51 0.17 [-0.65; 0.98] 2.6% 2.6%
Kim YM et al., 2009 16 33.10 34.51 16 20.10 31.99 0.38 [-0.32; 1.08] 3.6% 3.6%
Lee SH et al., 2012 20 6.40 24.76 20 2.50 18.47 0.18 [-0.45; 0.80] 4.5% 4.5%
Lin Q et al., 2015 32 41.77 12.59 32 40.13 13.51 0.12 [-0.37; 0.61] 7.2% 7.2%
Merkert et al., 2011 25 27.20 22.30 23 14.10 20.00 0.61 [0.03; 1.19] 5.2% 5.2%
Nadeau et al., 2013 126 13.00 16.90 71 7.00 17.80 0.35 [0.05; 0.64] 20.3% 20.3%
Nadeau et al., 2013 139 9.80 17.20 72 7.00 17.80 0.16 [-0.12; 0.45] 21.5% 21.5%
Park HK et al., 2018 14 8.93 19.02 15 1.14 25.35 0.34 [-0.40; 1.07] 3.2% 3.2%
You et al., 2014 19 37.40 27.25 18 23.60 24.25 0.52 [-0.13; 1.18] 4.0% 4.0%
Yu et Cho, 2016 10 10.30 6.58 10 3.80 2.48 1.25 [0.27; 2.23] 1.8% 1.8%
Zhang et al., 2015 30 16.96 12.03 30 10.19 9.79 0.61 [0.09; 1.13] 6.5% 6.5%
Fixed effect model 529 412 0.36 [0.23; 0.49] 100.0% --
Random effects model 0.36 [0.23; 0.49] -- 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.71
Fixed effect model 529 412 0.36 [0.23; 0.49] 100.0% --
Random effects model 0.36 [0.23; 0.49] -- 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.71
Residual heterogeneity: I^2 = 0%, p = 0.71
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

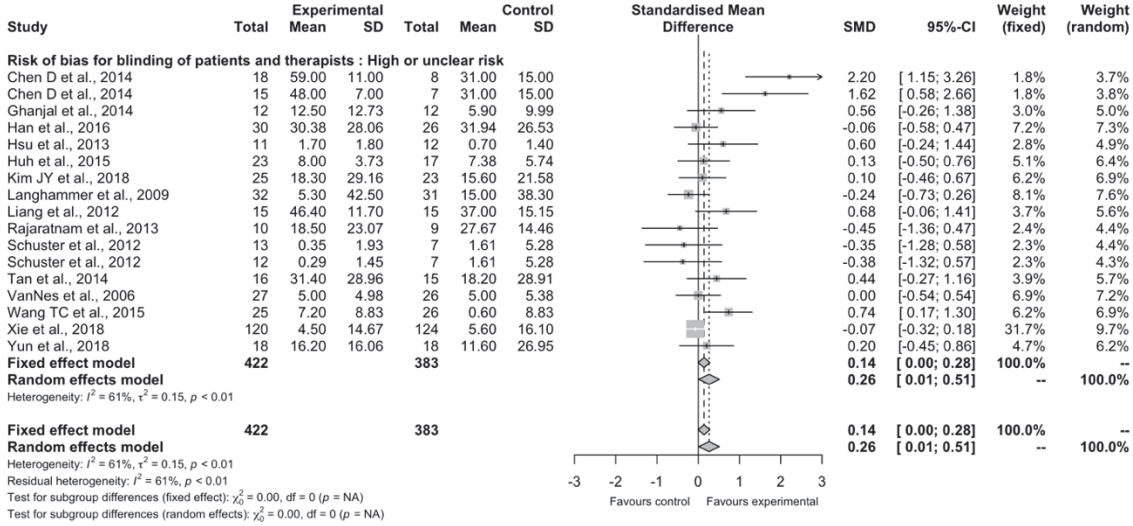
S13 Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Autonomy, post-intervention effects. Subgroup: risk of bias

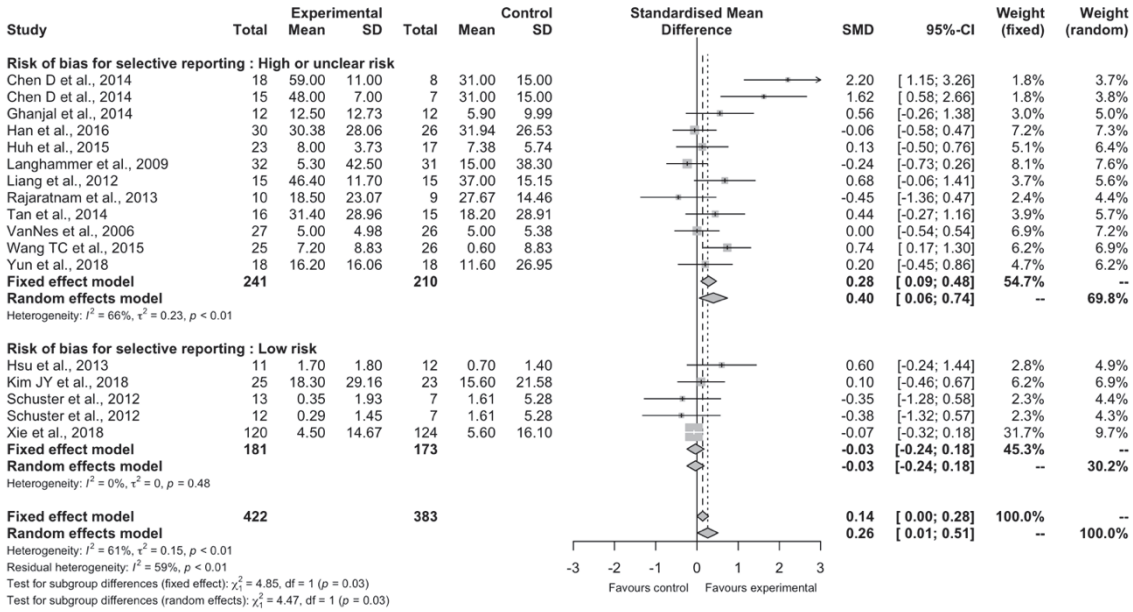


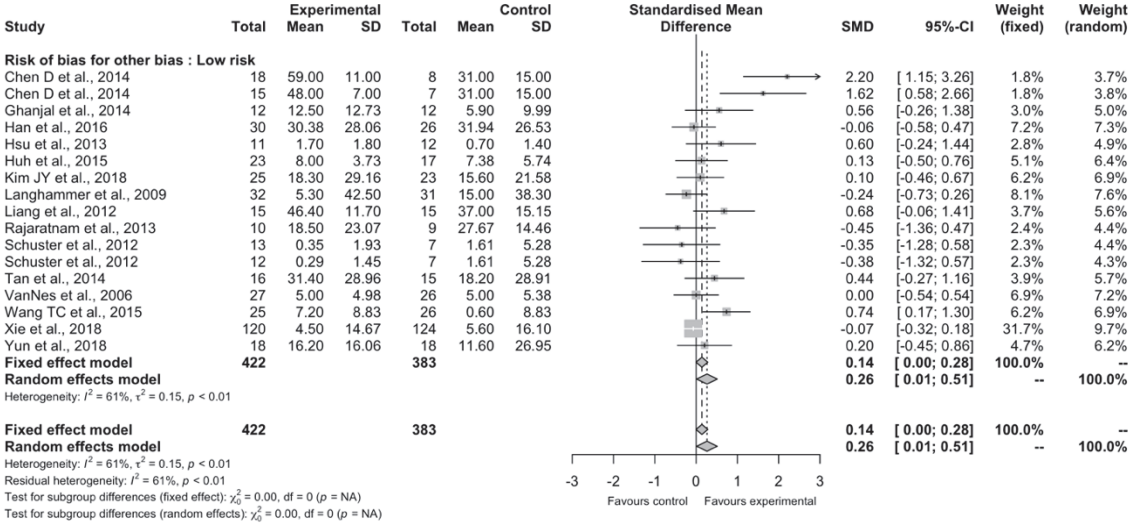



Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for blinding of outcome assessment : High or unclear risk
Chen D et al., 2014 18 59.00 11.00 8 31.00 15.00 2.20 [1.15; 3.26] 1.8% 3.7%
Chen D et al., 2014 15 48.00 7.00 7 31.00 15.00 1.62 [0.58; 2.66] 1.8% 3.8%
Ghanjal et al., 2014 12 12.50 12.73 12 5.90 9.99 0.56 [-0.26; 1.38] 3.0% 5.0%
Han et al., 2016 30 30.38 28.06 26 31.94 26.53 -0.06 [-0.58; 0.47] 7.2% 7.3%
Huh et al., 2015 23 8.00 3.73 17 7.38 5.74 0.13 [-0.50; 0.76] 5.1% 6.4%
Kim JY et al., 2018 25 18.30 29.16 23 15.60 21.58 0.10 [-0.46; 0.67] 6.2% 6.9%
Liang et al., 2012 15 46.40 11.70 15 37.00 15.15 0.68 [-0.06; 1.41] 3.7% 5.6%
Tan et al., 2014 16 31.40 28.96 15 18.20 28.91 0.44 [-0.27; 1.16] 3.9% 5.7%
Yun et al., 2018 18 16.20 16.06 18 11.60 26.95 0.20 [-0.45; 0.86] 4.7% 6.2%
Fixed effect model 172 141 0.39 [0.16; 0.62] 37.4% --
Random effects model 0.53 [0.14; 0.93] -- 50.7%
Heterogeneity: I^2 = 64%, τ^2 = 0.23, p < 0.01
Risk of bias for blinding of outcome assessment : Low risk
Hsu et al., 2013 11 1.70 1.80 12 0.70 1.40 0.60 [-0.24; 1.44] 2.8% 4.9%
Langhammer et al., 2009 32 5.30 42.50 31 15.00 38.30 -0.24 [-0.73; 0.26] 8.1% 7.6%
Rajaratnam et al., 2013 10 18.50 23.07 9 27.67 14.46 -0.45 [-1.36; 0.47] 2.4% 4.4%
Schuster et al., 2012 13 0.35 1.93 7 1.61 5.28 -0.35 [-1.28; 0.58] 2.3% 4.4%
Schuster et al., 2012 12 0.29 1.45 7 1.61 5.28 -0.38 [-1.32; 0.57] 2.3% 4.3%
VanNes et al., 2006 27 5.00 4.98 26 5.00 5.38 0.00 [-0.54; 0.54] 6.9% 7.2%
Wang TC et al., 2015 25 7.20 8.83 26 0.60 8.83 0.74 [0.17; 1.30] 6.2% 6.9%
Xie et al., 2018 120 4.50 14.67 124 5.60 16.10 -0.07 [-0.32; 0.18] 31.7% 9.7%
Fixed effect model 250 242 -0.01 [-0.19; 0.17] 62.6% --
Random effects model 0.01 [-0.26; 0.28] -- 49.3%
Heterogeneity: I^2 = 40%, τ^2 = 0.06, p = 0.11
Fixed effect model 422 383 0.14 [0.00; 0.28] 100.0% --
Random effects model 0.26 [0.01; 0.51] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.15, p < 0.01
Residual heterogeneity: I^2 = 56%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 7.29, df = 1 (p < 0.01)
Test for subgroup differences (random effects): χ^2_1 = 4.53, df = 1 (p = 0.03)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for incomplete outcome data : High or unclear risk
Chen D et al., 2014 18 59.00 11.00 8 31.00 15.00 2.20 [1.15; 3.26] 1.8% 3.7%
Chen D et al., 2014 15 48.00 7.00 7 31.00 15.00 1.62 [0.58; 2.66] 1.8% 3.8%
Ghanjal et al., 2014 12 12.50 12.73 12 5.90 9.99 0.56 [-0.26; 1.38] 3.0% 5.0%
Han et al., 2016 30 30.38 28.06 26 31.94 26.53 -0.06 [-0.58; 0.47] 7.2% 7.3%
Hsu et al., 2013 11 1.70 1.80 12 0.70 1.40 0.60 [-0.24; 1.44] 2.8% 4.9%
Huh et al., 2015 23 8.00 3.73 17 7.38 5.74 0.13 [-0.50; 0.76] 5.1% 6.4%
Kim JY et al., 2018 25 18.30 29.16 23 15.60 21.58 0.10 [-0.46; 0.67] 6.2% 6.9%
Langhammer et al., 2009 32 5.30 42.50 31 15.00 38.30 -0.24 [-0.73; 0.26] 8.1% 7.6%
Liang et al., 2012 15 46.40 11.70 15 37.00 15.15 0.68 [-0.06; 1.41] 3.7% 5.6%
Schuster et al., 2012 13 0.35 1.93 7 1.61 5.28 -0.35 [-1.28; 0.58] 2.3% 4.4%
Schuster et al., 2012 12 0.29 1.45 7 1.61 5.28 -0.38 [-1.32; 0.57] 2.3% 4.3%
Tan et al., 2014 16 31.40 28.96 15 18.20 28.91 0.44 [-0.27; 1.16] 3.9% 5.7%
VanNes et al., 2006 27 5.00 4.98 26 5.00 5.38 0.00 [-0.54; 0.54] 6.9% 7.2%
Xie et al., 2018 120 4.50 14.67 124 5.60 16.10 -0.07 [-0.32; 0.18] 31.7% 9.7%
Yun et al., 2018 18 16.20 16.06 18 11.60 26.95 0.20 [-0.45; 0.86] 4.7% 6.2%
Fixed effect model 387 348 0.11 [-0.03; 0.26] 91.4% --
Random effects model 0.26 [0.00; 0.52] -- 88.7%
Heterogeneity: I^2 = 60%, τ^2 = 0.14, p < 0.01
Risk of bias for incomplete outcome data : Low risk
Rajaratnam et al., 2013 10 18.50 23.07 9 27.67 14.46 -0.45 [-1.36; 0.47] 2.4% 4.4%
Wang TC et al., 2015 25 7.20 8.83 26 0.60 8.83 0.74 [0.17; 1.30] 6.2% 6.9%
Fixed effect model 35 35 0.41 [-0.08; 0.89] 8.6% --
Random effects model 0.20 [-0.96; 1.36] -- 11.3%
Heterogeneity: I^2 = 78%, τ^2 = 0.55, p = 0.03
Fixed effect model 422 383 0.14 [0.00; 0.28] 100.0% --
Random effects model 0.26 [0.01; 0.51] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.15, p < 0.01
Residual heterogeneity: I^2 = 62%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 1.27, df = 1 (p = 0.26)
Test for subgroup differences (random effects): χ^2_1 = 0.01, df = 1 (p = 0.92)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for blinding of patients and therapists : High or unclear risk
Chen D et al., 2014 18 59.00 11.00 8 31.00 15.00 2.20 [1.15; 3.26] 1.8% 3.7%
Chen D et al., 2014 15 48.00 7.00 7 31.00 15.00 1.62 [0.58; 2.66] 1.8% 3.8%
Ghanjal et al., 2014 12 12.50 12.73 12 5.90 9.99 0.56 [-0.26; 1.38] 3.0% 5.0%
Han et al., 2016 30 30.38 28.06 26 31.94 26.53 -0.06 [-0.58; 0.47] 7.2% 7.3%
Hsu et al., 2013 11 1.70 1.80 12 0.70 1.40 0.60 [-0.24; 1.44] 2.8% 4.9%
Huh et al., 2015 23 8.00 3.73 17 7.38 5.74 0.13 [-0.50; 0.76] 5.1% 6.4%
Kim JY et al., 2018 25 18.30 29.16 23 15.60 21.58 0.10 [-0.46; 0.67] 6.2% 6.9%
Langhammer et al., 2009 32 5.30 42.50 31 15.00 38.30 -0.24 [-0.73; 0.26] 8.1% 7.6%
Liang et al., 2012 15 46.40 11.70 15 37.00 15.15 0.68 [-0.06; 1.41] 3.7% 5.6%
Rajaratnam et al., 2013 10 18.50 23.07 9 27.67 14.46 -0.45 [-1.36; 0.47] 2.4% 4.4%
Schuster et al., 2012 13 0.35 1.93 7 1.61 5.28 -0.35 [-1.28; 0.58] 2.3% 4.4%
Schuster et al., 2012 12 0.29 1.45 7 1.61 5.28 -0.38 [-1.32; 0.57] 2.3% 4.3%
Tan et al., 2014 16 31.40 28.96 15 18.20 28.91 0.44 [-0.27; 1.16] 3.9% 5.7%
VanNes et al., 2006 27 5.00 4.98 26 5.00 5.38 0.00 [-0.54; 0.54] 6.9% 7.2%
Wang TC et al., 2015 25 7.20 8.83 26 0.60 8.83 0.74 [0.17; 1.30] 6.2% 6.9%
Xie et al., 2018 120 4.50 14.67 124 5.60 16.10 -0.07 [-0.32; 0.18] 31.7% 9.7%
Yun et al., 2018 18 16.20 16.06 18 11.60 26.95 0.20 [-0.45; 0.86] 4.7% 6.2%
Fixed effect model 422 383 0.14 [0.00; 0.28] 100.0% --
Random effects model 0.26 [0.01; 0.51] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.15, p < 0.01
Fixed effect model 422 383 0.14 [0.00; 0.28] 100.0% --
Random effects model 0.26 [0.01; 0.51] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.15, p < 0.01
Residual heterogeneity: I^2 = 61%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for selective reporting : High or unclear risk
Chen D et al., 2014 18 59.00 11.00 8 31.00 15.00 2.20 [1.15; 3.26] 1.8% 3.7%
Chen D et al., 2014 15 48.00 7.00 7 31.00 15.00 1.62 [0.58; 2.66] 1.8% 3.8%
Ghanjal et al., 2014 12 12.50 12.73 12 5.90 9.99 0.56 [-0.26; 1.38] 3.0% 5.0%
Han et al., 2016 30 30.38 28.06 26 31.94 26.53 -0.06 [-0.58; 0.47] 7.2% 7.3%
Huh et al., 2015 23 8.00 3.73 17 7.38 5.74 0.13 [-0.50; 0.76] 5.1% 6.4%
Langhammer et al., 2009 32 5.30 42.50 31 15.00 38.30 -0.24 [-0.73; 0.26] 8.1% 7.6%
Liang et al., 2012 15 46.40 11.70 15 37.00 15.15 0.68 [-0.06; 1.41] 3.7% 5.6%
Rajaratnam et al., 2013 10 18.50 23.07 9 27.67 14.46 -0.45 [-1.36; 0.47] 2.4% 4.4%
Tan et al., 2014 16 31.40 28.96 15 18.20 28.91 0.44 [-0.27; 1.16] 3.9% 5.7%
VanNes et al., 2006 27 5.00 4.98 26 5.00 5.38 0.00 [-0.54; 0.54] 6.9% 7.2%
Wang TC et al., 2015 25 7.20 8.83 26 0.60 8.83 0.74 [0.17; 1.30] 6.2% 6.9%
Yun et al., 2018 18 16.20 16.06 18 11.60 26.95 0.20 [-0.45; 0.86] 4.7% 6.2%
Fixed effect model 241 210 0.28 [0.09; 0.48] 54.7% --
Random effects model 0.40 [0.06; 0.74] -- 69.8%
Heterogeneity: I^2 = 66%, τ^2 = 0.23, p < 0.01
Risk of bias for selective reporting : Low risk
Hsu et al., 2013 11 1.70 1.80 12 0.70 1.40 0.60 [-0.24; 1.44] 2.8% 4.9%
Kim JY et al., 2018 25 18.30 29.16 23 15.60 21.58 0.10 [-0.46; 0.67] 6.2% 6.9%
Schuster et al., 2012 13 0.35 1.93 7 1.61 5.28 -0.35 [-1.28; 0.58] 2.3% 4.4%
Schuster et al., 2012 12 0.29 1.45 7 1.61 5.28 -0.38 [-1.32; 0.57] 2.3% 4.3%
Xie et al., 2018 120 4.50 14.67 124 5.60 16.10 -0.07 [-0.32; 0.18] 31.7% 9.7%
Fixed effect model 181 173 -0.03 [-0.24; 0.18] 45.3% --
Random effects model -0.03 [-0.24; 0.18] -- 30.2%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.48
Fixed effect model 422 383 0.14 [0.00; 0.28] 100.0% --
Random effects model 0.26 [0.01; 0.51] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.15, p < 0.01
Residual heterogeneity: I^2 = 59%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_1 = 4.85, df = 1 (p = 0.03)
Test for subgroup differences (random effects): χ^2_1 = 4.47, df = 1 (p = 0.03)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental


Experimental
Control
Standardised Mean Difference
Weight (fixed)
Weight (random)
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%-CI
Risk of bias for other bias : Low risk
Chen D et al., 2014 18 59.00 11.00 8 31.00 15.00 2.20 [1.15; 3.26] 1.8% 3.7%
Chen D et al., 2014 15 48.00 7.00 7 31.00 15.00 1.62 [0.58; 2.66] 1.8% 3.8%
Ghanjal et al., 2014 12 12.50 12.73 12 5.90 9.99 0.56 [-0.26; 1.38] 3.0% 5.0%
Han et al., 2016 30 30.38 28.06 26 31.94 26.53 -0.06 [-0.58; 0.47] 7.2% 7.3%
Hsu et al., 2013 11 1.70 1.80 12 0.70 1.40 0.60 [-0.24; 1.44] 2.8% 4.9%
Huh et al., 2015 23 8.00 3.73 17 7.38 5.74 0.13 [-0.50; 0.76] 5.1% 6.4%
Kim JY et al., 2018 25 18.30 29.16 23 15.60 21.58 0.10 [-0.46; 0.67] 6.2% 6.9%
Langhammer et al., 2009 32 5.30 42.50 31 15.00 38.30 -0.24 [-0.73; 0.26] 8.1% 7.6%
Liang et al., 2012 15 46.40 11.70 15 37.00 15.15 0.68 [-0.06; 1.41] 3.7% 5.6%
Rajaratnam et al., 2013 10 18.50 23.07 9 27.67 14.46 -0.45 [-1.36; 0.47] 2.4% 4.4%
Schuster et al., 2012 13 0.35 1.93 7 1.61 5.28 -0.35 [-1.28; 0.58] 2.3% 4.4%
Schuster et al., 2012 12 0.29 1.45 7 1.61 5.28 -0.38 [-1.32; 0.57] 2.3% 4.3%
Tan et al., 2014 16 31.40 28.96 15 18.20 28.91 0.44 [-0.27; 1.16] 3.9% 5.7%
VanNes et al., 2006 27 5.00 4.98 26 5.00 5.38 0.00 [-0.54; 0.54] 6.9% 7.2%
Wang TC et al., 2015 25 7.20 8.83 26 0.60 8.83 0.74 [0.17; 1.30] 6.2% 6.9%
Xie et al., 2018 120 4.50 14.67 124 5.60 16.10 -0.07 [-0.32; 0.18] 31.7% 9.7%
Yun et al., 2018 18 16.20 16.06 18 11.60 26.95 0.20 [-0.45; 0.86] 4.7% 6.2%
Fixed effect model 422 383 0.14 [0.00; 0.28] 100.0% --
Random effects model 0.26 [0.01; 0.51] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.15, p < 0.01
Fixed effect model 422 383 0.14 [0.00; 0.28] 100.0% --
Random effects model 0.26 [0.01; 0.51] -- 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.15, p < 0.01
Residual heterogeneity: I^2 = 61%, p < 0.01
Test for subgroup differences (fixed effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)
-3 -2 -1 0 1 2 3
Favours control
Favours experimental

MATERIEL SUPPLEMENTAIRE DE L'ARTICLE 3 – HUGUES *ET AL.*, 2020

S1 Table. Studies included in the systematic review and meta-analysis

S1A Table. Identification of studies included in the systematic review and meta-analysis
Se reporter à S2 Table dans matériel supplémentaire de l'article 2 – Hugues *et al.*, 2019

S1B Table. Publication language of included studies

Study	Language	Study	Language
Allison et Dennett, 2007	English	Liang et al., 2012	English
Arabzadeh et al., 2018	English	Lin Q et al., 2015	Chinese
Askim et al., 2010	English	Lindvall et Forsberg, 2014	English
Au-Yeung et al., 2009	English	Lisinski et al., 2012	English
Bae et al., 2015	English	Liu-Ambrose et Eng, 2015	English
Barcala et al., 2011	Portuguese	Lu et al., 1997	English
Brogardh et al., 2012	English	Lynch et al., 2007	English
Bunketorp-Kall et al., 2017	English	Marin et al., 2013	English
Buyukavci et al., 2016	English	Merkert et al., 2011	English
Buyukvural Sen et al., 2015	English	Milczarek et al., 1993	English
Cabanas-Valdes et al., 2015	English	Mojica et al., 1988	English
Chan KS et al., 2012	English	Moore JL et al., 2010	English
Chen CH et al., 2010	English	Morioka et Yagi, 2003	English
Chen CL et al., 2015	English	Mudie et al., 2002	English
Chen D et al., 2014	Chinese	Nadeau et al., 2013	English
Chen IC et al., 2002	English	Ng et al., 2016	English
Chen JC et al., 2011	English	Nikamp et al., 2017	English
Chen, 2018	English	Noh et al., 2008	English
Chern et al., 2013	English	Ordahan et al., 2015	English
Cho HY et al., 2013	English	Page et al., 2008	English
Cho KH et al., 2012	English	Park D et al., 2018	English
Cho MK et al., 2015	English	Park DS et al., 2017	English
Choi HS et al., 2017	English	Park et al., 2014	English
Chu et al., 2015	Chinese	Park HK et al., 2018	English
Chung et al., 2014	English	Park J et al., 2017	English
Dault et al., 2003	English	Pollock et al., 2002	English
Dujovic et al., 2017	English	Pomeroy et al., 2001	English
Duncan et al., 1998	English	Rajaratnam et al., 2013	English
Duncan et al., 2003	English	Robertson et al., 2010	English
Erbil et al., 2018	English	Rougier et Boudrahem, 2010	English
Fernandez-Gonzalo et al., 2016	English	Salgueiro et Marquez, 2018	Spanish
Ferreira et al., 2017	English	Sanchez-Mila et al., 2018	English
Fritz et al., 2013	English	Schmid et al., 2012	English
Furnari et al., 2014	English	Schuster et al., 2012	English
Geiger et al., 2001	English	Shatil et al., 2005	English
Ghanjal et al., 2014	Persian	Shin et al., 2016	English
Globas et al., 2012	English	Simons et al., 2009	English
Goliwas et al., 2017	English	Sohn et al., 2015	English
Han et al., 2016	English	Song et al., 2014	English
Hart et al., 2004	English	Stein et al., 2014	English
Heller et al., 2005	English	Suh et al., 2014	English
Hollands et al., 2015	English	Tan et al., 2014	English

Holmgren et al., 2010	English	Tan et al., 2016	Chinese
Hosseini et al., 2012	English	Tian et al., 2014	Chinese
Howe et al., 2005	English	Tilikete et al., 2001	English
Hsieh, 2019	English	Tripp and Krakow, 2014	English
Hsu et al., 2013	English	Tung et al., 2010	English
Huh et al., 2015	English	Vahlberg et al., 2017	English
Hung et al., 2016	English	VanNes et al., 2006	English
Hwang et al., 2015	English	Waldron et Bohannon, 1989	English
Immink et al., 2014	English	Wang et al., 2017	English
In et al., 2016	English	Wang RY, Lin PY et al., 2007	English
Janssen et al., 2008	English	Wang RY, Yen LL et al., 2005 part 1	English
Jung et al., 2015	English	Wang RY, Yen LL et al., 2005 part 2	English
Jung et al., 2017	English	Wang TC et al., 2015	English
Kamps et Schule, 2005	English	Xie et al., 2018	English
Karasu et al., 2018	English	Xing et al., 2007	Chinese
Katz-Leurer et al., 2006	English	Yadav et al., 2015	English
Khumsapsiri et al., 2018	English	Yeung et al., 2018	English
Kilinc et al., 2015	English	Yoo et al., 2010	English
Kim DH et al., 2008	Korean	Yoo et al., 2018	English
Kim JC et Lee, 2018	English	You et al., 2014	English
Kim JH et al., 2009	English	Yu et Cho, 2016	English
Kim JY et al., 2018	English	Yun et al., 2018	English
Kim SL et Lee, 2018	English	Zhang et al., 2015	Chinese
Kim YH et al., 2004	Korean		
Kim YM et al., 2009	Korean		
Knox et al., 2018	English		
Kunkel et al., 2013	English		
Kwong et al., 2018	English		
Langhammer et al., 2009	English		
Lau RWK et al., 2012	English		
Laufer, 2003	English		
Lee CH et al., 2014	English		
Lee D et al., 2016	English		
Lee HJ et al., 2018	English		
Lee MM et al., 2018	English		
Lee NK et al., 2013	English		
Lee SH et al., 2012	English		
Lee SW et al., 2013	English		

S1C Table. Summary of publication language of included studies

Language of publication	Number of studies
English	132
Chinese	7
Korean	3
Persian	1
Portuguese	1
Spanish	1

S2 Table. Summary of risk of bias of studies included

SPEL only			
Risk of bias	Number of studies with high risk	Number of studies with unclear risk	Number of studies with low risk
Random sequence generation, n (%)	0 (0%)	58 (44%)	74 (56%)
Allocation concealment, n (%)	18 (14%)	95 (72%)	19 (14%)
Blinding of outcome assessment, n (%)	13 (10%)	55 (42%)	64 (48%)
Incomplete outcome data, n (%)	71 (54%)	36 (27%)	25 (19%)
Blinding of patients and therapists, n (%)	116 (88%)	14 (11%)	2 (1%)
Selective reporting, n (%)	20 (15%)	89 (68%)	23 (17%)
Other bias, n (%)	2 (2%)	8 (6%)	122 (92%)

SPNEL only			
Risk of bias	Number of studies with high risk	Number of studies with unclear risk	Number of studies with low risk
Random sequence generation, n (%)	0 (0%)	7 (54%)	6 (46%)
Allocation concealment, n (%)	0 (0%)	13 (100%)	0 (0%)
Blinding of outcome assessment, n (%)	0 (0%)	13 (100%)	0 (0%)
Incomplete outcome data, n (%)	3 (23%)	10 (77%)	0 (0%)
Blinding of patients and therapists, n (%)	13 (100%)	0 (0%)	0 (0%)
Selective reporting, n (%)	2 (15%)	11 (85%)	0 (0%)
Other bias, n (%)	0 (0%)	2 (15%)	11 (85%)

Difference between SPEL and SPNEL: p-value of Chi^2 test		
Item of risk of bias	Low risk versus high and unclear risks	Proportion of unclear
Random sequence generation, n (%)	p=0.69	p=0.69
Allocation concealment, n (%)	p=0.30	p=0.06
Blinding of outcome assessment, n (%)	p=0.002*	p<0.001*
Incomplete outcome data, n (%)	p=0.18	p<0.001*
Blinding of patients and therapists, n (%)	p=1.00	p=0.46
Selective reporting, n (%)	p=0.21	p=0.34
Other bias, n (%)	p=0.65	p=0.49

* Significant difference ($p \leq 0.05$) between SPEL and SPNEL

SPEL, studies published in English language; SPNEL, studies published in non-English language

S3 Table. Summary of overall score of risk of bias

Overall score of risk of bias	Mean (SD)	Median	Min-max	Wilcoxon rank sum test
SPEL	7.67 (1.53)	8	3-12	0.07
SPNEL	6.92 (0.86)	7	6-8	

SPEL, studies published in English language; SPNEL, studies published in non-English language

S4 Table. Results of Egger tests detecting bias of publication for all studies (SPEL and SPNEL)

Comparison	Outcome	Post-intervention or persisting effects	Number of points	P value
PT vs NT	Balance	Post-intervention effects	40	0.10
PT vs NT	Mediolateral postural deviation EO, crossover RCTs	Post-intervention effects	16	0.70
PT vs NT	Postural stability EO	Post-intervention effects	18	0.44
PT vs NT	Autonomy	Post-intervention effects	16	0.33
PT vs NT	Balance	Persisting effects	12	0.93
PT vs NT	Mediolateral postural deviation EO	Persisting effects	5	0.45
PT vs NT	Postural stability EO	Persisting effects	3	0.58
PT vs NT	Autonomy	Persisting effects	6	0.98
PT vs ST/UC	Balance	Post-intervention effects	51	<0.01
PT vs ST/UC	Mediolateral postural deviation EO, parallel RCTs	Post-intervention effects	5	0.83
PT vs ST/UC	Postural stability EO	Post-intervention effects	17	<0.01
PT vs ST/UC	Autonomy	Post-intervention effects	17	0.03
PT vs ST/UC	Balance	Persisting effects	21	<0.01
PT vs ST/UC	Mediolateral postural deviation EO	Persisting effects	0	NC
PT vs ST/UC	Postural stability EO	Persisting effects	2	NC
PT vs ST/UC	Autonomy	Persisting effects	11	<0.01

EO, eyes open; NC, not calculable; RCT, randomized controlled trial; SPEL, studies published in English language; SPNEL, studies published in non-English language; ST, sham treatment; UC, usual care; vs, versus

S5 Table. Results of Egger test detecting bias of publication for SPEL only

Comparison	Outcome	Post-intervention or persisting effects	Number of points	P value
PT vs NT	Balance	Post-intervention effects	32	0.31
PT vs NT	Mediolateral postural deviation EO, crossover RCTs	Post-intervention effects	16	0.70
PT vs NT	Postural stability EO	Post-intervention effects	16	0.43
PT vs NT	Autonomy	Post-intervention effects	12	0.32
PT vs NT	Balance	Persisting effects	11	0.83
PT vs NT	Mediolateral postural deviation EO	Persisting effects	5	0.45
PT vs NT	Postural stability EO	Persisting effects	3	0.57
PT vs NT	Autonomy	Persisting effects	5	0.87
PT vs ST/UC	Balance	Post-intervention effects	48	<0.01
PT vs ST/UC	Mediolateral postural deviation EO, parallel RCTs	Post-intervention effects	5	0.83
PT vs ST/UC	Postural stability EO	Post-intervention effects	17	<0.01
PT vs ST/UC	Autonomy	Post-intervention effects	14	0.62
PT vs ST/UC	Balance	Persisting effects	19	<0.001
PT vs ST/UC	Mediolateral postural deviation EO	Persisting effects	0	NC
PT vs ST/UC	Postural stability EO	Persisting effects	2	NC
PT vs ST/UC	Autonomy	Persisting effects	9	0.02

EO, eyes open; NC, not calculable; RCT, randomized controlled trial; SPEL, studies published in English language; ST, sham treatment; UC, usual care; vs, versus

S6 Table. Summary of comparisons of intervention

Characteristics	SPEL	SPNEL	Chi^2 test
Design of comparison			p=0.03
Direct comparison (e.g. A vs B), n (%)	65 (42%)	2 (12%)	
Comparison “on-top” or “add-on” (e.g. A+B versus C+B), n (%)	90 (58%)	15 (88%)	
Comparator group (control treatment)			p=0.85
No treatment, n (%)	82 (53%)	9 (53%)	
Sham treatment, n (%)	29 (19%)	4 (23.5%)	
Usual care, n (%)	44 (28%)	4 (23.5%)	

SPEL, studies published in English language; SPNEL, studies published in non-English language; vs, versus

S7 Table. Summary of categories of physical therapy investigated in studies included

Categories of PT	SPEL			SPNEL		
	Number of comparisons	Compared to all categories in SPEL	Compared to SPEL and SPNEL of the category	Number of comparisons	Compared to all categories in SPNEL	Compared to SPEL and SPNEL of the category
Acupuncture	1	1%	20%	4	24%	80%
Assistive devices	21	14%	100%	0	0%	0%
Constraint-induced therapy	3	2%	75%	1	6%	25%
Functional task-training	51	33%	91%	5	29%	9%
Functional task-training + other intervention	1	1%	100%	0	0%	0%
Functional task-training and musculoskeletal intervention and/or cardiopulmonary intervention	29	19%	100%	0	0%	0%
Functional task-training and neurophysiological intervention	2	1%	100%	0	0%	0%
Musculoskeletal intervention and body awareness therapy	1	1%	100%	0	0%	0%
Musculoskeletal intervention: active strengthening	8	5%	89%	1	6%	11%
Musculoskeletal intervention: electrostimulation	11	7%	69%	5	29%	31%
Musculoskeletal intervention: immobilization	4	3%	100%	0	0%	0%
Musculoskeletal intervention: mobilisation	2	1%	100%	0	0%	0%
Respiratory training	2	1%	100%	0	0%	0%
Sensory intervention	19	12%	100%	0	0%	0%
Visual and occulomotor training	0	0%	0%	1	6%	100%

PT, physical therapy; SPEL, studies published in English language; SPNEL, studies published in non-English language

S8 Table. Summary of duration of physical therapy compared

	SPEL	SPNEL	Difference
Mean duration of session in minutes	33.0 ± 70.2 / 20.0 / 0.5-600.0	34.3 ± 29.8 / 30.0 / 15.0-100.0	0.35[a]
Number of sessions by week	3.1 ± 1.9 / 3.0 / 1.0-7.5	4.6 ± 1.6 / 5.0 / 1.7-7.0	0.04[a*]
Number of weeks	3.6 ± 3.0 / 3.0 / 1.0-12.0	4.5 ± 1.7 / 4 / 3-8.0	0.11[a]
Total number of sessions	13.6 ± 14.7 / 10.0 / 1-72	20.2 ± 10.8 / 20.0 / 5-40	0.04[a*]
Total duration in minutes	813.4 ± 2937.6 / 300.0 / 0.5-25200.0	792.1 ± 1006.1 / 450.0 / 75.0-3000.0	0.14[a]

mean ± standard deviation / median / minimum-maximum; [a] Wilcoxon rank sum test; [*] Significant difference ($p \leq 0.05$)

SPEL, studies published in English language; SPNEL, studies published in non-English language

S9 Table. Summary of outcome measures

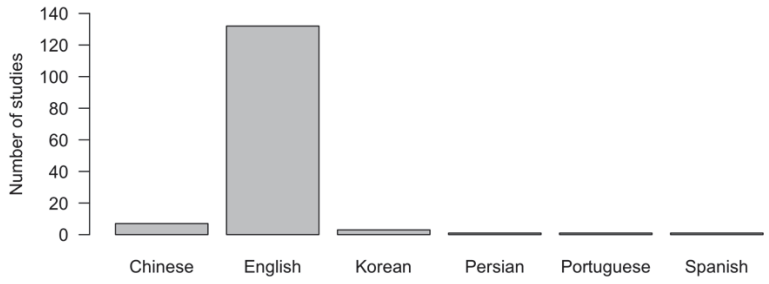
Measures of outcomes	SPEL	SPNEL
Balance		
BBS (post-intervention), n (%)	88 (67%)	10 (77%)
BBS (follow-up), n (%)	29 (22%)	2 (15%)
PASS (post-intervention), n (%)	9 (7%)	2 (15%)
PASS (follow-up), n (%)	6 (5%)	0 (0%)
Autonomy		
Barthel index (post-intervention), n (%)	25 (19%)	5 (38%)
Barthel index (follow-up), n (%)	11 (8%)	2 (15%)
ADL (post-intervention), n (%)	2 (2%)	0 (0%)
IADL (post-intervention), n (%)	0 (0%)	0 (0%)
IADL (follow-up), n (%)	4 (3%)	0 (0%)
FIM (post-intervention), n (%)	1 (1%)	0 (0%)
FIM (follow-up), n (%)	3 (2%)	0 (0%)
Mediolateral and anteroposterior postural deviation (COP, WBA)		
WB on paretic limb, EO (post-intervention), n (%)	22 (17%)	1 (8%)
WB on paretic limb, EO (follow-up), n (%)	4 (3%)	0 (0%)
WB on paretic limb, EC (post-intervention), n (%)	2 (2%)	0 (0%)
Mediolateral position of COP, EO (post-intervention), n (%)	4 (3%)	2 (15%)
Anteroposterior position of COP, EO (post-intervention), n (%)	3 (2%)	1 (8%)
Anteroposterior position of COP, EO (follow-up), n (%)	0 (0%)	1 (8%)
Postural stability (COP, LOS)		
Sway length EO (post-intervention), n (%)	12 (9%)	1 (8%)
Sway area EO (post-intervention), n (%)	10 (8%)	0 (0%)
Sway length EC (post-intervention), n (%)	9 (7%)	0 (0%)
Velocity COP EO (post-intervention), n (%)	9 (7%)	0 (0%)
Anteroposterior velocity COP EO (post-intervention), n (%)	8 (6%)	0 (0%)
Mediolateral velocity COP EO (post-intervention), n (%)	8 (6%)	0 (0%)
Anteroposterior velocity COP EC (post-intervention), n (%)	7 (5%)	0 (0%)
LOS, maximum excursion, affected side EO (post-intervention), n (%)	7 (5%)	0 (0%)
LOS, maximum excursion, anterior, EO (post-intervention), n (%)	7 (5%)	0 (0%)
LOS, maximum excursion, non-affected side EO (post-intervention), n (%)	7 (5%)	0 (0%)
Mediolateral velocity COP EC (post-intervention), n (%)	7 (5%)	0 (0%)
LOS, Movement velocity, affected side EO (post-intervention), n (%)	6 (5%)	0 (0%)
LOS, Movement velocity, anterior, EO (post-intervention), n (%)	6 (5%)	0 (0%)
LOS, Movement velocity, non-affected side EO (post-intervention), n (%)	6 (5%)	0 (0%)

LOS, directional control non-affected side EO (post-intervention), n (%)	5 (4%)	0 (0%)
LOS, directional control, affected side EO (post-intervention), n (%)	5 (4%)	0 (0%)
LOS, directional control, anterior, EO (post-intervention), n (%)	5 (4%)	0 (0%)
LOS, maximum excursion, posterior EO (post-intervention), n (%)	5 (4%)	0 (0%)
LOS, Movement velocity, posterior EO (post-intervention), n (%)	5 (4%)	0 (0%)
LOS, directional control posterior EO (post-intervention), n (%)	4 (3%)	0 (0%)
Sway area EC (post-intervention), n (%)	4 (3%)	0 (0%)
Velocity COP EC (post-intervention), n (%)	4 (3%)	0 (0%)
Anteroposterior sway length EO (post-intervention), n (%)	3 (2%)	0 (0%)
LOS, end-point excursion, affected side, EO (post-intervention), n (%)	3 (2%)	0 (0%)
LOS, end-point excursion, backward, EO (post-intervention), n (%)	3 (2%)	0 (0%)
LOS, end-point excursion, forward, EO (post-intervention), n (%)	3 (2%)	0 (0%)
LOS, end-point excursion, non-affected side, EO (post-intervention), n (%)	3 (2%)	0 (0%)
Mediolateral sway length EO (post-intervention), n (%)	3 (2%)	0 (0%)
Anteroposterior variability COP EO (post-intervention), n (%)	2 (2%)	1 (8%)
Mediolateral variability COP EO (post-intervention), n (%)	2 (2%)	1 (8%)
Velocity moment EC (post-intervention), n (%)	3 (2%)	0 (0%)
Velocity moment EO (post-intervention), n (%)	3 (2%)	0 (0%)
LOS EO (post-intervention), n (%)	2 (2%)	0 (0%)
LOS, end-point excursion, affected side, EO (follow-up)	2 (2%)	0 (0%)
LOS, end-point excursion, backward, EO (follow-up)	2 (2%)	0 (0%)
LOS, end-point excursion, forward, EO (follow-up), n (%)	2 (2%)	0 (0%)
LOS, end-point excursion, non-affected side, EO (follow-up), n (%)	2 (2%)	0 (0%)
Maximum COP displacement in anteroposterior direction EO (post-intervention), n (%)	2 (2%)	0 (0%)
Maximum COP displacement in mediolateral direction EO (post-intervention), n (%)	2 (2%)	0 (0%)
Stability index EO (post-intervention), n (%)	1 (1%)	1 (8%)
Velocity COP EC (post-intervention), n (%)	2 (2%)	0 (0%)
Velocity COP EO (post-intervention), n (%)	1 (1%)	1 (8%)
Anteroposterior sway length EC (post-intervention), n (%)	1 (1%)	0 (0%)
COP excursion EO (post-intervention), n (%)	1 (1%)	0 (0%)
LOS, Ankle strategy, EC (follow up), n (%)	1 (1%)	0 (0%)
LOS, Ankle strategy, EO (follow up), n (%)	1 (1%)	0 (0%)
LOS, COG alignment, EC (follow up), n (%)	1 (1%)	0 (0%)
LOS, COG alignment, EO (follow up), n (%)	1 (1%)	0 (0%)
LOS, Maximal stability, EC (follow up), n (%)	1 (1%)	0 (0%)
LOS, Maximal stability, EO (follow up), n (%)	1 (1%)	0 (0%)
LOS, maximum excursion, affected side EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, maximum excursion, anterior, EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, maximum excursion, non-affected side EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, maximum excursion, posterior EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, Movement velocity, affected side EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, Movement velocity, anterior, EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, Movement velocity, non-affected side EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, Movement velocity, posterior EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, reaction time, affected side, EO (post-intervention), n (%)	1 (1%)	0 (0%)
LOS, reaction time, affected side, EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, reaction time, backward, EO (post-intervention), n (%)	1 (1%)	0 (0%)
LOS, reaction time, backward, EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, reaction time, forward, EO (post-intervention), n (%)	1 (1%)	0 (0%)
LOS, reaction time, forward, EO (follow-up), n (%)	1 (1%)	0 (0%)
LOS, reaction time, non-affected side, EO (post-intervention), n (%)	1 (1%)	0 (0%)
LOS, reaction time, non-affected side, EO (follow-up), n (%)	1 (1%)	0 (0%)
Maximum COP displacement in anteroposterior direction EC (post-intervention), n (%)	1 (1%)	0 (0%)

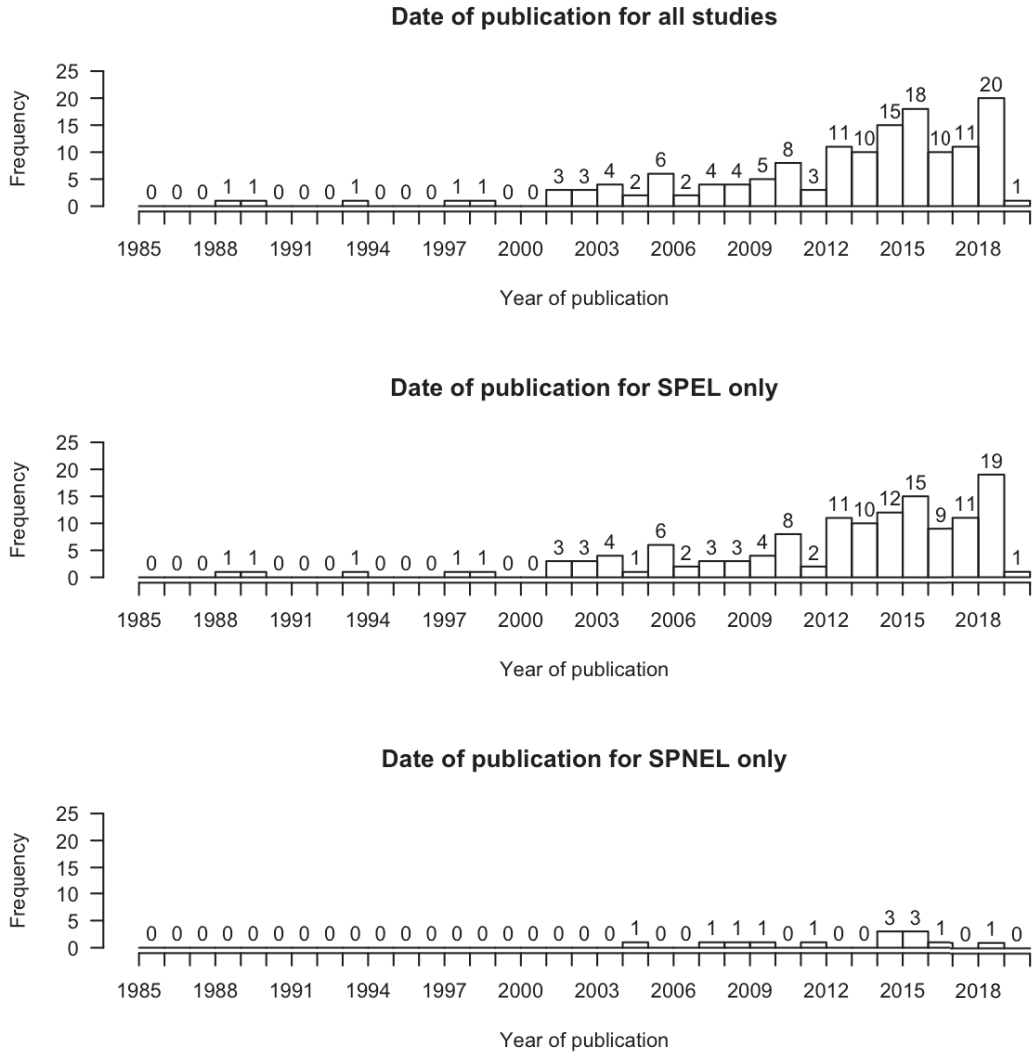
Maximum COP displacement in anteroposterior direction EC (follow-up), n (%)	1 (1%)	0 (0%)
Maximum COP displacement in anteroposterior direction EO (follow-up), n (%)	1 (1%)	0 (0%)
Maximum COP displacement in mediolateral direction EC (post-intervention), n (%)	1 (1%)	0 (0%)
Maximum COP displacement in mediolateral direction EC (follow-up), n (%)	1 (1%)	0 (0%)
Maximum COP displacement in mediolateral direction EO (follow-up), n (%)	1 (1%)	0 (0%)
Mediolateral sway length EC (post-intervention), n (%)	1 (1%)	0 (0%)
Stability index EC (post-intervention), n (%)	1 (1%)	0 (0%)
Sway area EC (follow-up), n (%)	1 (1%)	0 (0%)
Sway length EC (follow-up), n (%)	1 (1%)	0 (0%)
Sway length EO (follow-up), n (%)	1 (1%)	0 (0%)
Anteroposterior variability COP EC (post-intervention), n (%)	0 (0%)	1 (%)
Mediolateral variability COP EC (post-intervention), n (%)	0 (0%)	1 (%)

ADL, activities of daily living; BBS, berg balance scale; COP, center of pressure; Deg, degree; EC, eyes closed; EO, eyes open; FIM, functional independence measure; IADL, instrumental activities of daily living; LOS, limit of stability; PASS, postural assessment scale for stroke; NT, no treatment; s, second; SPEL, studies published in English language; SPNEL, studies published in non-English language; ST, sham treatment; UC, usual care; WB, weight bearing; WBA, weight bearing asymmetry

S1 Fig. Histogram of studies according to the language of publication for studies included



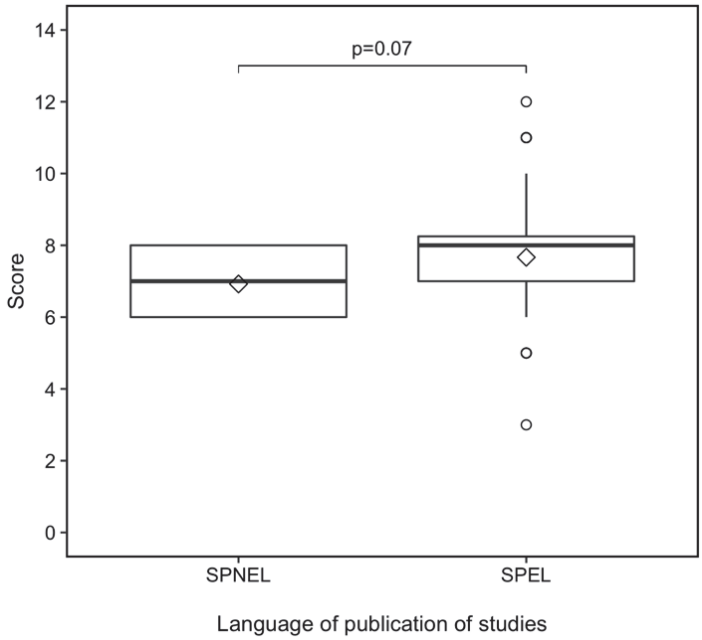
S2 Fig. Date of publication for studies included



SPEL, studies published in English language; SPNEL, studies published in non-English language

S3 Fig. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.
Voir S1B Fig. du matériel supplémentaire de l'article 2 - Hugues *et al.* (2019)

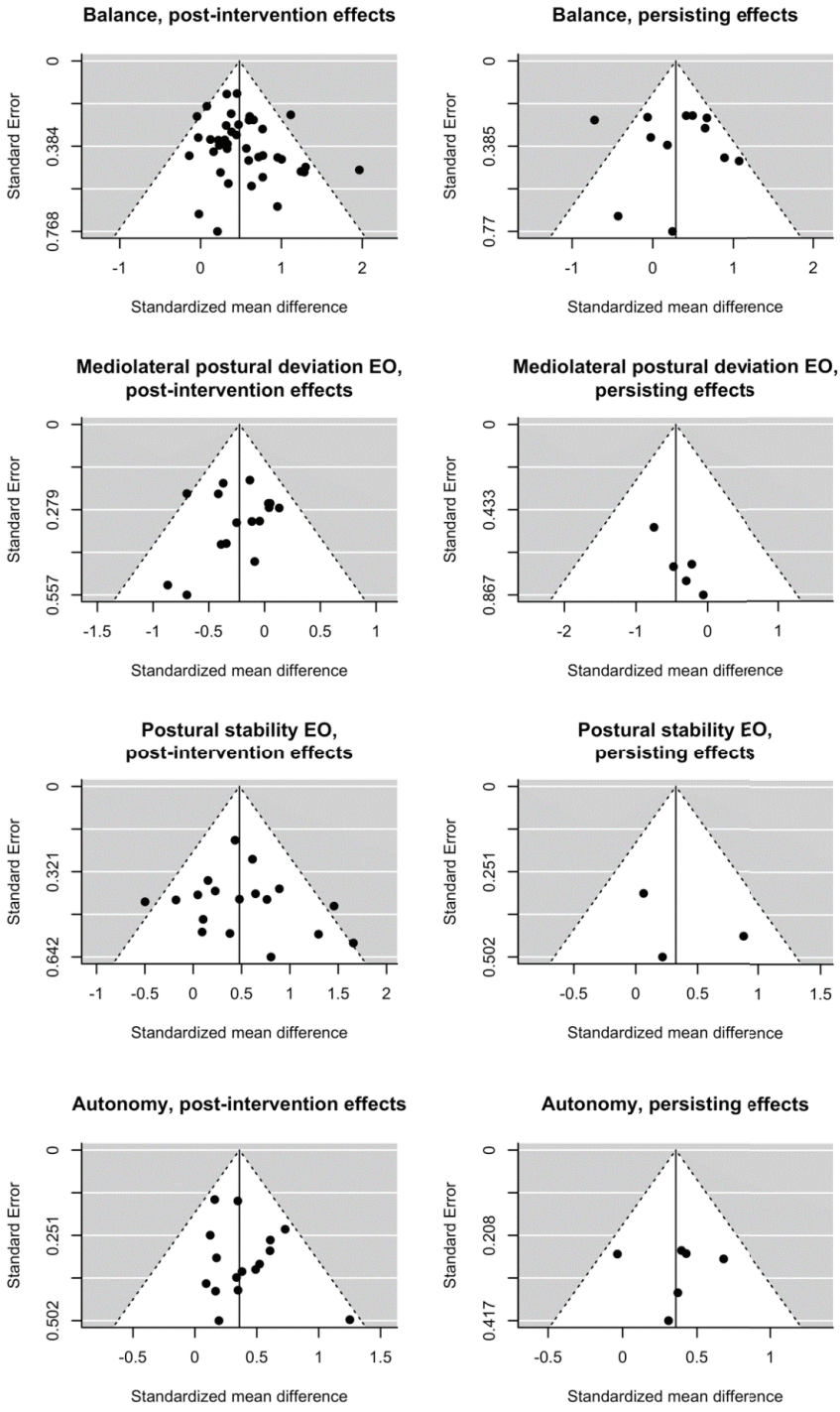
S4 Fig. Summary of overall score of risk of bias



SPEL, studies published in English language; SPNEL, studies published in non-English language

S5 Fig. Funnel plot for all studies (SPEL and SPNEL)

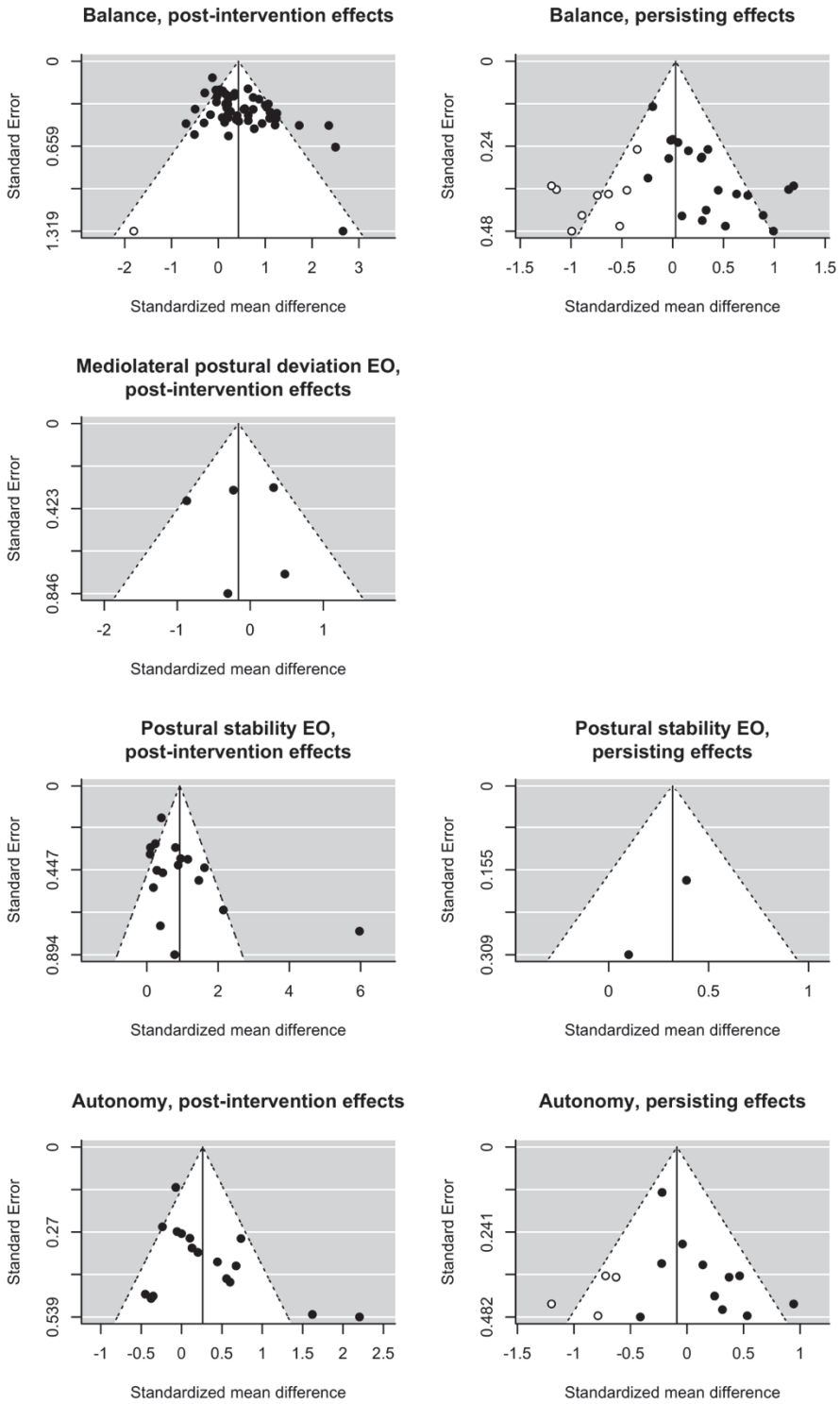
S5A Fig. Funnel plot of comparison PT versus no treatment for all studies (SPEL and SPNEL)



Dotted line: 95% confidence interval; black filled circle: study

EO, eyes open; SPEL, studies published in English language; SPNEL, studies published in non-English language

S5B Fig. Funnel plot of comparison PT versus sham treatment or usual care for all studies (SPEL and SPNEL)

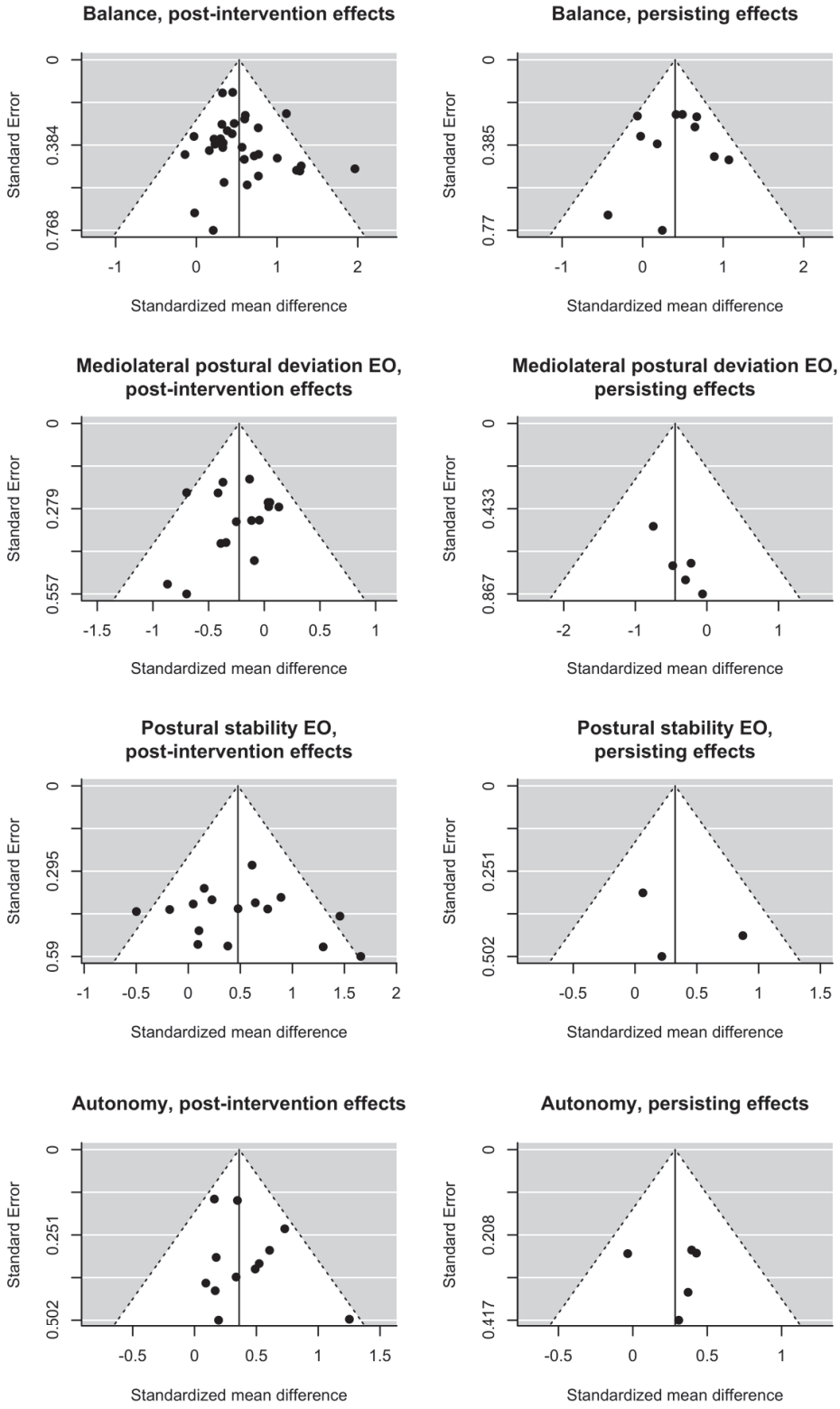


Dotted line: 95% confidence interval; black filled circle: study; white filled circle: "missing" study

EO, eyes open; SPEL, studies published in English language; SPNEL, studies published in non-English language

S6 Fig. Funnel plot for all studies for SPEL only

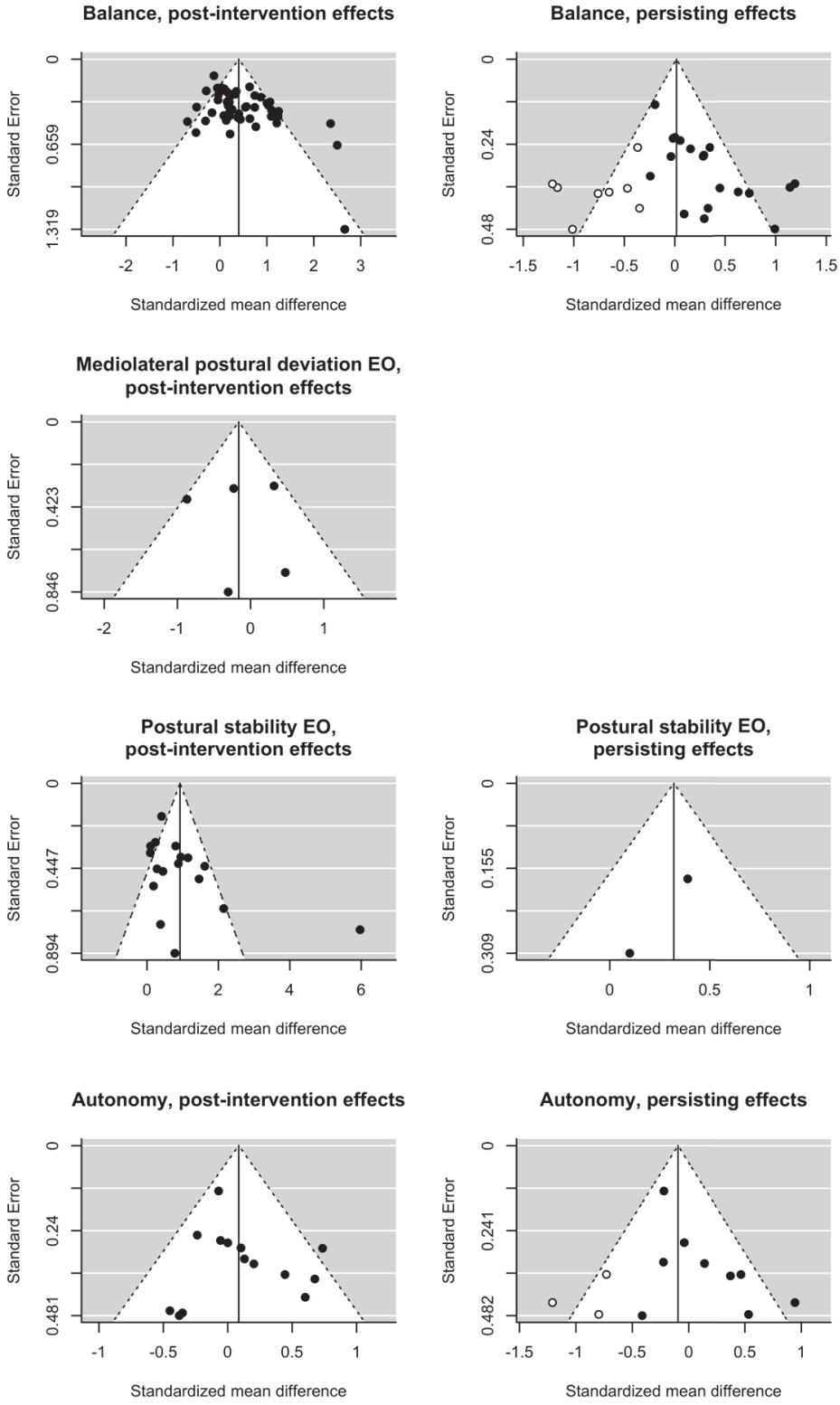
S6A Fig. Funnel plot of comparison PT versus no treatment for SPEL only



Dotted line: 95% confidence interval; black filled circle: study

EO, eyes open; SPEL, studies published in English language

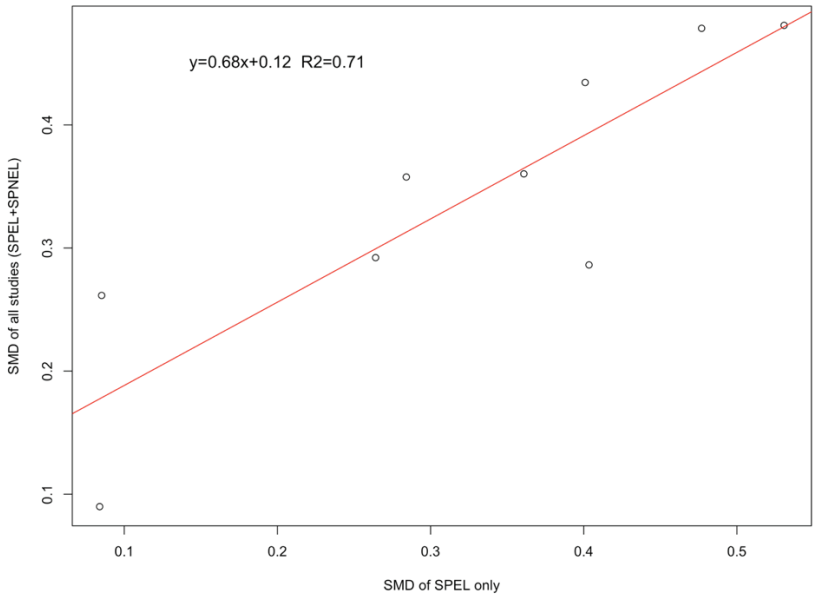
S6B Fig. Funnel plot of comparison PT versus sham treatment or usual care for SPEL only



Dotted line: 95% confidence interval; black filled circle: study; white filled circle: "missing" study

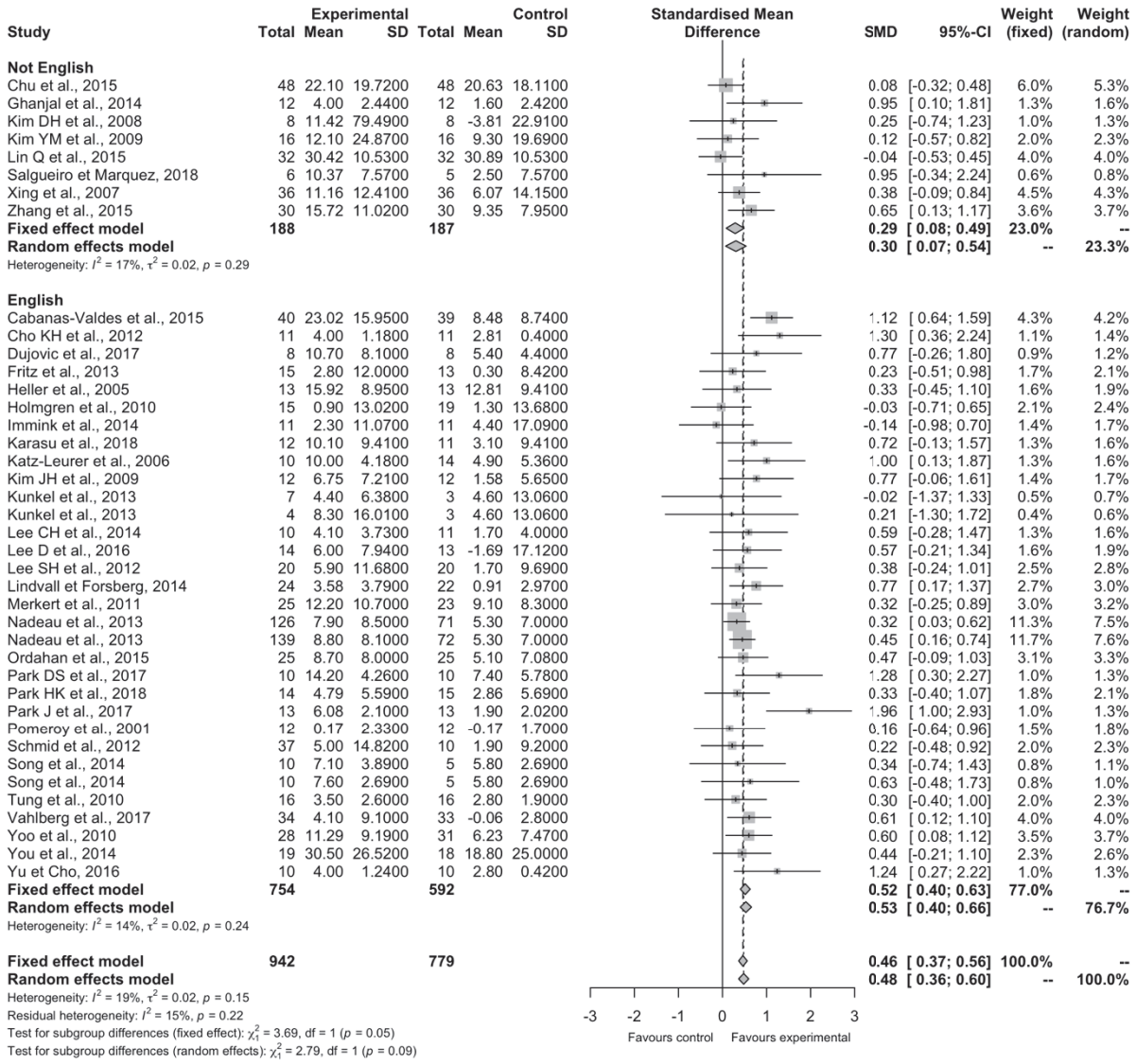
EO, eyes open; SPEL, studies published in English language; ST, sham treatment; UC, usual care

S7 Fig. Linear regression between treatment effect estimates of all studies (SPEL and SPNEL) and these of SPEL only

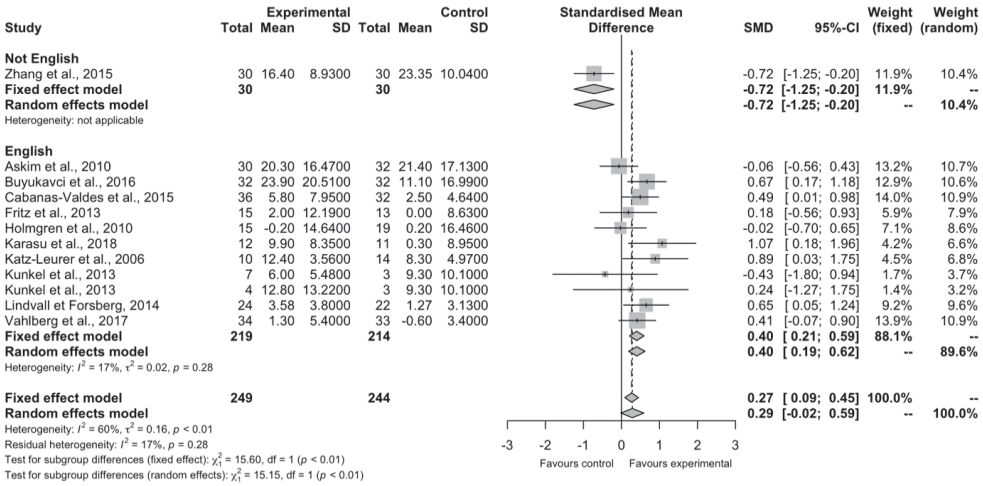


S8 Fig. Forest plots of physical therapy versus no treatment. Subgroup: Language of publication of studies

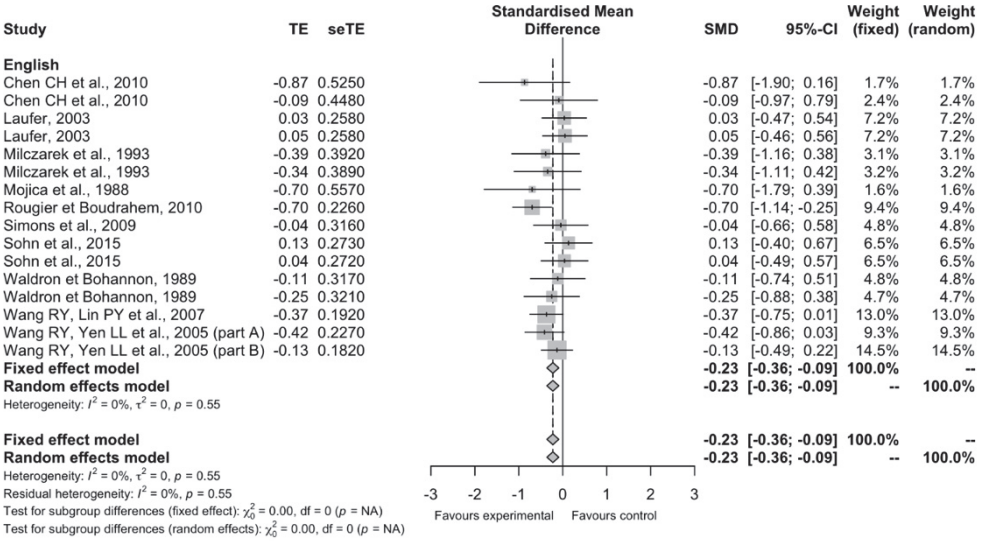
S8A Fig. Forest plot of physical therapy versus no treatment. Outcome: Balance, immediate effects. Subgroup: Language of publication of studies



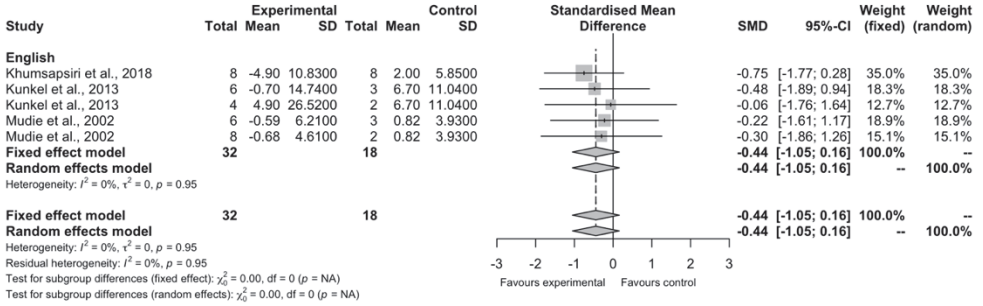
S8B Fig. Forest plot of physical therapy versus no treatment. Outcome: Balance, persisting effects. Subgroup: Language of publication of studies



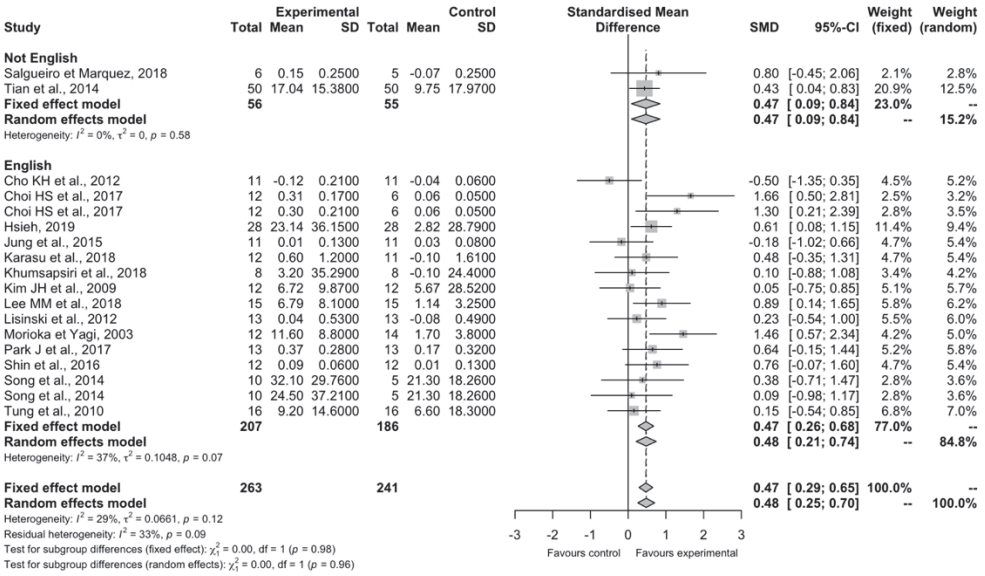
S8C Fig. Forest plot of physical therapy versus no treatment. Outcome: Mediolateral postural deviation EO, immediate effects. Subgroup: Language of publication of studies



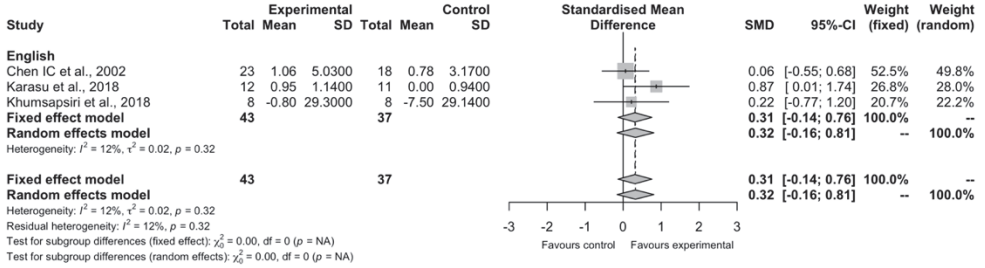
S8D Fig. Forest plot of physical therapy versus no treatment. Outcome: Mediolateral postural deviation EO, persisting effects. Subgroup: Language of publication of studies



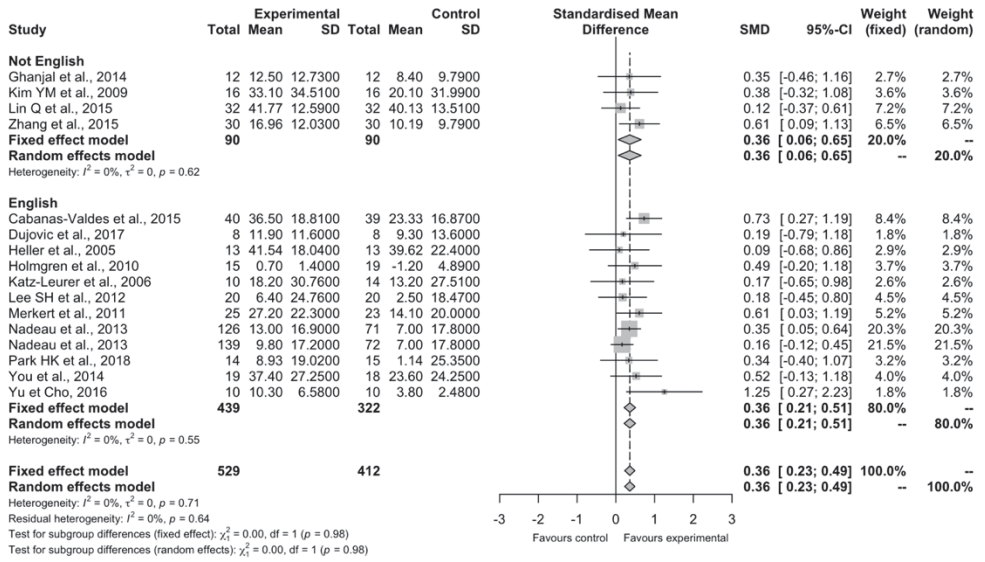
S8E Fig. Forest plot of physical therapy versus no treatment. Outcome: Postural stability EO, immediate effects. Subgroup: Language of publication of studies



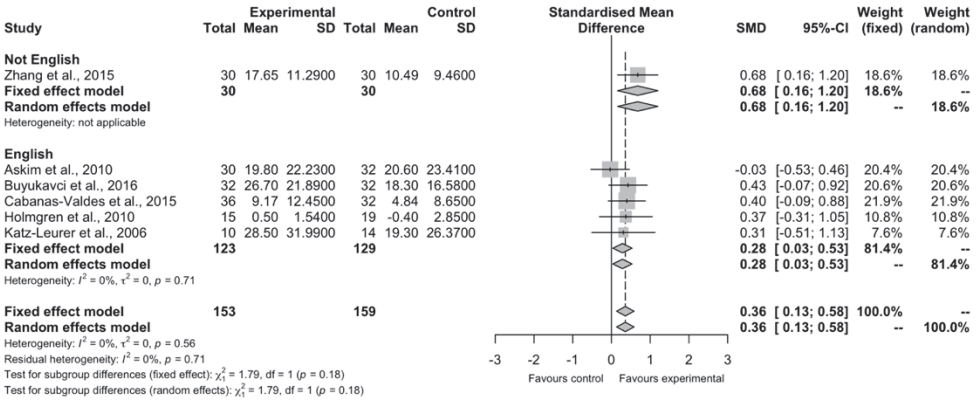
S8F Fig. Forest plot of physical therapy versus no treatment. Outcome: Postural stability EO, persisting effects. Subgroup: Language of publication of studies



S8G Fig. Forest plot of physical therapy versus no treatment. Outcome: Autonomy, immediate effects. Subgroup: Language of publication of studies

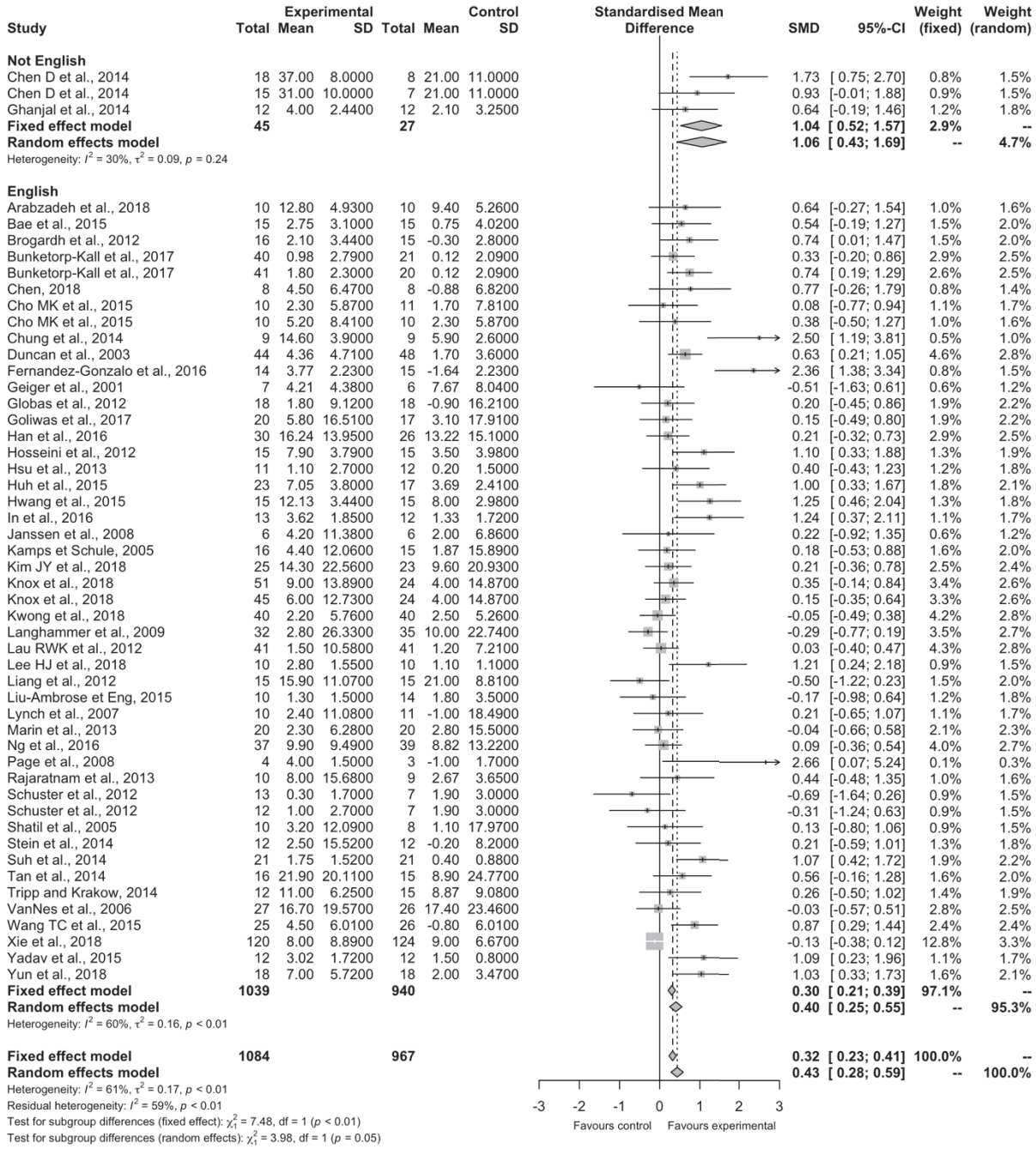


S8H Fig. Forest plot of physical therapy versus no treatment. Outcome: Autonomy, persisting effects. Subgroup: Language of publication of studies

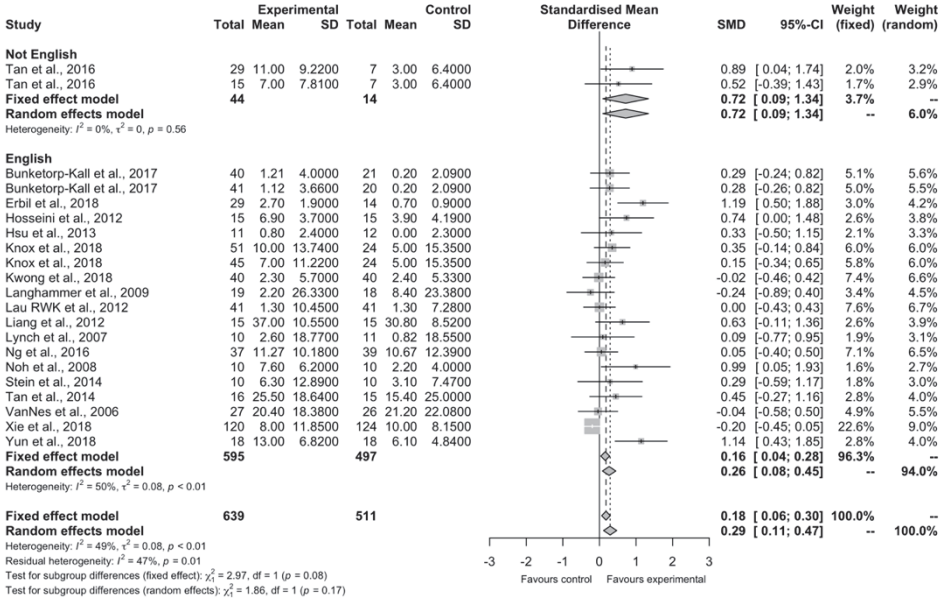


S9 Fig. Forest plots of physical therapy versus sham treatment or usual care. Subgroup: Language of publication of studies

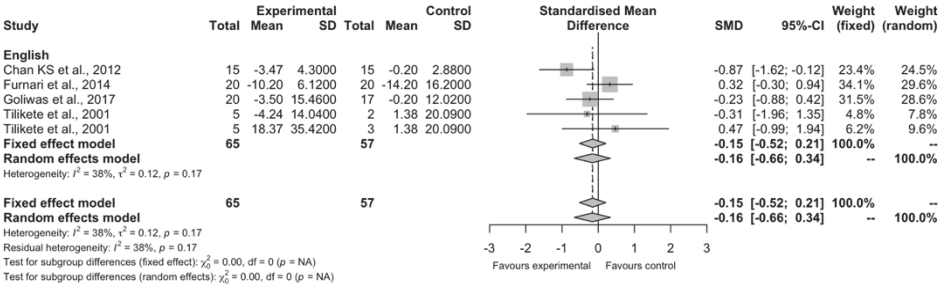
S9A Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Balance, immediate effects. Subgroup: Language of publication of studies



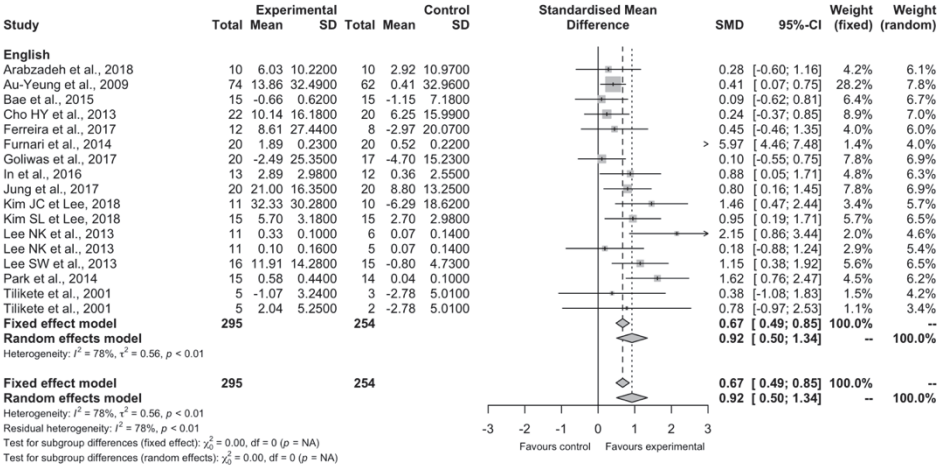
S9B Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Balance, persisting effects. Subgroup: Language of publication of studies



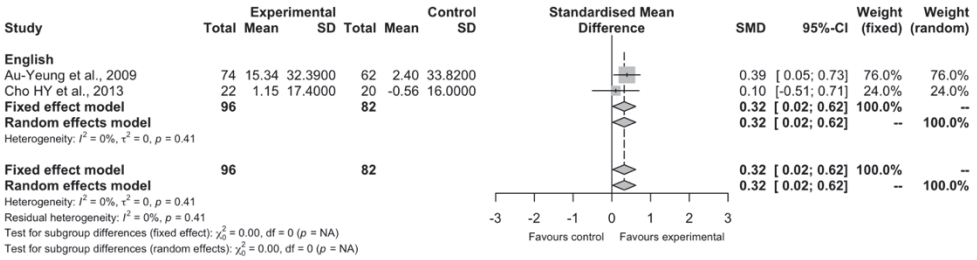
S9C Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Mediolateral postural deviation EO, immediate effects. Subgroup: Language of publication of studies



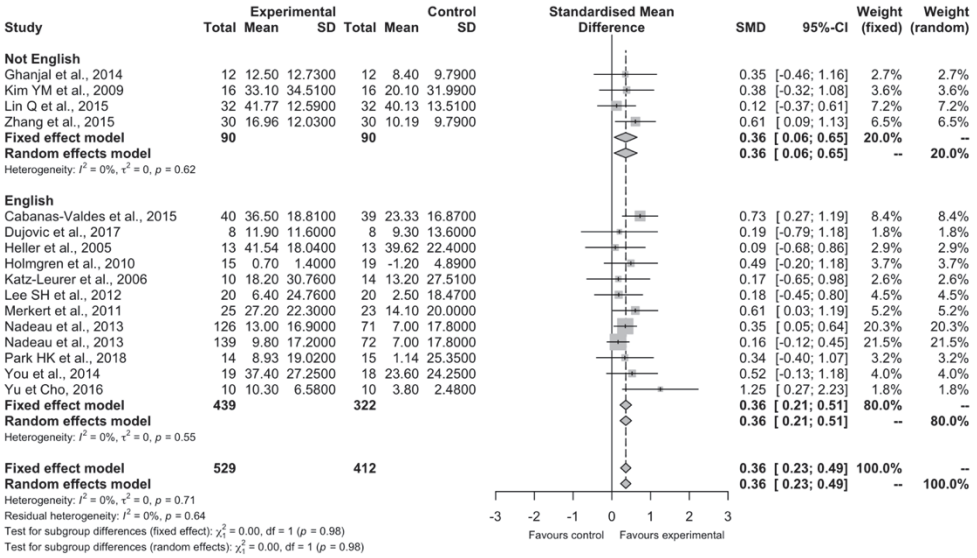
S9D Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Postural stability EO, immediate effects. Subgroup: Language of publication of studies



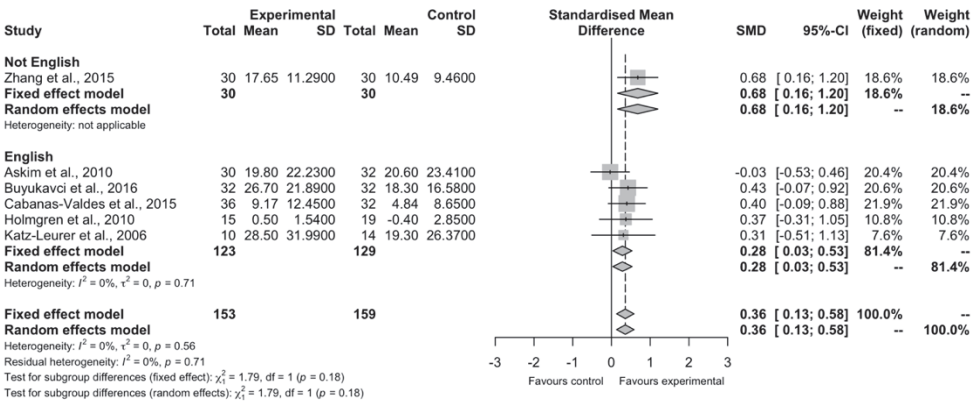
S9E Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Postural stability EO, persisting effects. Subgroup: Language of publication of studies



S9F Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Autonomy, immediate effects. Subgroup: Language of publication of studies



S9G Fig. Forest plot of physical therapy versus sham treatment or usual care. Outcome: Autonomy, persisting effects. Subgroup: Language of publication of studies



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Appendix 1. Type of approach for each comparison of studies included.

Study	Physical therapy	Approach
Allison et Dennett, 2007	additional standing practice + CPT versus CPT	TD
Arabzadeh et al., 2018	task-oriented exercise program versus traditional physiotherapy	TD
Askim et al., 2010	intensive motor training after early supported discharge + standard training (PT) versus standard treatment (PT) after early supported discharge	TD
Bae et al., 2015	lower-leg flexible kinesiology taping of paralyzed side versus lower-leg inflexible (sham) taping	BU
Barcala et al., 2011	wii Fit program + CPT versus CPT	TD
Brogardh et al., 2012	whole body vibration (standing static posture) versus sham whole body vibration (standing static posture)	BU
Bunketorp-Kall et al., 2017	multimodal interventions based on rhythm-and-music therapy versus UC	TD
Bunketorp-Kall et al., 2017	multimodal interventions based on horse-riding therapy versus UC	TD
Buyukavci et al., 2016	trunk balance exercises + CR program versus CR program	TD
Büyükvural Şen et al., 2015	isokinetic strengthening training (knee + ankle) + CR versus CR	TD
Cabanas-Valdés et al., 2015	core stability exercises + CT versus CT	TD
Chen D et al., 2014	FES + routine treatment (medication + basic rehabilitation) versus comfort stimulation	BU
Chen D et al., 2014	FES + routine treatment (medication + basic rehabilitation) versus comfort stimulation	BU
Chen JC et al., 2011	thermal stimulation + SR versus visits and discussions + SR	BU
Chen, 2018	tai Chi Yunshou versus traditional rehabilitation	TD
Cho KH et al., 2012	BT with VR + SR versus SR	TD
Cho MK et al., 2015	treadmill GT with FES GM+TA + regular PT versus treadmill GT + sham FES GM+TA + regular PT	BU
Cho MK et al., 2015	treadmill GT with FES GM+TA + regular PT versus treadmill GT with FES TA + sham FES GM + regular PT	BU
Cho MK et al., 2015	treadmill GT with FES TA + sham FES GM + regular PT versus treadmill GT + sham FES GM+TA + regular PT	BU
Chu et al., 2015	electroacupuncture stimulation of lateral side of Tianzhu (para-BL 10) + traditional acupuncture + CBT + CRT + routine treatment of neurology versus CBT + CRT + routine treatment of neurology	ND
Chung et al., 2014	GT with FES (GM + TA) versus GT with sham FES (GM + TA)	BU
Dujovic et al., 2017	novel multi-pad functional electrical stimulation + CSR versus CSR	Mixed
Duncan et al., 1998	exercise program at home versus UC at home or outpatient	TD
Duncan et al., 2003	exercise program at home versus UC at home	TD

Erbil et al., 2018	robot-assisted training + PT versus PT	Mixed
Fernandez-Gonzalo et al., 2016	eccentric-overload flywheel resistance exercise training program versus daily routines	TD
Fritz et al., 2013	video games (Wii and PS) versus no treatment	TD
Geiger et al., 2001	balance training with biofeedback + PT versus PT	TD
Ghanjal et al., 2014	observation and imitation of functional tasks + standard PT versus standard PT	TD
Ghanjal et al., 2014	observation and imitation of functional tasks + standard PT versus observation of symbols (no functional tasks) + standard PT	TD
Globas et al., 2012	aerobic treadmill GT versus CPT	TD
Goliwas et al., 2017	sensorimotor stimulation of the paretic foot + PT versus PT	Mixed
Han et al., 2016	robot-assisted gait training + CR therapy versus CPT + CR therapy	Mixed
Hart et al., 2004	tai chi chuan versus balance group exercises	TD
Heller et al., 2005	BT with biofeedback (barofeedback) + CR (neuromotor therapy) versus CR (neuromotor therapy)	TD
Hollands et al., 2015	treadmill visual cue training + SR versus UC + SR	TD
Hollands et al., 2015	over-ground visual cue training + SR versus UC + SR	TD
Holmgren et al., 2010	high intensity functional exercises versus educational program	TD
Hosseini et al., 2012	mental practice + PT versus PT	TD
Hsu et al., 2013	noxious thermal stimulation + PT + OT versus innocuous thermal stimulation + PT + OT	BU
Huh et al., 2015	balance training with a new lower limb balance control trainer + CR therapy versus CR therapy	TD
Hwang et al., 2015	treadmill GT combined with FES using a tilt sensor + CPT versus treadmill GT combined with sham FES using a tilt sensor + CPT	BU
Immink et al., 2014	yoga (group + home) + usual treatment and lifestyle behavior versus wait list (no treatment) + usual treatment and lifestyle behavior	TD
In et al., 2016	virtual reality reflection therapy (mirror therapy) + CR program versus sham virtual reality reflection therapy + CR program	TD
Janssen et al., 2008	leg cycling exercise with maximally tolerable electrical stimulation versus leg cycling exercise with just sensible electrical stimulation	BU
Kamps et Schule, 2005	cyclic movement training of the lower limb versus CPT + conventional OT	TD
Karasu et al., 2018	wii Fit-based balance rehabilitation + CR versus CR	TD
Katz-Leurer et al., 2006	early cycling training + regular rehabilitation versus regular rehabilitation	TD
Kilinc et al., 2015	bobath-based trunk training versus physiotherapy	Mixed
Kim DH et al., 2008	isokinetic strengthening of trunk muscles + NDT and GT versus NDT and GT	TD
Kim JH et al., 2009	VR + CPT versus CPT	TD

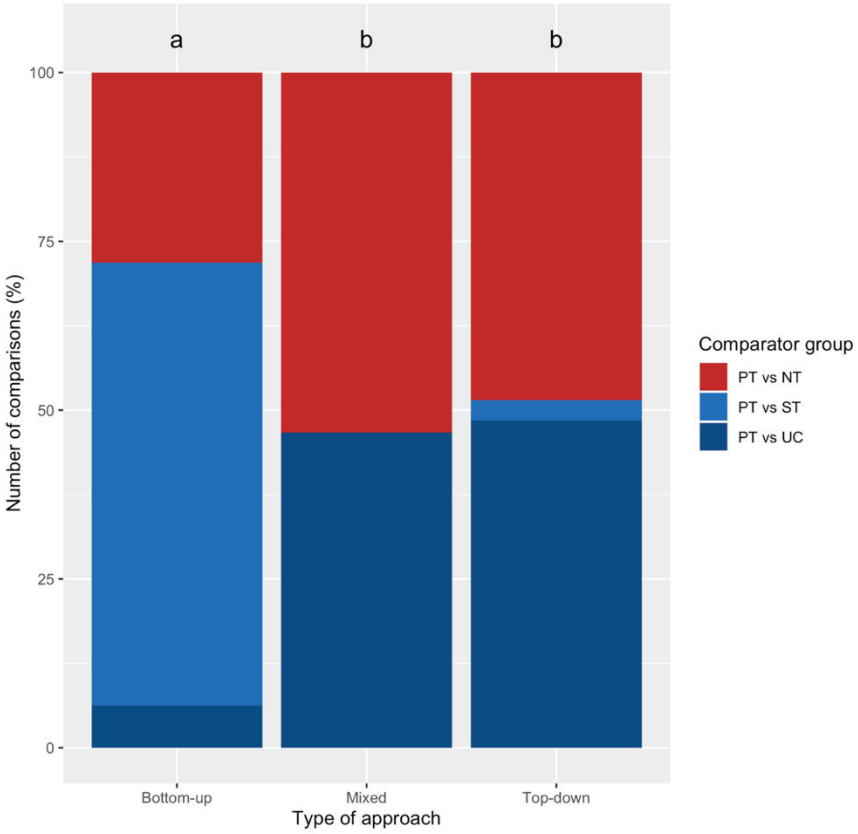
Kim JY et al., 2018	robot-(Morning Walk®) assisted gait training + conventional physiotherapy versus conventional physiotherapy	Mixed
Kim YM et al., 2009	ES of trunc muscles + ES of lower limb muscles + PT + OT versus ES of lower limb muscles + PT + OT	BU
Knox et al., 2018	task-oriented circuit gait training versus educational therapy	TD
Knox et al., 2018	conventional strength training versus educational therapy	TD
Kunkel et al., 2013	exercises + UC versus UC	TD
Kunkel et al., 2013	FES during exercises + UC versus UC	Mixed
Kwong et al., 2018	bilateral Transcutaneous Electrical Nerve Stimulation during functional task-oriented training versus Unilateral transcutaneous Electrical Nerve Stimulation (on paretic lower limb et sham on non-paretic lower limb) during functional task-oriented training	BU
Langhammer et al., 2009	specific intensive exercises versus exercises (UC)	TD
Lau RWK et al., 2012	whole body vibration + (while) exercise and BT versus sham whole body vibration + (while) exercise and BT	BU
Lee CH et al., 2014	VR + general PT versus general PT	TD
Lee D et al., 2016	mirror Therapy combined with NeuroMuscular Electrical Stimulation + CPT versus CPT	Mixed
Lee HJ et al., 2018	diaphragm and deep abdominal muscle exercise versus Traditional exercise	ND
Lee SH et al., 2012	visual feedback BT (standing) + CPT versus CPT	TD
Liang et al., 2012	thermal stimulation + PT + OT versus PT + OT + discussion sessions	BU
Lin Q et al., 2015	acupuncture + routine rehabilitation training versus routine rehabilitation training	ND
Lindvall et Forsberg, 2014	body awareness therapy + usual daily activities, ongoing PT or other training versus no treatment + usual daily activities, ongoing PT or other training	TD
Liu-Ambrose et Eng, 2015	immediate community-based exercises + recreation and leisure activities versus UC	TD
Lynch et al., 2007	sensory retraining + standard PT versus relaxation + standard standard PT	TD
Marin et al., 2013	whole body vibration during isometric position exercises + SR versus isometric position (without vibration) + SR	BU
Merkert et al., 2011	vibration training + conventional comprehensive geriatric rehabilitation versus conventional comprehensive geriatric rehabilitation	Mixed
Moore JL et al., 2010	intensive LT (intensity stepping practice + BWS) versus no treatment	Mixed
Nadeau et al., 2013	GT + BWS + UC versus UC	Mixed
Nadeau et al., 2013	home exercise program + UC versus UC	TD
Ng et al., 2016	transcutaneous electrical nerve stimulation during task-oriented balance training + CR versus placebo-TENS during task-oriented balance training + CR	BU
Nikamp et al., 2017	early ankle-foot orthosis + UC versus Delayed ankle-foot orthosis + UC	BU
Noh et al., 2008	aquatic therapy (Halliwick and Ai Chi methods) versus CT	TD
Ordahan et al., 2015	balance training with balance trainer + CR versus CR	Mixed

Page et al., 2008	bilateral reciprocal locomotor training with device versus home exercice program	TD
Park DS et al., 2017	virtual reality training using Xbox Kinect + CPT versus CPT	TD
Park HK et al., 2018	land trunk exercise + aquatic trunk exercises (Halliwick) + CPT versus CPT	TD
Park J et al., 2017	boxing program + CPT versus CPT	Mixed
Pomeroy et al., 2001	weight garments versus no weighted garment	TD
Rajaratnam et al., 2013	BT with biofeedback + CR versus CR	TD
Robertson et al., 2010	FES versus no FES	BU
Salgueiro et Marquez, 2018	visual and occulomotor training + CT versus CT	TD
Schmid et al., 2012	yoga +/- relaxation audio recording versus no treatment	TD
Schuster et al., 2012	PT + embedded motor imagery training versus PT + audio tapes with information related to stroke	TD
Schuster et al., 2012	PT + added motor imagery training versus PT + audio tapes with information related to stroke	TD
Shatil et al., 2005	therapeutic golf rehabilitation (PT + golf) + regular routine versus hand therapy + regular routine (regular routine = no treatment)	TD
Simons et al., 2009	ankle-foot orthosis versus no ankle-foot orthosis	BU
Sohn et al., 2015	bobath sling versus no sling	BU
Sohn et al., 2015	simple arm sling versus no sling	BU
Song et al., 2014	tetra-ataxiometric posturography program + CBT versus CBT	TD
Song et al., 2014	VR during BT + CBT versus CBT	TD
Stein et al., 2014	PT with robotic knee brace versus exercises	Mixed
Suh et al., 2014	interferential current therapy + SR versus sham Interferential current therapy + SR	BU
Tan et al., 2014	four-channel FES (tibialis anterior, quadriceps, hamstrings, and gastrocnemius of the affected leg) + CR versus placebo four-channel FES (tibialis anterior, quadriceps, hamstrings, and gastrocnemius of the affected leg) + CR	BU
Tan et al., 2016	four-channel functional electrical stimulation + medicines and routine rehabilitation training versus Placebo functional electrical stimulation + medicines and routine rehabilitation training	BU
Tan et al., 2016	single channel functional electrical stimulation + medicines and routine rehabilitation training versus Placebo functional electrical stimulation + medicines and routine rehabilitation training	BU
Tripp and Krakow, 2014	halliwick-therapy + CPT versus CPT	TD
Tung et al., 2010	sit-to-stand + general PT versus general PT	TD
Vahlberg et al., 2017	progressive resistance and balance exercise program + motivational group discussions versus regular activities	TD
VanNes et al., 2006	whole body vibration (standing posture) + PT rehabilitation (individualized and group) (+ occupational and speech therapy and psychologic treatment) versus exercise therapy on music + PT rehabilitation (individualized and group) (+ occupational and speech therapy and psychologic treatment)	BU

Wang et al., 2017	mirror therapy + CR versus passive or active supplementary training of the lower extremities of the affected side (as mirror therapy) + CR	TD
Wang RY, Yen LL et al., 2005 part 1	ankle-foot orthosis versus no ankle-foot orthosis	BU
Wang RY, Yen LL et al., 2005 part 2	ankle-foot orthosis versus no ankle-foot orthosis	BU
Wang TC et al., 2015	caregiver-mediated training (home-based intervention) versus routine care + visits or telephone calls	TD
Xie et al., 2018	tai chi yunshou exercise versus Balance rehabilitation training	TD
Xing et al., 2007	acupuncture + hyperbaric oxygen therapy + conventional drug treatment versus hyperbaric oxygen therapy + conventional drug treatment	ND
Yadav et al., 2015	specific balance strategy training versus general balance exercise	TD
Yeung et al., 2018	gait training + Robot-assisted ankle foot orthosis with dorsiflexion assistance versus gait training + sham Robot-assisted ankle foot orthosis with dorsiflexion assistance	BU
Yoo et al., 2010	core strengthening program + CPT versus CPT	TD
Yoo et al., 2018	bedside respiratory muscle training + CSR versus CSR	ND
You et al., 2014	FES + SR (PT + OT) versus SR (PT + OT)	BU
Yu et Cho, 2016	virtual reality game + SR program versus SR program	TD
Yun et al., 2018	robot-assisted gait training versus CPT	Mixed
Zhang et al., 2015	modified CITUL + routine rehabilitation versus routine rehabilitation	TD

BT, balance training; BU, bottom-up; BWS, body weight support; CBT, conventional balance training; CITUL, constraint-induced movement therapy of upper limb; CPI, cardiopulmonary intervention; CPT, conventional physical therapy; CPR, conventional physical rehabilitation; CR, conventional rehabilitation; CRT, comprehensive rehabilitation therapy; CSR, conventional stroke rehabilitation; CT, conventional therapy; Deg, degree; EMA, electromechanical assistance; EMR, electromechanical resistance; EO, eyes opened; FES, functional electrostimulation; FTT, functional task training; GM, gluteus medius; GT, gait training; LT, locomotor training; LT-RGO, locomotor training with a robotic gait orthosis; MI, musculoskeletal intervention; MM, musculoskeletal mobilization; MS, muscle strengthening; ND, not determined; NDT, neurodevelopmental treatment; NPI, neurophysiological intervention; OT, occupational therapy; PT, physical therapy; rTMS, repetitive transcranial magnetic stimulation; SR, standard rehabilitation; TA, tibial anterior; TD, top-down; tDCS, transcranial direct current stimulation; TENS, transcutaneous electrical nerve stimulation; UC, usual care; VR, virtual reality

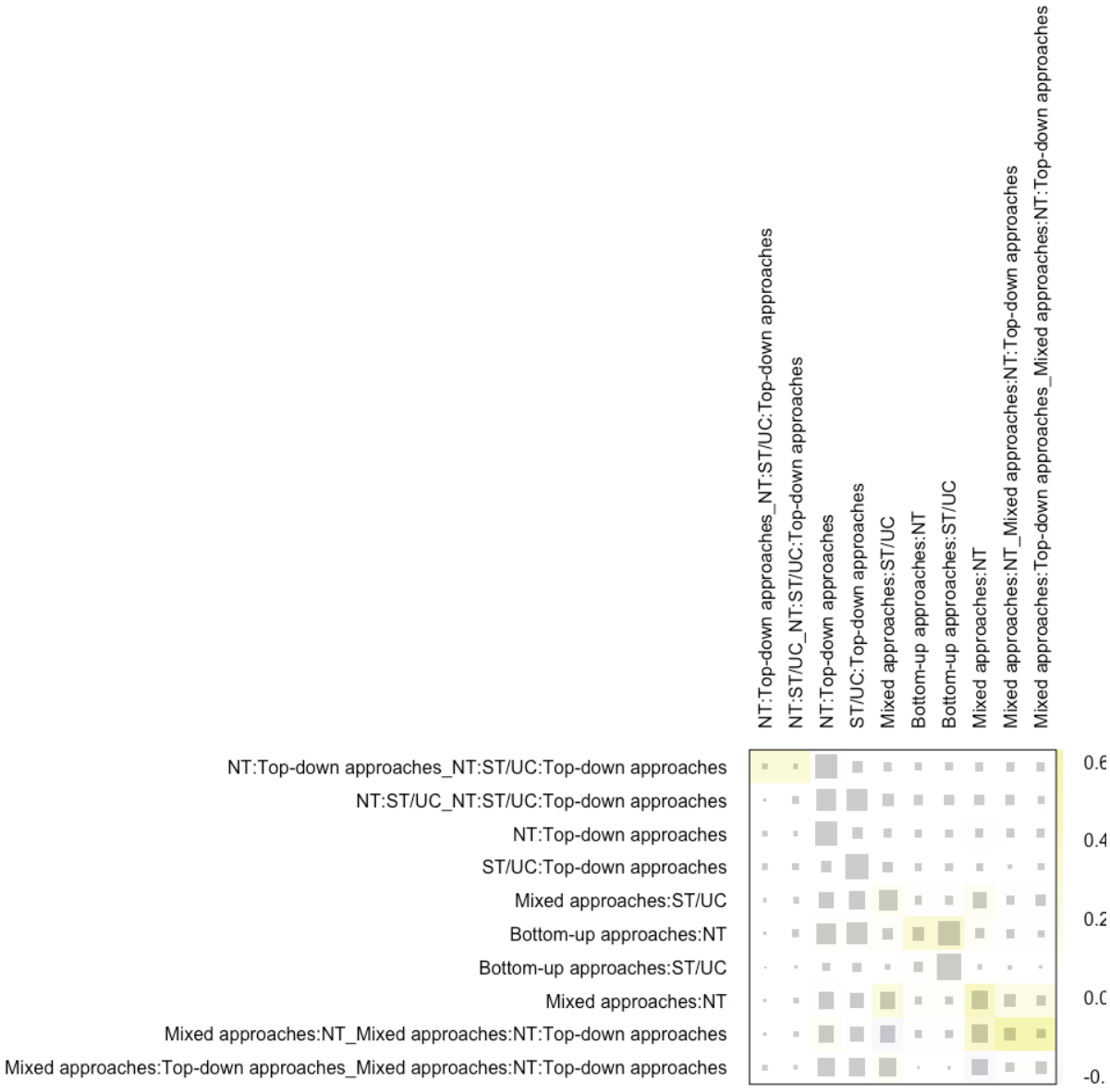
Appendix 2. Comparator group according to type of approach.



Two approaches were significantly different if no letter was shared between them. Otherwise, the two approaches were not significantly different.

Appendix 3. Global and local inconsistency for network meta-analysis of post-intervention effects on balance

The net heat plot for global inconsistency



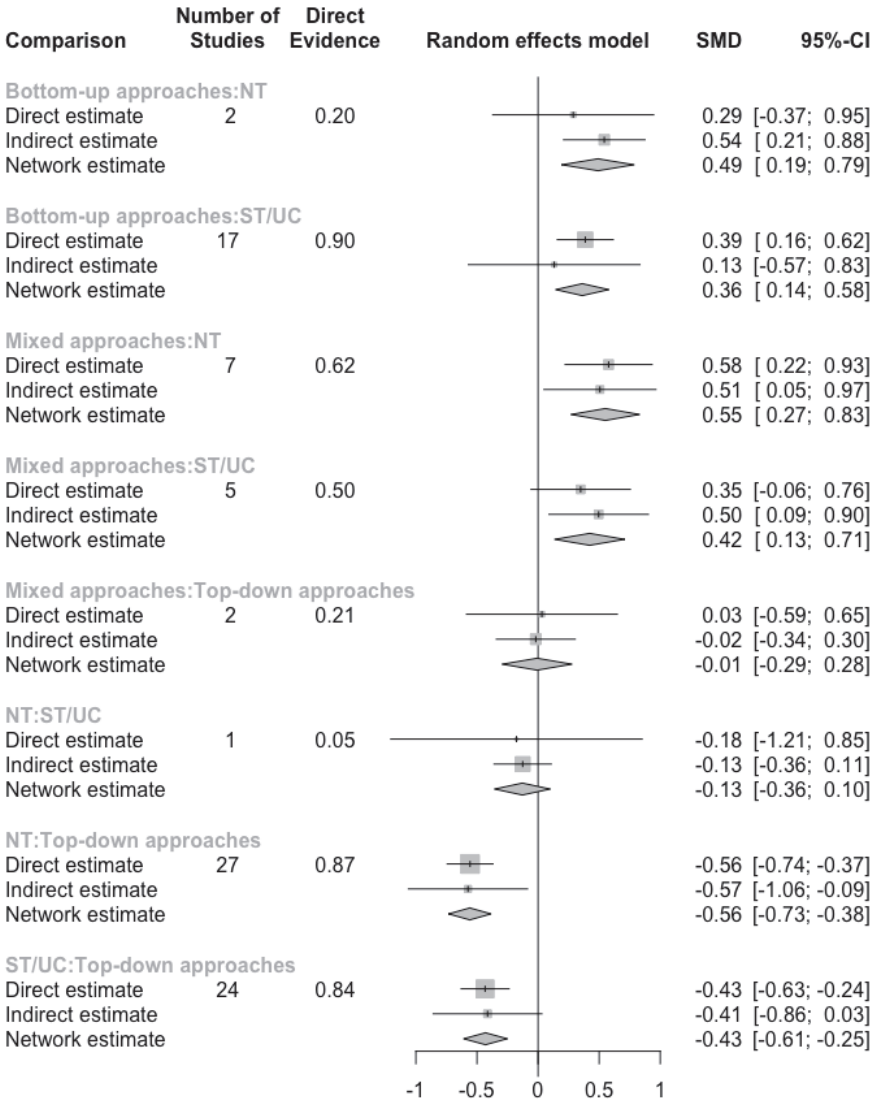
NT, no treatment; ST/UC, sham treatment and usual care

The node splitting for local inconsistency

Comparison	k	prop	nma	direct	indir.	Diff	z	p-value
Bottom-up approaches:Mixed approaches	0	0	-0.0605	.	-0.0605	.	.	.
Bottom-up approaches:NT	2	0.2	0.4901	0.2878	0.542	-0.2542	-0.67	0.5002
Bottom-up approaches:ST/UC	17	0.9	0.3618	0.3863	0.1321	0.2542	0.67	0.5002
Bottom-up approaches:Top-down approaches	0	0	-0.0684	.	-0.0684	.	.	.
Mixed approaches:NT	7	0.62	0.5507	0.5774	0.5065	0.0709	0.24	0.811
Mixed approaches:ST/UC	5	0.5	0.4223	0.3486	0.4961	-0.1475	-0.5	0.6157
Mixed approaches:Top-down approaches	2	0.21	-0.0078	0.0314	-0.0186	0.05	0.14	0.8882
NT:ST/UC	1	0.05	-0.1283	-0.1768	-0.1258	-0.051	-0.09	0.9246
NT:Top-down approaches	27	0.87	-0.5585	-0.5563	-0.5733	0.017	0.06	0.9493
ST/UC:Top-down approaches	24	0.84	-0.4301	-0.4334	-0.4134	-0.02	-0.08	0.9358

A random effects model was used.

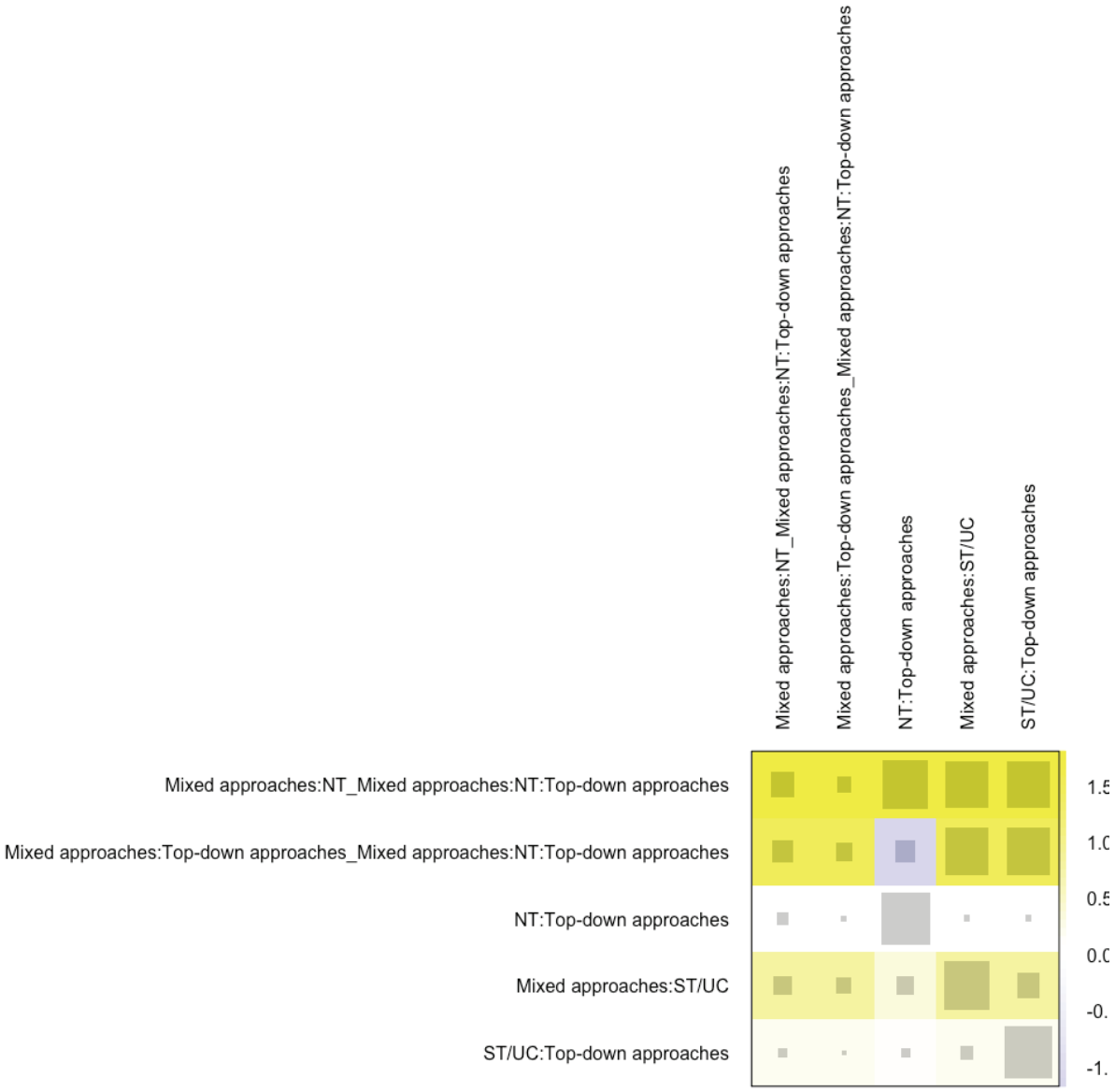
diff, difference between direct and indirect treatment estimates; direct, estimated treatment effect (SMD) derived from direct evidence; indir., estimated treatment effect (SMD) derived from indirect evidence; k, number of studies providing direct evidence; nma, estimated treatment effect (SMD) in network meta-analysis; p-value, p-value of test for disagreement (direct versus indirect); prop, direct evidence proportion; z, z-value of test for disagreement (direct versus indirect)



:, compared to; CI, confidence interval; NT, no treatment; SMD, standardised mean difference; STUC, sham treatment and usual care;

Appendix 4. Assessment of global and local inconsistency for network meta-analysis of persisting effects on balance

The net heat plot for global inconsistency



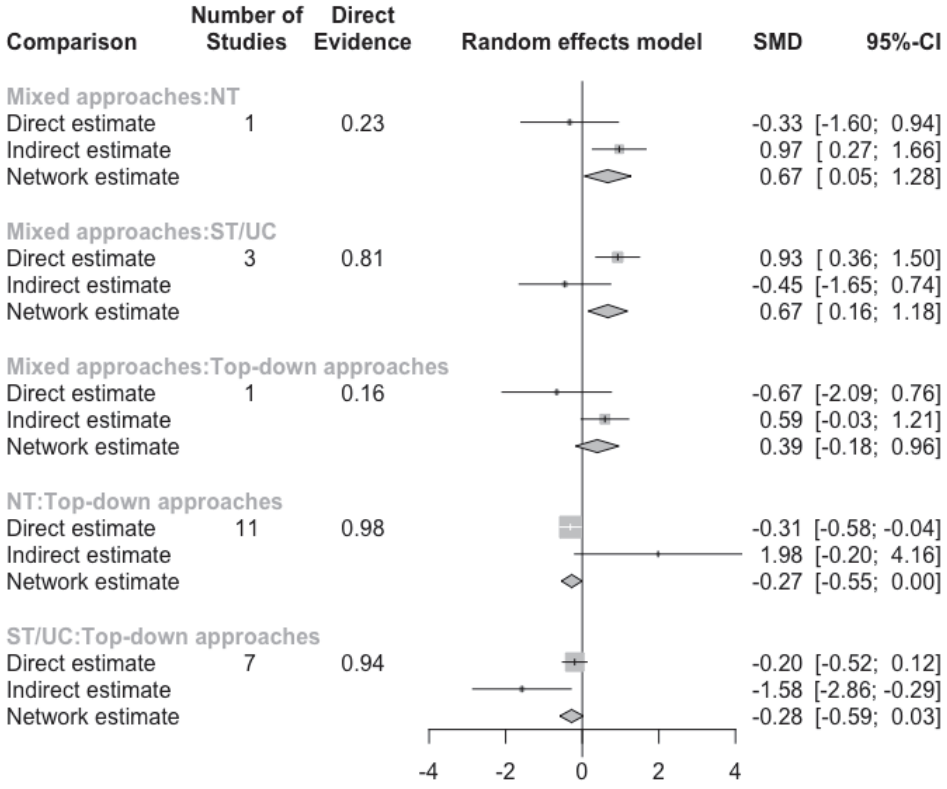
NT, no treatment; STUC, sham treatment and usual care

The node splitting for local inconsistency

Comparison	k	prop	nma	direct	indir.	Diff	z	p-value
Bottom-up approaches:Mixed approaches	0	0	-0.4424	.	-0.4424	.	.	.
Bottom-up approaches:NT	0	0	0.223	.	0.223	.	.	.
Bottom-up approaches:ST/UC	8	1	0.2271	0.2271	.	.	.	.
Bottom-up approaches:Top-down approaches	0	0	-0.0511	.	-0.0511	.	.	.
Mixed approaches:NT	1	0.23	0.6654	-0.3296	0.9653	-1.2949	-1.75	0.0802
Mixed approaches:ST/UC	3	0.81	0.6695	0.9256	-0.453	1.3786	2.04	0.041
Mixed approaches:Top-down approaches	1	0.16	0.3914	-0.6675	0.591	-1.2585	-1.59	0.1128
NT:ST/UC	0	0	0.0041	.	0.0041	.	.	.
NT:Top-down approaches	11	0.98	-0.2741	-0.3096	1.9803	-2.2899	-2.04	0.0409
ST/UC:Top-down approaches	7	0.94	-0.2781	-0.1974	-1.5761	1.3786	2.04	0.041

A random effects model was used.

diff, difference between direct and indirect treatment estimates; direct, estimated treatment effect (SMD) derived from direct evidence; indir., estimated treatment effect (SMD) derived from indirect evidence; k, number of studies providing direct evidence; nma, estimated treatment effect (SMD) in network meta-analysis; p-value, p-value of test for disagreement (direct versus indirect); prop, direct evidence proportion; z, z-value of test for disagreement (direct versus indirect)



:, compared to; CI, confidence interval; NT, no treatment; SMD, standardised mean difference; STUC, sham treatment and usual care;

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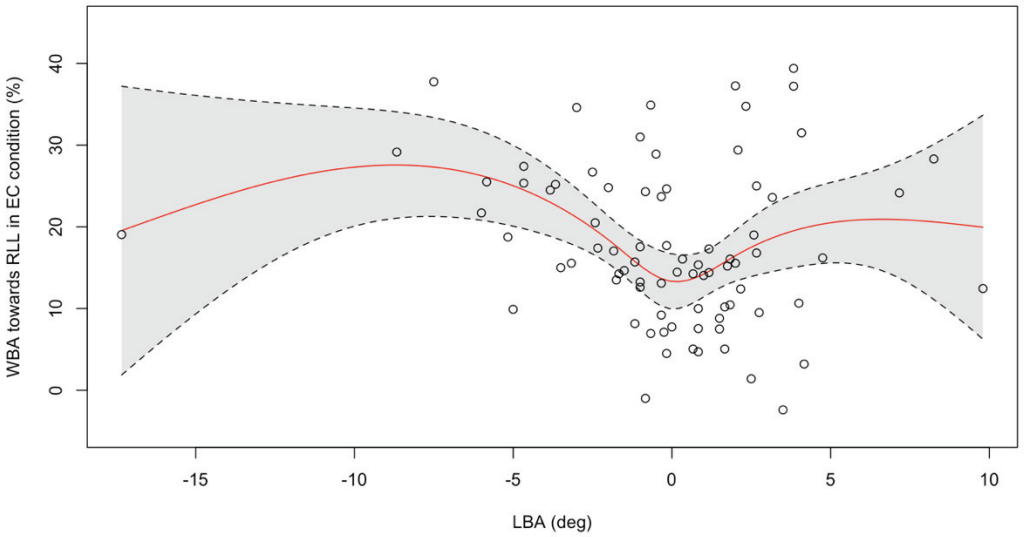
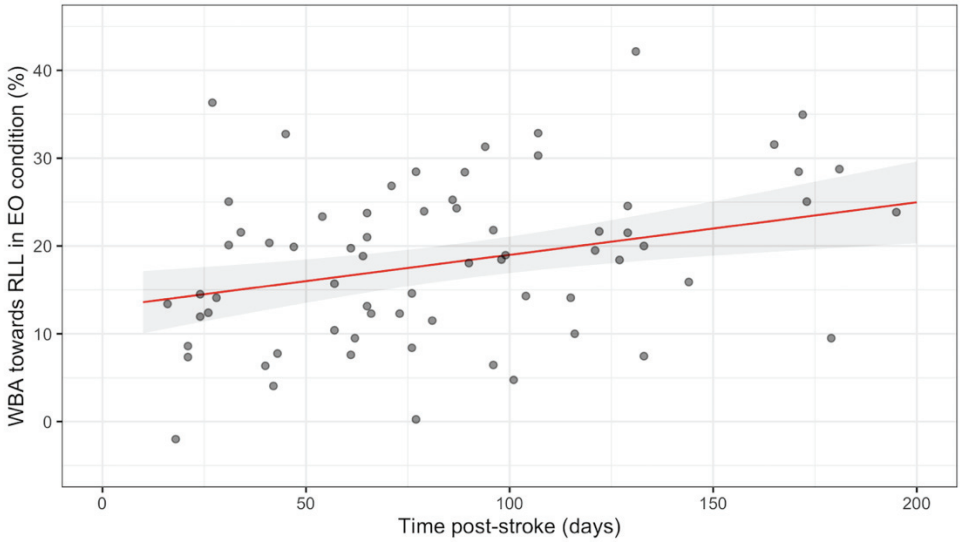
Supplementary Figure 1. Regression between WBA in EC condition and LBA



The grey area represents the 95% confidence interval.

EC, eyes closed; LBA, longitudinal body axis; RLL, right lower limb; WBA, weight bearing asymmetry

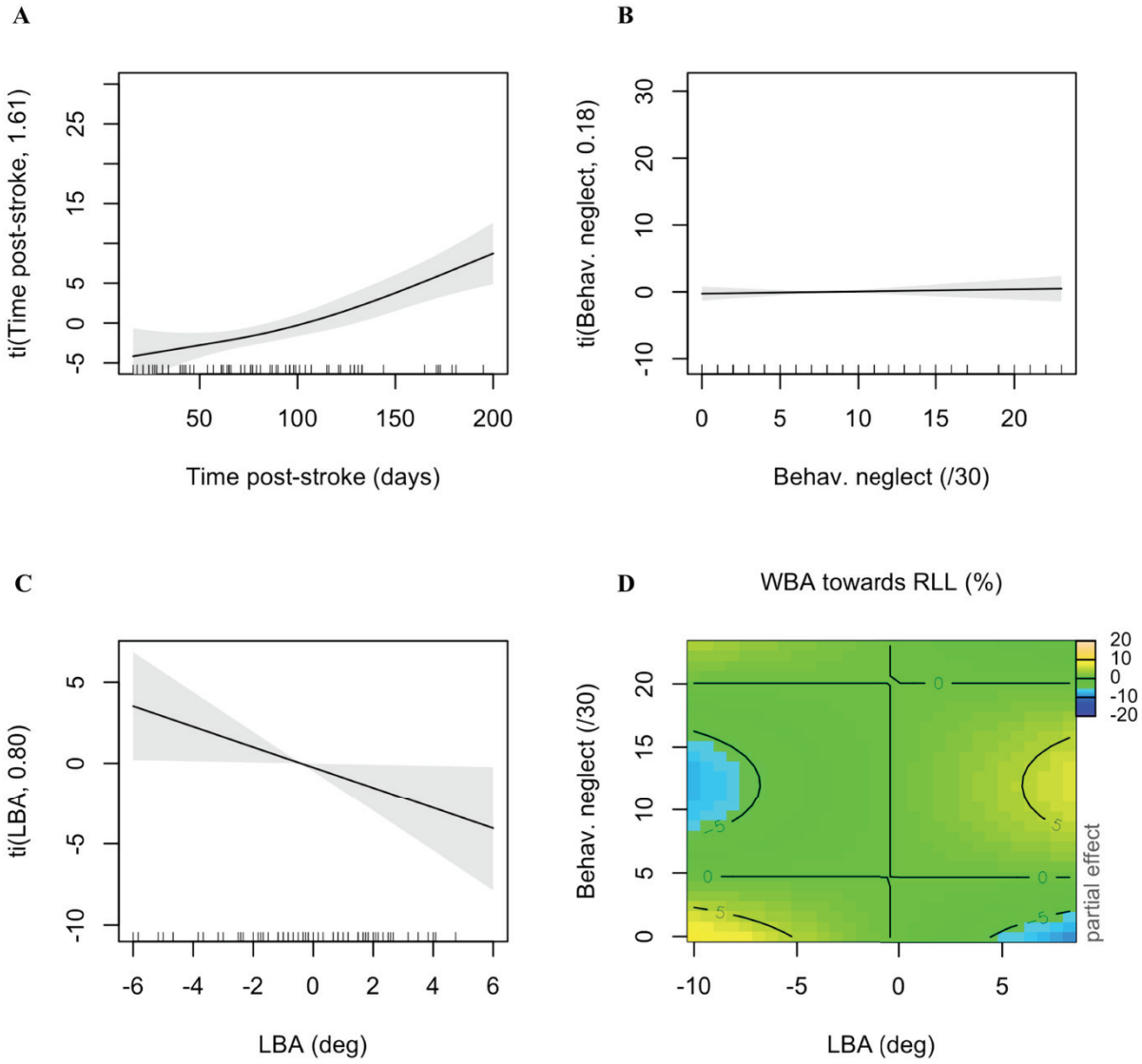
Supplementary Figure 2. Regression between WBA in EO condition and time post-stroke in patients with right stroke.



It is to note that in the present study, the time post-stroke reflects the delay from stroke until the patient was able to stand alone (see methods and discussion). The grey area represents the 95% confidence interval.

EO, eyes open; RLL, right lower limb; WBA, weight bearing asymmetry

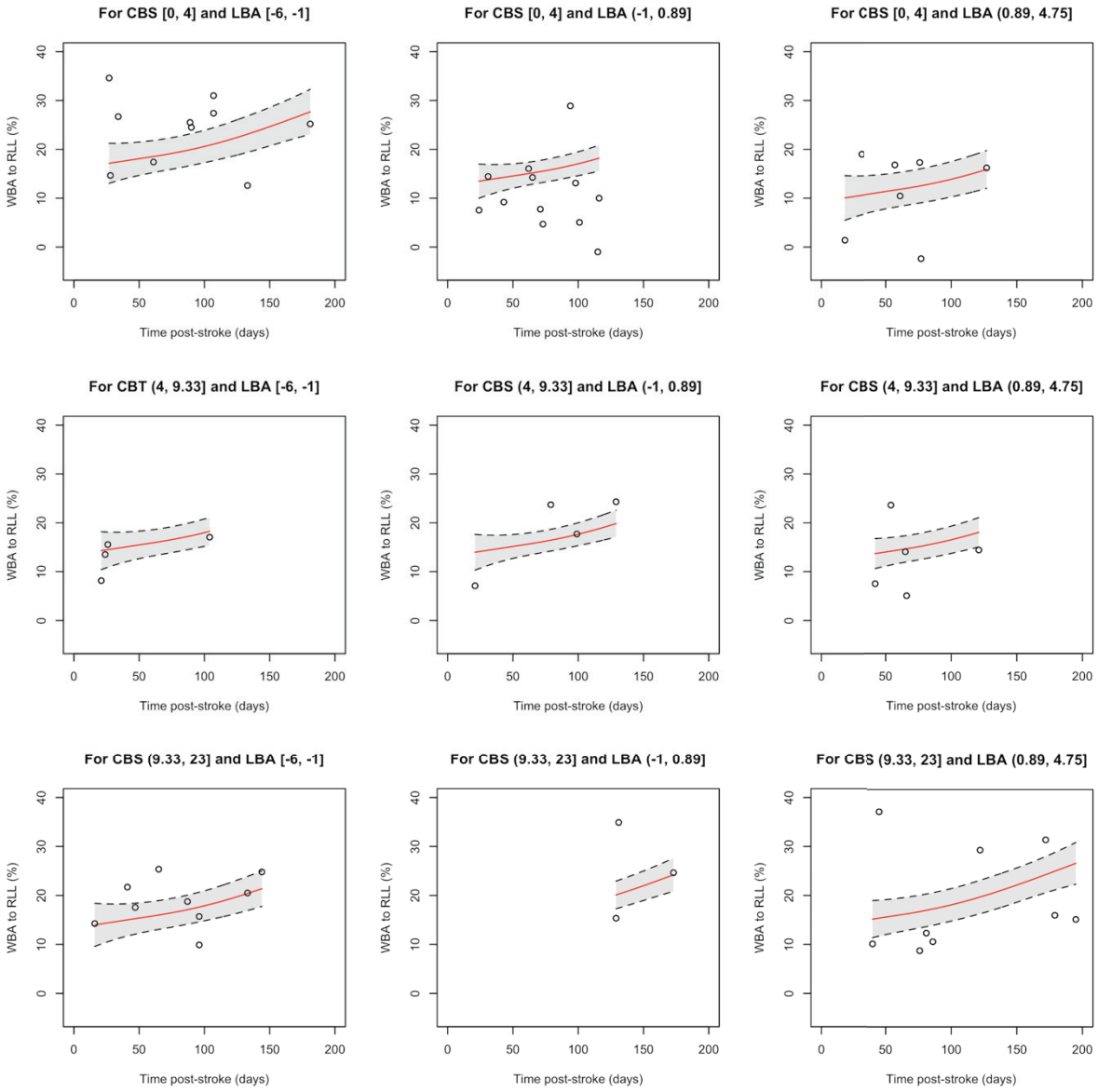
Supplementary Figure 3. Plots of partial effects of time post-stroke (4A), behavioural neglect (4B), LBA (4C), and the interaction between behavioural neglect and LBA (4D) on WBA in EC condition.



For LBA, a negative value means a position on the left side while a positive value means a position on the right side. The grey area represents the confidence band (+/-2se).

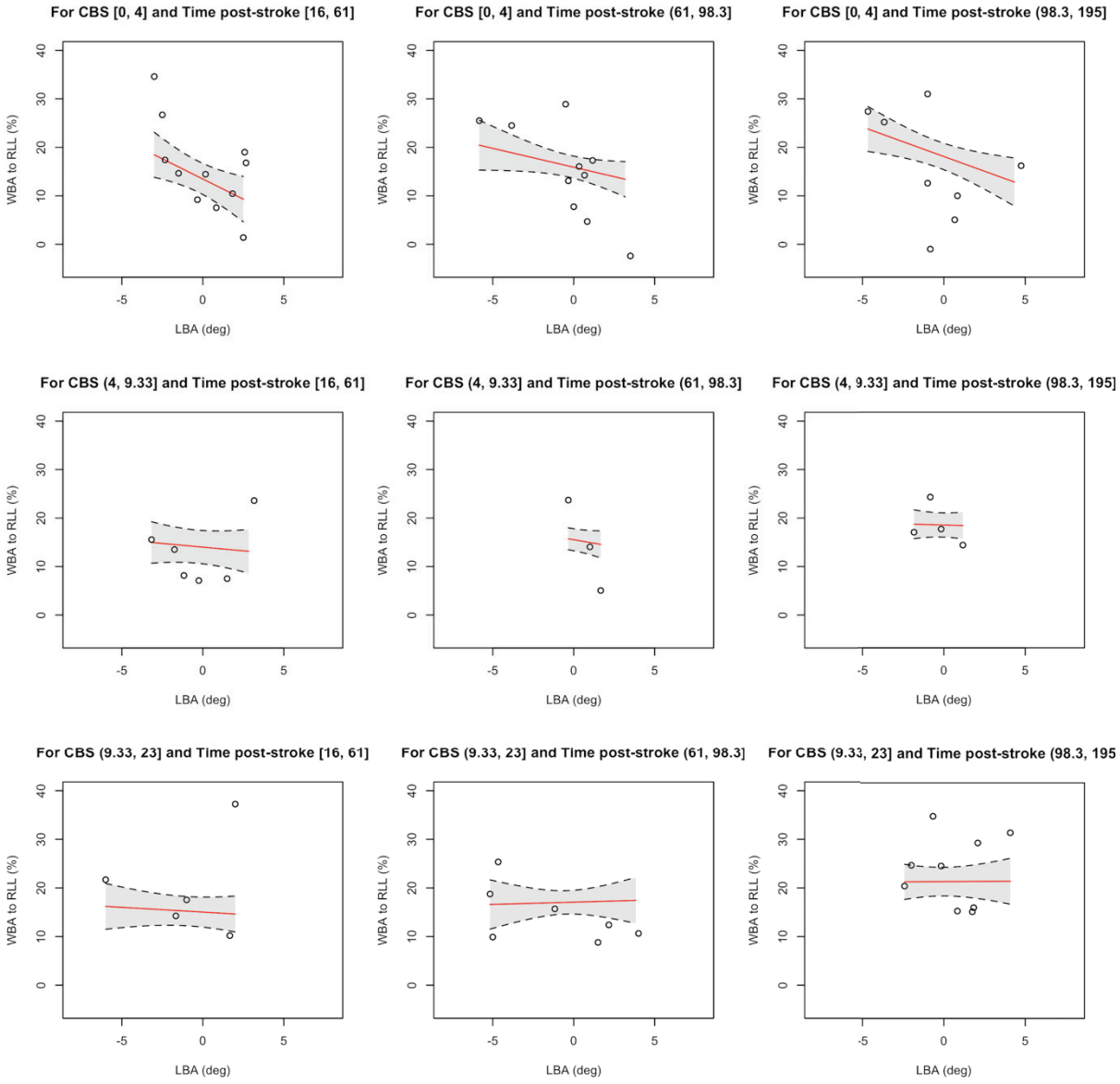
Behav, behavioural; EC, eyes closed; LBA, longitudinal body axis; ti, tensor; RLL, right lower limb; WBA, weight bearing asymmetry

Supplementary Figure 4. Adequacy checking plots for final model predicting WBA in eyes closed condition.



For LBA, a negative value means a position on the left side while a positive value means a position on the right side. The grey area represents the 95% confidence interval.

CBS, Catherine Bergego Scale; LBA, longitudinal body axis; RLL, right lower limb; WBA, weight bearing asymmetry



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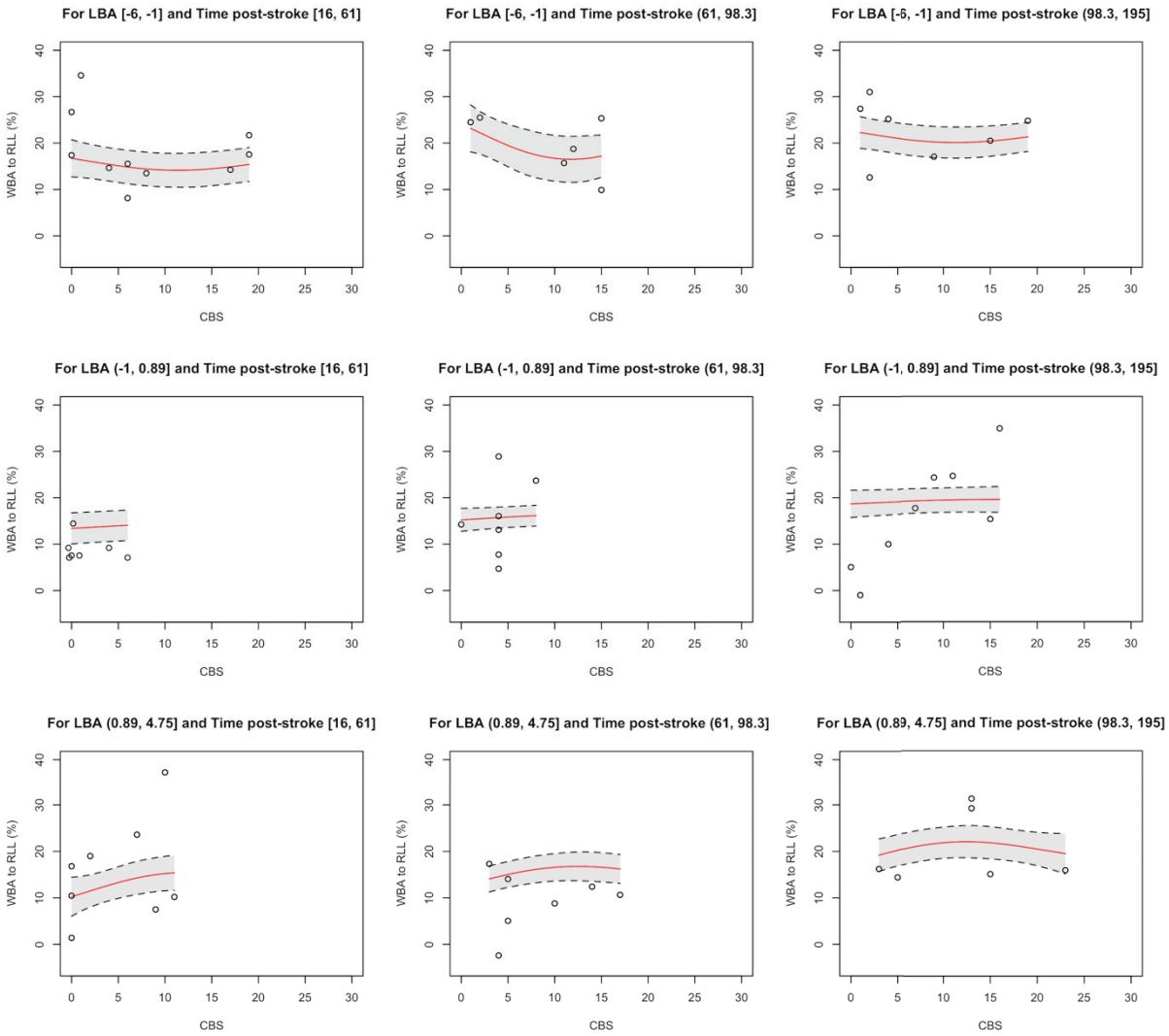

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MATERIEL SUPPLEMENTAIRE DU PROTOCOLE D'ESSAI CLINIQUE CONTROLE RANDOMISE MULTICENTRIQUE « PEQUIE »

Assessments at baseline

We will assess motor weakness at baseline: (1) global motor weakness (0 for no deficit, 1 for monoparesis, 2 for hemiparesis, 3 for monoplegia, and 4 for hemiplegia), (2) facial motor weakness (0 for no deficit, 1 for incomplete deficit, 2 for complete deficit), (3) motor weakness of left upper limb (scored from 0 to 5 using the Medical Research Council), (4) motor weakness of left lower limb (scored from 0 to 5 using the Medical Research Council), (5) left motor weakness measured using upper and lower limb subscales of motricity index (each with a score between 1 to 100). We will assess the spasticity of quadriceps, adductor, and surae triceps muscles of left lower limb using the modified Ashworth score. The superficial sensibility of the left lower limb will be examined by a light touch test on left thigh, calf, and foot. For the deep sensibility of the left lower limb, the assessor will ask the patient: (1) the orientation of hallux without visual input (up, neutral, down), but also (2) to reproduce the position and the orientation of the paretic knee and ankle positioned by the assessor with the nonparetic lower limb without visual input. These 2 tests will be scored between 0 and 2 (0 for no estimation, 1 for altered estimation, and 2 for correct estimation).

Statistical analysis

Exploratory analyses will be conducted with an adjustment controlling for time post-stroke, left motor weakness (measured on motor index), deep sensibility of the left lower limb, presence or absence of USN, and size of the stroke lesion. Potential interactions between variables may be examined.

Correlations between changes in the mean of pre-intervention assessments and post-intervention assessments on BBS, postural disorders (*i.e.* WBA, body sway, and lateropulsion), and spatial reference frames (*i.e.* SSA and LBA) will be also performed using multivariate regressions with linear mixed models including group and time as covariates. Potential interactions between variables may be added if needed.

Data management and monitoring

The investigators will be in charge of reminding patients of their follow-up by contacting them upstream of the assessments. Given the nature of the intervention frequently used for the rehabilitation of USN, and the low risk of occurrence of serious adverse event, no data-monitoring committee will be created. All the data relative to the study will be registered in patient medical records and recorded on a data collection notebook specifically dedicated to the trial, on which the patient identification will be coded. Potential adverse events will also be recorded. Data for outcomes will be extracted on a excel sheet for analyses to be

performed by an investigator (AH). All electronic data will be secured on a password-protected laptop. All investigators will be able get access to all documents if necessary. The promoter of the trial will be in charge to ensure the integrity of data and process by means of monitoring visits in the different centres.