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Stéphanie Challos-Leplaideur

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Par

Stéphanie LEPLAIDEUR

The neural basis of egocentric spatial representation and neck muscle vibration effects on spatial cognition, in healthy subjects and patients who had a right stroke

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Ko koe tēnā ko au tēnei kīwai o te kete

(You take that handle, and I'll take this handle of the kete . working together we will succeed)

Abstract

Balance disorders affect the prognosis of stroke, increasing the risk of falls and gait disorders. As they are partly related to spatial cognition disorders, we studied the correlates of the egocentric referential frame. Using functional MRI, we analysed 17 healthy subjects' brain activations during the subjective straight-ahead task (SSA) and the subjective longitudinal body plan task (SLB). They activated superior and inferior parietal areas and the lateral occipital cortex with a right predominance. The same analysis was performed on 14 patients who had a right stroke. We distinguished three patterns of activation reorganisation: perilesional, contra-lesional and bilateral. The underlying question is the specific management of these spatial cognition disorders after stroke. Despite the primary issue of managing balance disorders, no treatment addressing the cognitive component of balance is commonly used. Preliminary studies have shown that sensory stimulation by neck muscle vibration (NMV) is a promising treatment for postural disorders. We studied the cumulative effect of NMV sessions on postural asymmetry in 89 patients within nine months of a right stroke. However, the improvement in mediolateral deviation immediately after the first NMV session was not sustainable after the interventions on day 14. Furthermore, the combination with prismatic adaptation did not show any beneficial effect. Future research will focus on including patients earlier after stroke using specific markers of spatial cognition: SSA and SLB.

Resumé (French abstract- long version)

Les **troubles de l'équilibre** après **accident vasculaire cérébral** (AVC) entraînent un risque accru de chutes et une altération de l'autonomie. Ils augmentent le retentissement de l'AVC d'un point de vue personnel et socio-économique (Fong et al., 2001; Nardone et al., 2009; Simpson et al., 2011). Chez une proportion significative de patients victimes d'un AVC, les **troubles de la cognition spatiale** impactent la capacité à maintenir l'équilibre en se surajoutant aux troubles moteurs ou à la spasticité (Rode et al., 1997; Pérennou, 2005; Saj et al., 2006; Rousseaux et al., 2014; Bonan I. et al., 2015; Tasseel-Ponche et al., 2015; Jamal et al., 2018). Cependant, les mécanismes sous tendant la **perception égocentrée** après un AVC et sa prise en charge ont été peu étudiés.

La littérature décrit une mauvaise perception du corps dans l'espace prédominant en cas de lésion droite (Rode et al., 1997; Pérennou and Bénéaim C, Rouget E, Rousseaux M, Blard JM, Pélissier J, 1999; Bonan et al., 2016). Le **rôle crucial du réseau cérébral droit dans le processus de cognition spatiale** pourrait expliquer cette spécificité, impliquant notamment le cortex pariétal postérieur (PPC) (Andersen, 1997; Neggers et al., 2006; Zaehle et al., 2007; Galati et al., 2010; Saj et al., 2014). Par conséquent, il nous a semblé pertinent de concentrer nos travaux sur les patients ayant subi un AVC de l'hémisphère droit.

La question sous-jacente est la **prise en charge spécifique de ces troubles de la cognition spatiale après un AVC** car aucun traitement de la composante cognitive du déséquilibre n'est actuellement couramment utilisé. Les approches traditionnelles consistent à stimuler la perception consciente de l'orientation du corps dans l'espace. Ces exercices Top-down sont laborieux et exigeants. Ils nécessitent une participation active, alors que la prise de conscience des troubles de la cognition spatiale est déjà une première étape difficile pour les patients victimes d'un AVC. Dans ce contexte, les **stimulations sensorielles** pourraient constituer un traitement prometteur en s'attaquant spécifiquement à la composante cognitive des troubles de l'équilibre. Les programmes de réhabilitation sensorielle ont été initialement appliqués pour améliorer la négligence visuospatiale (Kerkhoff et Schenk, 2012). En raison des mécanismes proches conduisant aux biais de négligence et aux troubles posturaux, ces techniques sont susceptibles d'avoir un impact positif sur les troubles de l'équilibre. Elles

diminueraient la distorsion de la perception du corps dans l'espace en rétablissant la symétrie des entrées sensorielles (Bonan I. et al., 2015).

Nous avons concentré nos recherches sur les **vibrations des muscles du cou** (NMV) car elles nécessitent une participation minimale des patients et peuvent être utilisées tôt après un AVC. La vibration est une stimulation sensorielle induisant une illusion d'étirement du muscle vibré. Des études antérieures ont montré que les NMV étaient efficaces sur les symptômes de négligence si elles étaient répétées (Johannsen et al., 2003 ; Schindler et Kerkhoff, 2004). Des études plus récentes suggèrent que les NMV pourraient réduire le biais spatial après un AVC (Bonan I. et al., 2015 ; Leplaideur et al., 2016). De plus, les données cliniques et de neuro-imagerie fonctionnelle suggèrent une action centrale directe sur les structures corticales impliquées dans l'élaboration de la représentation spatiale (Bottini et al., 2001). Nous avons voulu tester les NMV dans des programmes de rééducation sur les biais d'équilibre après un AVC. De plus, des travaux antérieurs ont suggéré un **effet positif de la combinaison de stimulations sensorielles** (Karnath, 1994 ; Saevarsson et al., 2010 ; Guinet et Michel, 2013). Nous abordons cette question en combinant plusieurs stimulations sensorielles.

Cette thèse est construite en quatre parties principales.

La première partie présente le **concept de cognition spatiale**. Les bases neuronales des tâches égocentrées chez des sujets sains sont présentées dans un 1^{er} article publié en 2021. Des analyses préliminaires de nos résultats dans le cas de patients ayant subi un AVC droit sont présentées dans un 2^{ème} article, en cours de rédaction.

La deuxième partie passe en revue les **principes des NMV** et les résultats des études antérieures réalisées dans notre équipe (3^{ème} et 4^{ème} articles publiés en 2020).

La troisième partie présente les **résultats cliniques du PHRC AVCPOSTIM**, étude randomisée contrôlée multicentrique, évaluant l'effet du NMV sur les troubles de l'équilibre après un AVC (seul ou en combinaison avec l'adaptation prismatique (PA)) (5^{ème} article soumis).

Enfin, la discussion développe les résultats et offre des perspectives de recherche.

Nous avons focalisé notre recherche sur les **référentiels égocentriques** en raison de son implication dans les activités de la vie quotidienne et de la relation significative retrouvée avec les troubles de l'équilibre après un AVC (Barra et al., 2009 ; Jamal et al., 2018). Les bases

neurales de la perception du référentiel égocentré peuvent être étudiées en utilisant deux tâches, le **droit devant subjectif** (SSA) et le **plan longitudinal du corps subjectif** (SLB).

En 2018, nous avons exploré le lien entre SSA, SLB et l'asymétrie d'appui (WBA weight bearing asymétrie) après AVC droit et gauche (annexe 1 - Jamal et al., 2018). **À un stade chronique de la récupération**, le **WBA était corrélé au SLB**, surtout en cas de lésion droite ($r = 0.77$, $p = 0.02$). Dans cet article, nous avons confirmé la relation entre les comportements posturaux asymétriques des patients atteints d'AVC chronique et leur perception biaisée du cadre spatial égocentrique. Ne retrouvant **pas de relation WBA/SSA**, nous avons émis l'hypothèse que les mécanismes sous-jacents à l'intégration de ces parties du schéma égocentrique (extracorporel et corporel) pourraient être différents.

Nous avons donc étudié et comparé les activations cérébrales lors de la réalisation des tâches égocentriques (SSA et SLB) en neuro-imagerie, dans un premier temps chez des participants sains :

The Neural Bases of Egocentric Spatial Representation for Extracorporeal and Corporeal Tasks: An fMRI Study. Stephanie Leplaideur , Annelise Moulinet-Raillon , Quentin Duché , Lucie Chochina , Karim Jamal , Jean-Christophe Ferré , Elise Banner * and Isabelle Bonan * . Brain Sci. 2021, 11, 963.

<https://doi.org/10.3390/brainsci11080963>

A notre connaissance, cette étude est le premier travail tentant de discriminer ces référentiels égocentriques distincts. Par ailleurs, nous avons utilisé un atlas cytoarchitectonique avec des sous-régions cérébrales anatomiques et fonctionnelles pour interpréter nos résultats et affiner notre compréhension des représentations centrées sur le corps. Nous avons donc implémenté ces deux tâches pour l'IRMf et avons étudié les points communs et les différences.

Les activations étaient superposées avec une prédominance dans **le réseau fronto-pariéto-occipital droit** (lobule pariétal supérieur et inférieur, precuneus, gyrus post central, cortex occipital latéral, cortex précentral), **suggérant le partage d'une large base neuronale**. Le contraste **SLB > SSA** a révélé plus **activations en angulaire et prémoteur gauches**. Ces zones, impliquées dans l'attention et l'imagerie motrice, suggèrent une plus grande complexité des processus corporels engageant la représentation du corps.

La deuxième publication, en cours de rédaction, a pour but d'étudier les activations cérébrales lors des tâches de cognition spatiale chez les sujets ayant présenté un AVC droit dans les 9 mois :

The reorganization of egocentric spatial representation in patients who had a right hemispheric stroke, an fMRI study. Leplaideur S, Moulinet-Raillon A, Duché Q, Chochina L, Jamal K, Ferré J-C, Bannier E, Bonan I. Article in progress

Nous avons utilisé le même protocole que celui des sujets sains, présenté dans la publication précédente. Quatorze patients d'un âge moyen de 61 ans ont été inclus à 82,3 jours depuis l'AVC. Par rapport aux activations au niveau du groupe obtenues chez les sujets sains, les activations cérébrales des patients étaient trop hétérogènes pour trouver des résultats significatifs au niveau du groupe. Au niveau individuel, nous avons observé **trois types d'activation** par ordre décroissant : 1) les patients présentant des **activations bilatérales** ; 2) les patients présentant uniquement des **activations contra lésionnelles** ; 3) les patients présentant des **activations ipsi lésionnelles prédominantes malgré la lésion**. Pendant le SSA, nous avons localisé des activations dans le gyrus frontal inférieur droit, le cervelet postérieur, le gyrus temporal moyen, le gyrus occipital moyen, le PPC, et dans le cuneus et le lobule pariétal supérieur gauche. Pendant le SLB, les patients ont activé le cervelet postérieur droit, le gyrus temporal moyen, le gyrus précentral, le gyrus angulaire et le gyrus occipital moyen. Des activations gauches ont été trouvées dans le gyrus occipital moyen, le cuneus, le gyrus temporal moyen, le gyrus frontal précentral et supérieur. Par rapport aux zones impliquées pendant ces tâches chez les sujets sains, nous avons trouvé deux localisations supplémentaires : le **cervelet postérieur** et le **gyrus temporal moyen et inférieur**. Étant donné le nombre limité de patients dans chaque groupe, nous n'avons pas pu identifier statistiquement un modèle de lésion ou de capacité spatiale. Cependant, il semble que les patients présentant une petite lésion soient plus susceptibles d'activer les zones ipsi lésionnelles. L'étude des réseaux sous-jacents à ces activations égocentriques et l'étude d'une plus grande population pourraient améliorer les connaissances sur la réorganisation potentielle des zones cérébrales d'intégration de haut niveau pendant les tâches de cognition spatiale. L'identification des profils de réorganisation pourrait permettre d'adapter leur programme de stimulation.

La **stimulation sensorielle par NMV** apparaît comme une voie prometteuse pour traiter les troubles de l'équilibre liés aux troubles de la cognition spatiale. L'hypothèse est qu'elles diminuent la distorsion de la perception du corps dans l'espace en rétablissant la symétrie des entrées sensorielles. Dans l'article suivant (Jamal et al., 2020), avec Karim Jamal, nous avons analysé les articles étudiant l'effet des NMV sur l'orientation posturale et la perception spatiale chez des sujets sains et chez des patients présentant une perception déformée de l'orientation du corps.

The effects of neck muscle vibration on postural orientation and spatial perception: A systematic review. Jamal K, Leplaideur S, Leblanche F, Moulinet Raillon A, Honoré T, Bonan I. *Neurophysiol Clin.* 2020 Sep;50(4):227-267.

<https://doi.org/10.1016/j.neucli.2019.10.003>

Après avoir passé en revue 290 références, 67 articles ont été inclus avec un total de 1522 participants (958 sujets sains, 235 patients présentant des lésions vestibulaires et 159 ayant subi un accident vasculaire cérébral). Malheureusement, les études étaient très hétérogènes, de sorte que les preuves sont faibles. Premièrement, notre revue a conclu que chez les participants sains, les NMV produisent une illusion d'un environnement visuel se déplaçant vers le côté opposé de la vibration et une déviation du SSA vers le côté vibré. Deuxièmement, chez les patients ayant subi un AVC, les **NMV semblent moduler le biais spatial et postural** (avec une déviation SSA et inclinaison mediolaterale vers le coté vibré).

Dans une étude préliminaire, nous avons réalisé une séance de NMV sur 31 patients ayant eu un AVC récent (Leplaideur et al., 2016, annexe 5). Nous avons rapporté qu'une séance de NMV diminue la déviation médio-latérale (ML) de la position du centre de pression (CoP) du patient. Cet effet semblait être plus élevé en cas de déficit de sensibilité et d'illusion visuelle vers le NMV côté controlatéral du déplacement de l'environnement lors de la vibration. De plus, la correction de la déviation ML du CoP était modulée par la vision.

Après ces résultats encourageants, nous avons étudié les séances cumulatives de NMV sur les troubles de l'équilibre chez les patients à la phase chronique d'un AVC.

The effects of repetitive neck muscle vibration on postural disturbances after a chronic stroke. Jamal K, Leplaideur S, Rousseau C, Cordillet S, Raillon AM, Butet S, Cretual A, Bonan I. *Neurophysiol Clin.* 2020 Sep;50(4):269-278.

<https://doi.org/10.1016/j.neucli.2020.01.005>

Trente-deux patients ayant subi un AVC chronique (âge moyen de $60,9 \pm 10$ ans et temps moyen depuis l'AVC de $4,9 \pm 4$ ans), 16 cérébrolésés droit, 16 cérébrolésés gauche, ont suivi un programme de 10 séances de NMV sur deux semaines. Initialement aucun des deux groupes n'a montré une altération de la représentation spatiale à cette phase chronique. Néanmoins, il y avait une amélioration significative de la motricité ($P = 0,02$), du TUG ($P = 0,0005$) et du BBS ($P < 0,0001$) dans les deux groupes à la fin du traitement. **Les NMV ont semblé corriger la WBA chez les patients cérébrolésés droit uniquement.**

Dans l'objectif d'évaluer l'effet dans une population plus précoce après AVC, nous avons mis en place un protocole hospitalier de recherche clinique (**PHRC AVCPOSTIM**). Le but de cet essai multicentrique randomisé, contrôlé, en simple aveugle était d'étudier les effets cumulatifs de l'adaptation au prisme (PA), de la vibration des muscles du cou (NMV) et des séances PA+NMV sur l'asymétrie posturale après un récent AVC de l'hémisphère droit. Nous avons émis l'hypothèse que la combinaison de PA et de NMV aurait un effet synergique.

Les résultats cliniques sont présentés dans un article en cours de soumission :

Combining prism adaptation and neck vibration for postural recovery after stroke: a multicenter randomized study. Leplaideur S, Allart E, Chochina L, Pérennou D, Rode G, Boyer F-C, Paysant J, Yelnik A, Jamal K, Duché Q, Combès B, Bannier E, Bonan I. In Submission

Les patients de huit service de MPR ont été sélectionnés dans les 9 mois suivant leur premier accident vasculaire cérébral supratentorial de l'hémisphère droit. Ils ont été inclus si leur membre parétique supportait moins de 40% de leur poids corporel. Les patients ont été répartis au hasard en quatre groupes : intervention contrôle, PA, NMV et NMV+PA, et ont suivi 10 séances sur 2 semaines. Le résultat primaire était la déviation moyenne du centre de pression sur l'axe mediolateral (ML), évaluée sur une plateforme de force à la fin de l'intervention (jour 14). Les résultats secondaires comprenaient les changements du ML immédiatement après la première séance, et aux jours 90 et 180.

Quatre-vingt-neuf patients ont été répartis au hasard dans l'un des quatre groupes suivants : contrôle ($n = 22$), PA ($n = 23$), NMV ($n = 22$) ou NMV+PA ($n = 22$). Pour notre résultat principal

à J14, nous n'avons **pas observé de différences d'évolution de la déviation ML entre les groupes**. Les analyses secondaires ont révélé 1) **immédiatement après la première séance, une amélioration de la déviation ML dans la condition yeux ouverts pour le groupe NMV**, par rapport au groupe contrôle (différence médiane : ML = -8,3 mm vs. 0,5 mm, IQR = 27, taille de l'effet (d de Cohen) = 0,56, p = 0,04), 2) à plus long terme (jours 90 et 180), une réduction plus faible du ML pour les groupes NMV et PA+NMV, par rapport aux groupes contrôle et PA (jour 90 : p = 0,013 ; jour 180 : p = 0,002).

Dans cet essai clinique, nous avons choisi **la WBA comme critère d'inclusion, marqueur du trouble postural** lié à la mauvaise représentation spatiale. Ce choix s'appuie sur des travaux antérieurs qui ont mis en évidence un lien entre le SLB et la WBA (Barra et al., 2009 ; Jamal et al., 2018). La WBA est associée à l'instabilité posturale et à la sévérité du handicap post-AVC (Pérennou, 2005 ; Kim et Kim, 2015). Cependant, la WBA est impactée par la cognition spatiale, les troubles de la commande motrice, de la sensibilité et la spasticité. De plus, la question de l'utilité de l'asymétrie d'appui reste ouverte. Ainsi, est ce que la WBA est une adaptation utile ou le reflet d'une mauvaise perception spatiale ? L'hypothèse est que la WBA pourrait être une adaptation limitant la sollicitation du membre inférieur parétique et diminuant le risque de chute. Cependant, il existe plusieurs arguments suggèrent la responsabilité de la mauvaise perception spatiale dans le WBA. Premièrement, l'asymétrie d'équilibre reste est liée aux troubles de la cognition spatiale quand les résultats sont ajustés à la motricité et la sensibilité (Barra et al., 2009). Deuxièmement, dans des études antérieures, aucun effet négatif sur la stabilité posturale n'a été trouvé dans les études diminuant l'WBA (Jamal et al., 2020). Le deuxième inconvénient de ce marqueur est qu'il faut attendre que le patient puisse se suffire à lui-même. Ce point entraîne deux conséquences. Le délai induit une hétérogénéité du temps entre l'AVC et l'inclusion. De plus, les troubles de la cognition spatiale ont pu retarder la récupération des capacités d'équilibre debout et au moment où nous avons appliqué la stimulation sensorielle, les troubles de la cognition spatiale ont pu fortement diminuer. Précisément, l'intérêt de la stimulation sensorielle est d'être utilisée tôt avant l'obtention d'un équilibre debout stable.

Une façon d'améliorer l'étude de l'effet du NMV sur la cognition spatiale serait d'utiliser des biomarqueurs plus spécifiques et plus sensibles. En effet, l'intérêt de cette stimulation sensorielle est son utilisation précoce, à un moment où les troubles de la cognition spatiale

sont prévalents. Ainsi, le SSA et le SLB seraient des marqueurs de choix, mesurables avant l'acquisition de l'équilibre debout et indépendants des autres facteurs impliqués dans la posture.

En conclusion,

Le référentiel égocentrique, souvent impliqué dans les troubles de la cognition spatiale après un AVC, doit être pris en compte dans les programmes d'évaluation et de rééducation. Deux biomarqueurs sont habituellement utilisés en pratique clinique pour tester la représentation spatiale dans le référentiel égocentrique, à savoir le SSA (espace extracorporel) et le SLB (espace corporel). Tous deux étudiés par IRMf chez des témoins sains, ils ont mis en évidence un réseau fronto-pariéto-occipital avec une prédominance droite. Le SLB apparaît comme un biomarqueur intéressant impliquant plus les aires angulaire et précentrale gauches suggérant une plus grande complexité des processus corporels engageant la représentation du corps. Cette activité controlatérale spécifique soutient le concept d'un réseau bilatéral sous-jacent aux tâches de cognition spatiale.

De manière intéressante, en utilisant l'IRMf chez des patients ayant subi un AVC droit, trois schémas d'activation ont été observés pour les deux biomarqueurs pendant les tâches extracorporelles et corporelles, recrutant soit des aires bilatérales, soit des aires gauches (controlatérales), soit des aires droites (péri lésionnelles). De plus, nous avons trouvé des activations dans le cervelet postérieur et le gyrus temporal impliqués dans le processus d'adaptation de la cognition spatiale. Cependant, nos données préliminaires n'ont pas permis d'établir un profil comportemental ou de lésion cérébrale (dans leur localisation ou leur volume). Enfin, les résultats de l'étude clinique randomisée multicentrique AVCPOSTIM évaluant l'effet de la stimulation sensorielle comme stratégie potentielle de réhabilitation chez des patients présentant une perturbation de l'équilibre liée à des troubles de la cognition spatiale n'ont pas confirmé notre hypothèse préalable. En effet, ni les séances prismatiques ni les séances NMV n'ont amélioré l'asymétrie en appui, qu'elles soient utilisées séparément ou combinées. Cependant, l'utilisation d'un autre critère comme le SSA et le SLB sans attendre la capacité à se lever pourrait modifier ces résultats.

Ce travail a des perspectives prometteuses. Une étude auxiliaire incluant des patients plus précoces sur le critère de la déviation des axes a été initiée, utilisant l'IRMf et la diffusion. L'analyse de la connectivité structurelle par imagerie pondérée de diffusion pendant les tâches

corporels et extracorporels, au repos et sous vibrations seront des avancées dans la compréhension de la perception du référentiel égo-centré et de la réorganisation en cas d'AVC. De même, l'étude de l'analyse du VLSM permettra de mieux comprendre l'impact des lésions sur ces capacités de cognition spatiale.

List of Original Papers

This thesis is based on the following papers, accepted or in progress, included in the manuscript. Published papers were reprinted with kind permission of editors (Experimental Brain Journal, Clinical neurophysiology, Brain sciences), two articles are under submission (Neurology, Gait and posture).

Publication 1 (p. 32)

The Neural Bases of Egocentric Spatial Representation for Extracorporeal and Corporeal Tasks: An fMRI Study.

Leplaideur S, Moulinet-Raillon A, Duché Q, Chochina L, Jamal K, Ferré J-C, Bannier E, Bonan I. Brain Sci. 2021, 11, 963. <https://doi.org/10.3390/brainsci11080963>

Publication 2 (p. 49)

The reorganization of egocentric spatial representation in patients who had a right hemispheric stroke, an fMRI study.

Leplaideur S, Moulinet-Raillon A, Duché Q, Chochina L, Jamal K, Ferré J-C, Bannier E, Bonan I. Article in progress

Publication 3 (p. 72)

The effects of neck muscle vibration on postural orientation and spatial perception: A systematic review.

Jamal K, **Leplaideur S**, Leblanche F, Moulinet Raillon A, Honoré T, Bonan I. Neurophysiol Clin. 2020 Sep;50(4):227-267. <https://doi.org/10.1016/j.neucli.2019.10.003>

Publication 4 (p. 81)

The effects of repetitive neck muscle vibration on postural disturbances after a chronic stroke. Jamal K, **Leplaideur S**, Rousseau C, Cordillet S, Raillon AM, Butet S, Cretual A, Bonan I. Neurophysiol Clin. 2020 Sep;50(4):269-278. <https://doi.org/10.1016/j.neucli.2020.01.005>

Publication 5 (p.102)

Combining prism adaptation and neck vibration for postural recovery after stroke: a multicenter randomized study

Leplaideur S, Allart E, Chochina L, Pérennou D, Rode G, Boyer F-C, Paysant J, Yelnik A, Jamal K, Duché Q, Combès B, Bannier E, Bonan I.
In submission

List of Appendix

Appendix 1

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Exp Brain Res. Aug 2018;236(8):2377-85

Appendix 2

Postural asymmetry and hemiplegia post-stroke: a systematic review and meta-analysis.
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Under proof reviewing in Gait and Posture (Oct 2021)

Appendix 3

Effect of sensorial stimulations on postural disturbances related to spatial cognition disorders after stroke.
Bonan I, Chochina L, Moulinet-Raillon A, leblong E, **Challois-Leplaideur S**.
Clin Neurophysiol 2015 (45) 297 : 303

Appendix 4

Tables of the article

The effects of neck muscle vibration on postural orientation and spatial perception: A systematic review.
Jamal K, **Leplaideur S**, Leblanche F, Moulinet Raillon A, Honoré T, Bonan I.
Neurophysiol Clin. 2020 Sep;50(4):227-267. doi: 10.1016/j.neucli.2019.10.003.

Appendix 5

Short term effects of neck muscle vibration on postural disturbances in stroke patients.
Leplaideur S, Leblong E, Jamal K, Moulinet-Raillon A, Coignard P, Damphousse M, Bonan I.
Exp Brain Res, 2016 (234) 2643-2651

Appendix 6

Curriculum Vitae S leplaideur

Keys words and Abbreviations

Key Words :

functional MRI

hemiplegia

Neck muscle vibration

Postural asymmetry

Prism adaptation

Rehabilitation

Sensorimotor cortex

Spatial cognition

Stroke

Abbreviations :

CoP Centre of pressure

CVS caloric vestibular stimulation

EPI echo planar imaging

FEF frontal eye field

FOV field of view

fMRI functional magnetic resonance imaging

LBA longitudinal body axis

LHL left hemispheric lesion

LIP lateral intraparietal area

ML mediolateral (deviation)

MRI magnetic resonance imaging

NCT national clinical Trial

NMV neck muscle vibration

PA prism adaptation

PET positron emission tomography

PIVC parieto-insular vestibular cortex

PPC posterior parietal cortex

PV	postural verticality
RCT	randomized control trial
RHL	right hemispheric lesion
S2	somatosensory area 2
SD	standard deviation
SLB	subjective longitudinal body plane
SMA	supplementary motor area
SPL	superior parietal lobule
SSA	subjective straight ahead
STG	superior temporal gyrus
SVV	subjective visual vertical
T	tesla
TE	echo time
TI	inversion time
TR	repetition time
USN	unilateral spatial neglect
VIP	ventral intraparietal area
WBA	weight bearing asymmetry

Introduction

Stroke remains the leading cause of long-term disability in the world. A large part of this impairment is related to balance disorders. Resulting in a greater risk of falls and impaired autonomy, they increase the repercussion of stroke from a personal and socioeconomic point of view (Fong et al., 2001; Nardone et al., 2009; Simpson et al., 2011; Bohannon and Leary, n.d.). Several factors impact balance control after stroke. Motor, sensory impairments, spasticity have been widely studied. In addition, misperception of body orientation in space is frequently superimposed upon these factors. Thus, in a significant proportion of stroke patients, spatial cognition disorders impact the ability to maintain balance (Rode et al., 1997; Pérennou, 2005; Saj et al., 2006; Rousseaux et al., 2014; Bonan I. et al., 2015; Tasseel-Ponche et al., 2015; Jamal et al., 2018). However, the mechanisms underlying the postural disturbance related to body misperception after stroke and its management have been poorly investigated. Notably, the neural basis of the subjective perception of the sagittal plane of the body remains scarce. This thesis aimed to investigate the neural bases of the perception of the body in space through two tasks, the subjective straight ahead (SSA) and the subjective longitudinal body plane (SLB).

The literature describes that body misperception in space occurs especially after right hemispheric stroke (Rode et al., 1997; Pérennou and Bénéaim C, Rouget E, Rousseaux M, Blard JM, Pélissier J, 1999; Bonan et al., 2016). The crucial role of the right brain network in the process of spatial cognition could explain this specificity, involving, in particular, the posterior parietal cortex (Andersen, 1997; Neggers et al., 2006; Zaehle et al., 2007; Galati et al., 2010; Saj et al., 2014). Therefore, we considered it relevant to focus our work on patients with right hemispheric stroke.

The underlying question is the specific management of these spatial cognition disorders after stroke. Despite this overriding issue, no treatment explicitly addressing the cognitive component of imbalance is commonly used (Bonan et al., 2015; Bonan I. et al., 2015). Traditional approaches consist in stimulating the conscious perception of body orientation in space. These top-down exercises are laborious and demanding. They require active participation, while the awareness of spatial cognition disorders is already a challenging first step for stroke patients. In this context, sensory stimulations could be a promising treatment

by addressing specifically the cognitive component of balance disorders. Thus, sensory rehabilitation programs were initially applied to improve visuospatial neglect (Kerkhoff and Schenk, 2012). Because of the closed mechanisms leading to biases in neglect and postural impairment, these techniques are likely to impact balance disorders positively. They are thought to decrease the distortion of the perception of the body in space by restoring the symmetry of sensory inputs (Bonan I. et al., 2015).

We focused our research on neck muscle vibration (NMV) because they require minimal participation of the patients and can be used early after stroke. The vibration is a sensory stimulation inducing a stretching illusion of the vibrated muscle. In particular, the NMV causes cervical proprioceptive stimulation (Jamal et al., 2020). Previous studies have shown that NMV was effective on neglect symptoms if repeated (Johannsen et al., 2003; Schindler and Kerkhoff, 2004). More recent studies suggest that NMV could reduce spatial bias after stroke (Bonan I. et al., 2015; Leplaideur et al., 2016). Moreover, clinical and functional neuro-imaging data suggest a direct central action on cortical structures involved in elaborating spatial representation (Bottini et al., 2001). Thus, the NMV appears as a promising field of postural disturbances rehabilitation related to spatial cognition. We aimed to test NMV in Rehabilitation programs on balance bias after stroke. In addition, previous works suggested a positive effect of sensory stimulation combination (Karnath, 1994; Saevarsson et al., 2010; Guinet and Michel, 2013). We address this question by combining several sensory stimulations.

Research questions

This thesis is built on four main parts.

The first part presents the concept of spatial cognition. The neural bases of egocentric tasks in healthy participants are exposed with a first article published in 2021. Preliminary report of our results in case of right stroke patients are presented. The second part reviews NMV principles and the results of preliminary studies realised in our team. The third part presents the clinical results of the RCT AVCPOSTIM, evaluating NMV effect on balance disorders after stroke (alone or in combination with prism adaptation) (submitted article). Finally, the discussion elaborates on the results and provides research perspectives.

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Part 1. Spatial cognition and egocentric tasks

Chapter 1. Spatial cognition, Theoretical framework.

What is the concept of spatial cognition?

Chapter 2. Neural bases of egocentric spatial representation in healthy subjects

What are the correlates of egocentric spatial representation for extracorporeal and corporeal tasks in fMRI ?

Publication 1

Chapter 3. The reorganization of egocentric spatial representation in patients who had a right hemispheric stroke, an fMRI study.

How do patients who had a right stroke achieve egocentric tasks from a neuroimaging point of view?

Publication 2 – in progress

Chapter 1. Theoretical framework

a. Spatial cognition

The elaboration of space and body perceptions in space involves multiple afferent information sources, i.e. from vestibular, visual, and proprioceptive receptors, as well as efferent information from motor effectors (Andersen and Snyder, 1993; Weniger et al., 2009; Rode et al., 2017). This information set is processed in several spatial reference frames used for various aspects of space-related behaviour, encompassing postural control, walking or grasping (Jeannerod and Biguer, 1989; Jamal et al., 2018). The different reference frames involved depend on the subject's position in space and the task to perform.

The literature describes two main spatial reference frames: the allocentric and the egocentric reference frames (Galati et al., 2010; Saj et al., 2014). They are used to integrate spatial information, encoding spatial relation between the objects and body position in space. In the allocentric frame, spatial information is encoded in relation to external references without reference to the subject's body. In contrast, in the egocentric frame, spatial information is encoded with regard to the body, in coordinates centred on the body.

b. Egocentric referential frame, extracorporeal and corporeal tasks

Several patterns of egocentric representation disabilities were first revealed by research on unilateral spatial neglect (USN). Indeed, USN is defined as a spatial cognition disorder impacting the integration of stimuli and actions in the side opposite to a stroke. USN could specifically affect the impairment of extracorporeal or corporeal space (Karnath et al., 1993; Azouvi et al., 2002; Schindler, 2002; Johannsen et al., 2003; Luaute et al., 2006; Chokron et al., 2008). These studies suggested that the difference in processing is likely due to the different actions in these specific spaces. The extracorporeal area is used in exploration and action in the extracorporeal environment. On the contrary, corporeal space is the space of self-location and representation of the body.

Thus, two body-centred tasks are classically used to explore the egocentric referential frame. The subjective straight ahead (SSA) explores the extracorporeal space perception centred on the participant who divides the straight-ahead extracorporeal space into two parts

(Bartolomeo, 1999; Chokron et al., 2004; Richard et al., 2004; Galati et al., 2010). This SSA task was adapted for fMRI by Vallar et al. (Vallar et al., 1999).

The subjective longitudinal body plane (SLB) explores the personal space perception (Bartolomeo, 1999; Barra et al., 2007; Rousseaux et al., 2014): the patient divides his body space into two parts. We adapted the test developed by Barra et al. for use in fMRI (Barra et al., 2007). This task was initially named LBA (longitudinal body axis). However, we prefer to refer to this task as SLB to show the subjective part of this test and to support that it assesses the plane more than the axis from our point of view.

To complete the presentation of these egocentric tasks (SSA and SLB), I would like to present two other assessments that will be used in the following studies. These subjective visual vertical (SVV) and the weight-bearing asymmetry (WBA). The SVV refers to the allocentric coordinate system. It assesses the perception of verticality by adjusting the orientation of a luminous line in the frontal plane (Bonan et al., 2006; Barra et al., 2008; Pérennou et al., 2014; Piscicelli and Pérennou, 2017). The WBA refers to the patient asymmetry inducing more weight-bearing on the non-affected side. Tested on a balance posturography, WBA is expressed as the percentage of the weight loading on the ipsilesional side.

c. Focus on egocentric tasks

We focused our research on the egocentric reference frames because of the significant relation between SLB impairment and balance disorders after stroke (Barra et al., 2009; Jamal et al., 2018).

Thus, Barra et al. tested the link between the WBA, SLB (egocentric referential) and SVV (allocentric referential) assessments after a recent stroke (Barra et al., 2009). In this study involving 22 patients at 13 weeks (Standard Deviation SD 7.5) after a first stroke, the SLB and the SVV were strongly linked ($r=0.7$; $p=0.001$). However, the SLB was a better predictor of WBA ($r=0.52$; $p<0.02$) than SVV ($r=-0.41$; $p=0.074$) after adjustment for motor weakness and hypoesthesia, showing the involvement of the egocentric reference frame in postural balance impairment and postural asymmetry in particular.

We thought that SSA perception, another egocentric assessment, could link with balance after a stroke. So, in 2018, we explored the link between SSA, SLB and WBA (Appendix 1) (Jamal et al., 2018). The population included 15 right hemispheric lesion (RHL) patients, 15 left hemispheric lesion (LHL) patients and 20 healthy participants. At this chronic stage of recovery

(mean time since stroke 4.78 years, SD 3), both groups of patients had a bodyweight asymmetry. This asymmetry (expressed in weight percentage on the affected side) was slightly superior in RHL patients ($35\% \pm 8$) as compared to LHL patients ($39\% \pm 4$). WBA was correlated with SLB when considering the whole population ($p = 0.03$). However, this correlation was dependent on the side of the lesion. The partial correlation confirmed the WBA/SLB relation in case of RHL ($r = 0.77, p = 0.02$) and not in case of LHL ($r = -0.46, p = 0.1$) (figure 1) . No relation with WBA was found neither with SVV ($p = 0.47$) nor with SSA ($p = 0.58$).

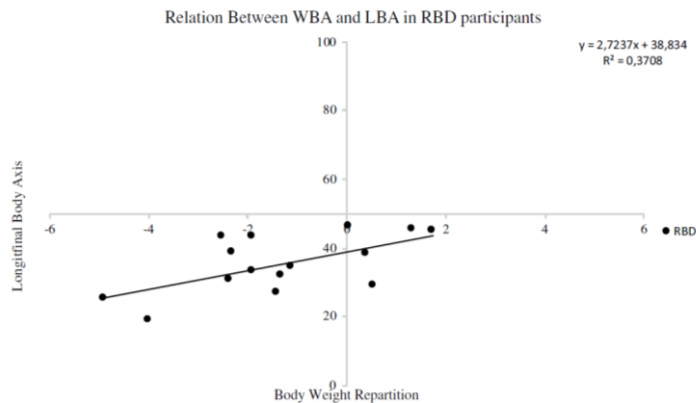


Figure 1 – From Jamal 2018 , Relation between WBA and longitudinal body axis (LBA = SLB) in patients with right brain damage (RBD)

In this paper, we confirmed the relationship between the asymmetrical postural behaviours of chronic stroke patients and their biased perception of the egocentric spatial frame (Appendix 1). In the light of this dissociation between the WBA/SLB relationship and the absence of a WBA/SSA relationship, we hypothesised that the mechanisms underlying the integration of these parts of egocentric patterns (extracorporeal and corporeal) could be different.

Upgrading the understanding of the egocentric referential frame is essential because it could improve the adaptation of balance rehabilitation programs influencing the evolution of patients who had a stroke.

Therefore, we investigated the neural basis of egocentric tasks (SSA and SLB) using neuroimaging, firstly in healthy participants (presented in chapter 2) and secondly in the patient who had a right stroke (presented in chapter 3).

Chapter 2. Neural bases of egocentric spatial representation in healthy subjects, an fMRI point of view

a. The current state of knowledge

Studies investigating egocentric reference frame started to use functional MRI twenty years ago in healthy participants. In 2010, Galati et al. published a review on studies exploring several kinds of straight-ahead tasks (Vallar et al., 1999; Galati et al., 2000, 2001, 2010; Neggers et al., 2006; Zaehle et al., 2007; Saj et al., 2014). Vallar et al. evaluated light scanning in seven healthy subjects (Vallar et al., 1999). Other teams compared a judgement of position on a line with respect to their body or the bar (comparing egocentric and allocentric reference frames with the same background) on eight and twelve participants, respectively (Galati et al., 2000; Neggers et al., 2006). Finally, two studies involved other tasks: haptic SSA based on finger location in ten subjects (Galati et al., 2001) or auditory stimulation (Zaehle et al., 2007). All studies reported bilateral activations with a predominance of right activity. The main clusters observed for egocentric tasks were located in the PPC, including precuneus (Galati et al., 2000; Zaehle et al., 2007), superior parietal lobule (Vallar et al., 1999; Galati et al., 2000; Neggers et al., 2006; Saj et al., 2014) and intraparietal sulcus (Vallar et al., 1999) (figure 2).

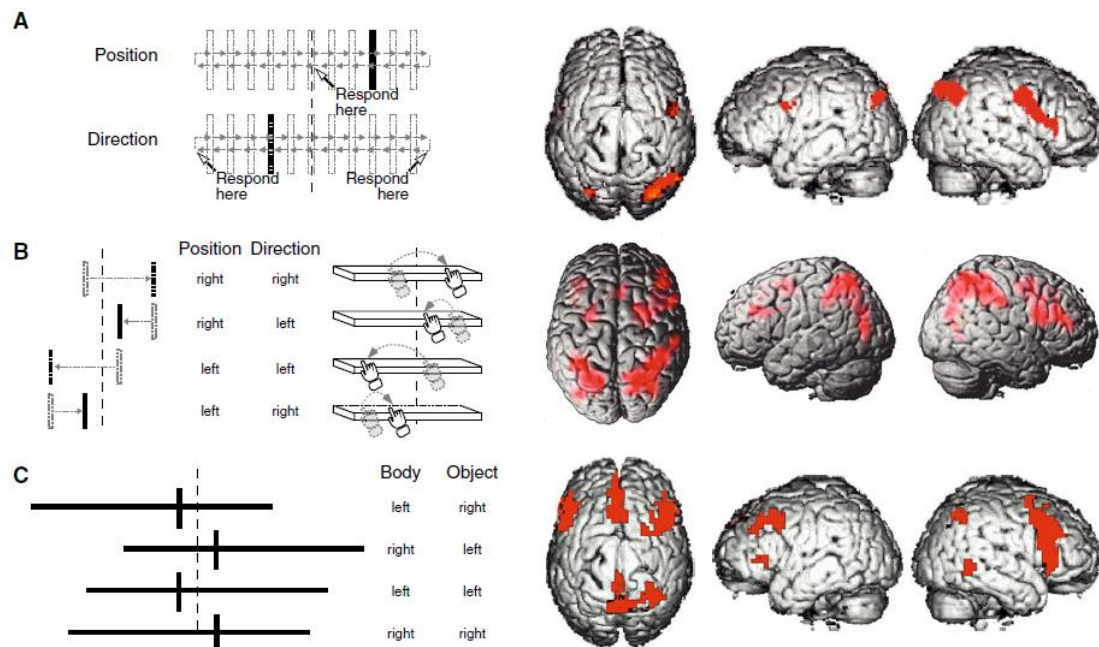


Figure 2 – From Galati 2010, selection of results of three studies : a) Vallar et al. (1999), b) Galati et al. 2001, c) Galati et al. 2000.

These results were consistent with the macro anatomy data defining the PPC as a sensory integration area. Indeed, the precuneus involves a range of functions such as the integration of information on the perception of the environment, mental imagery strategy; the superior parietal lobule is involved in visuospatial perception; and the intraparietal sulcus in several sensorimotor functions as planning movements. In the right hemisphere, the activations extended to the supramarginalis gyrus and the angular gyrus of the inferior parietal lobule (Vallar et al., 1999; Galati et al., 2000; Saj et al., 2014). These areas are known to be involved in space perception and body location identification. Also, connections with the lateral premotor cortex (Vallar et al., 1999) and supplementary motor area (SMA) were reported (Galati et al., 2000). Some activations were reported in the superior occipital gyrus (Vallar et al., 1999; Saj et al., 2014), inferior frontal gyrus and inferior parietal lobule down to the parieto-temporal junction (Galati et al., 2000). In addition, the activity was found in frontal regions around the precentral, superior frontal sulci, inferior frontal gyrus and superior frontal gyrus (Galati et al., 2000; Zaehle et al., 2007) as well as right cerebellum (Saj et al., 2014). Activity in the right hippocampus and around the superior temporal gyrus was also observed (Neggers et al., 2006).

The diversity of results in these studies could be related to the known variability in the achievement of cognitive tasks. Thus, the elaboration of a cognitive task depends on subjects, whereas in the case of a motor task, the achievement is more repeatable. Another reason could be the difference in task presentation and instruction. The visual modality was most often used (Vallar et al., 1999; Galati et al., 2000, 2001; Neggers et al., 2006; Saj et al., 2014). In two studies, they used an auditory instruction or somatic sensory modality (Galati et al., 2001; Zaehle et al., 2007). In most cases, the egocentric task was compared to an allocentric task, combining the representation of the two tasks. Even if the instruction differed, the mixed background could disrupt the participant. Moreover, most of these studies concerned a small number of subjects using a first-level analysis with individual interpretations.

To summarize, in healthy controls, previous works described the crucial role of a bilateral fronto-parietal network with a right predominance. Moreover, they found a major involvement of the PPC (Vallar et al., 1999; Galati et al., 2000; Neggers et al., 2006; Zaehle et al., 2007; Saj et al., 2014) and an extension to the superior frontal lobule (Vallar et al., 1999; Galati et al., 2000; Zaehle et al., 2007; Saj et al., 2014). In addition, some other activations

were noted in the superior occipital gyrus and inferior frontal gyrus (Vallar et al., 1999; Saj et al., 2014).

These studies enlightened the understanding of the spatial cognition network for egocentric tasks. In the hypothesis of different neural bases of extracorporeal and corporeal referential, it appeared interesting to investigate deeper these two parts of the egocentric referential frame of reference. Therefore, we elaborated on a study aiming to explore their neural basis first in healthy patients and secondly in stroke patients.

b. The Neural Bases of Egocentric Spatial Representation for Extracorporeal and Corporeal Tasks: An fMRI Study (*publication 1*)



The following manuscript aimed to assess extracorporeal and corporeal egocentric tasks using fMRI and study the difference in brain activations during these tasks. This first manuscript focuses on the results obtained in healthy participants.

To our knowledge, this study is the first work attempting to discriminate these distinct egocentric reference frames. Besides, we used a cytoarchitectonic atlas with anatomical and functional brain subregions to interpret our results and sharpen our understanding of body-centred representations. Therefore, we implemented these two tasks for the MRI scanner and investigated the common grounds and differences.

The activations were superimposed with a predominance in the right fronto-parieto-occipital network, suggesting they share a large neural basis. However, with SLB, we observed additional activations towards a ventral proprioceptive network.

Article

The Neural Bases of Egocentric Spatial Representation for Extracorporeal and Corporeal Tasks: An fMRI Study

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Abstract: (1) Background: Humans use reference frames to elaborate the spatial representations needed for all space-oriented behaviors such as postural control, walking, or grasping. We investigated the neural bases of two egocentric tasks: the extracorporeal subjective straight-ahead task (SSA) and the corporeal subjective longitudinal body plane task (SLB) in healthy participants using functional magnetic resonance imaging (fMRI). This work was an ancillary part of a study involving stroke patients. (2) Methods: Seventeen healthy participants underwent a 3T fMRI examination. During the SSA, participants had to divide the extracorporeal space into two equal parts. During the SLB, they had to divide their body along the midsagittal plane. (3) Results: Both tasks elicited a parieto-occipital network encompassing the superior and inferior parietal lobules and lateral occipital cortex, with a right hemispheric dominance. Additionally, the SLB > SSA contrast revealed activations of the left angular and premotor cortices. These areas, involved in attention and motor imagery suggest a greater complexity of corporeal processes engaging body representation. (4) Conclusions: This was the first fMRI study to explore the SLB-related activity and its complementarity with the SSA. Our results pave the way for the exploration of spatial cognitive impairment in patients.

Keywords: spatial cognition; egocentric reference frame; functional MRI

1. Introduction

Multiple sources of afferent information (from vestibular, visual, and proprioceptive receptors) and efferent information (from motor effectors) are needed to elaborate internal spatial representations of the body in space [1,2]. These inputs can be integrated into different and changing systems of coordinates, depending on the person's position in space and the nature of the task. The egocentric reference frame encodes spatial information centered on body coordinates [3–8]. This frame involves two spatial components, depending on the intended action: extracorporeal and corporeal [9]. The extracorporeal component enables individuals to locate stimuli perceived in the extrapersonal space relative to their body and orient their actions in the environment. The corporeal component allows individuals to elaborate personal representations of the location and configuration of their body centered in space, in order to perform tasks such as personal care [4,10]. Two tasks have been used to explore these egocentric reference frames: the subjective straight-ahead task (SSA) and, more recently, the subjective longitudinal body plane task (SLB). The SSA explores extracorporeal space perception centered on the body. Participants

imagine a plane starting from their midsagittal body and going straight ahead, dividing the extracorporeal space into two parts [4,10,11]. In the SLB, participants are asked to divide their corporeal space into two parts. They indicate with a button press when the bar virtually divided their corporeal space into two equal parts along their body's midsagittal plane [5,11–14]. There are well-known clinical differences between extracorporeal and corporeal tasks [5,12], and the integration of relevant information can be differentially affected following brain damage [15]. For example, differences between extracorporeal and corporeal abilities have been identified when assessing unilateral spatial neglect. An impact of body representation in space on asymmetrical postural behaviors has also been reported. One previous study highlighted a strong relationship between SLB disturbance and postural asymmetry in patients with chronic stroke [5]. However, the neural basis of these differences has never been investigated. It is essential to improve knowledge in this field, as gaining a better understanding of the mechanisms involved in elaborating the egocentric reference frame would inform rehabilitation strategies for patients with spatial cognition disorders following stroke.

The present work was the first to use fMRI to study the commonalities and differences in brain activity between two egocentric tasks involving either extracorporeal or corporeal space. We hypothesized that both tasks would activate a bilateral fronto-parieto-occipital network, especially the posterior parietal and premotor cortices, with right hemispheric predominance [15–18]. Moreover, we expected the two tasks to activate distinct subregions of the network. This research among healthy participants was an ancillary study to a multicenter study exploring spatial cognitive disorders in patients with stroke.

2. Materials and Methods

2.1. Participants

We included 17 healthy volunteers (7 men and 10 women: Mean age = 50.4 years, SD = 14.9, range 23–70). They were all right handed on their declaration. All participants gave their written informed consent to take part in this study, which was approved by the Poitiers-France III West institutional review board (no. 05/12/16; AVCPOSTIM study—clinical trial identifier NCT01677091). Exclusion criteria were (1) contraindication to magnetic field exposure, (2) neurological disease, and (3) history of balance disorders. All participants had normal or corrected-to-normal vision.

2.2. Experimental Design

The SSA and SLB tasks were performed in a supine position in an MRI scanner. For the SSA task, participants were instructed to divide the extracorporeal space in front of them into two halves [5,10,12,19]. A vertical green bar scanned the black screen from left to right and from right to left, with different random starting positions within the range of -7° to $+7^\circ$, at a speed of 2° per second [20]. The instruction was “Press the button when the bar is straight ahead and divides the space in front of you into two equal parts” (Figure 1 and Supplementary File S1).

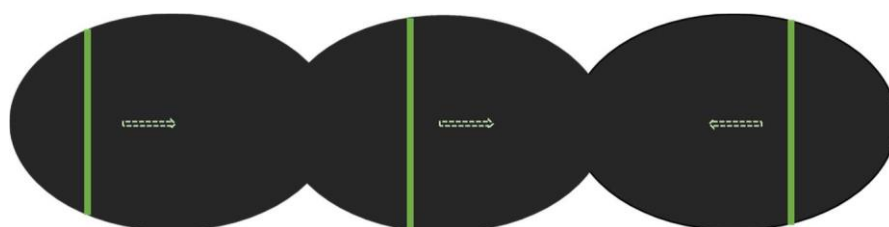


Figure 1. Schematic diagram of the subjective straight-ahead (SSA) fMRI task. Dotted arrows represent the direction of motion.

During the SLB task, a green bar moved along the plane orthogonal to the line going through the navel [5,13,21]. The bar rotated alternately leftward and rightward, with different random starting angles within the range of $-30^\circ/+30^\circ$, at a speed of 2° per

second. The instruction was “Press the button when the bar is aligned with a virtual plane dividing your corporeal space into two equal parts” (Figure 2 and Supplementary File S2).

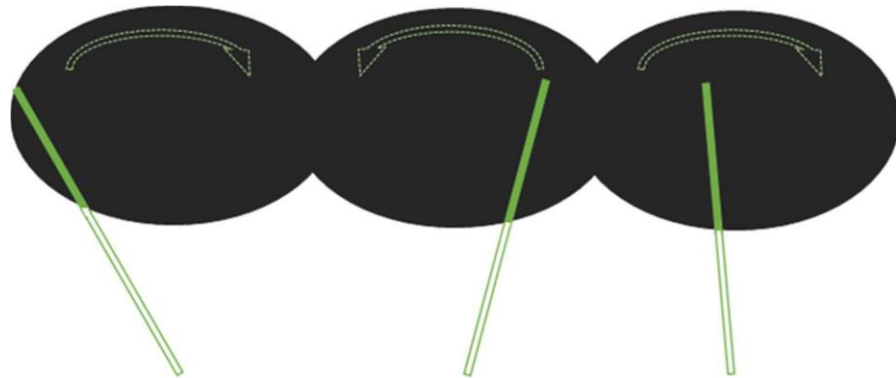


Figure 2. Schematic diagram of the subjective longitudinal body fMRI task. The dotted arrow represents the bar’s motion. The empty bars represent the virtual continuous plane centered on the navel.

During the control condition, the same sequence of bar movements was presented, but participants were instructed to press the button when the bar changed direction.

Each fMRI sequence lasted 3 min and followed a block design: 30 s blocks of task and 30 s block of control conditions. In each block, the bar passed through the center six times at a constant speed of two degrees per second [20]. The process is similar for both tasks. The tasks were implemented using E-Prime 2.0 Professional software (Psychology Software Tools, Pittsburgh, PA, USA) and presented using goggles (NordicNeuroLab, Bergen, Norway) attached to the head coil to immerse participants in the task without any spatial clues. The instruction was presented via the goggles just before the task, in different colors for task and rest at the beginning of each block. To perform the tasks, participants reported their perception by pressing a button with their right index finger. Before the experiment, they practiced outside the scanner until they were able to perform the tasks. They all confirmed they understood the instructions. The difference between target identification (respectively, straight ahead or longitudinal axis) and button press time were computed both for SSA and SLB tasks.

2.3. MRI Acquisition

MRI acquisition was performed on a 3 tesla scanner (Magnetom Verio; Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil. The alignment of head, shoulders, trunk, and limbs was checked by the experimenter before MRI acquisition. The head and the trunk were maintained with foam pads.

The following MR sequences were acquired:

- sagittal morphological isotropic 3D T1 MPRAGE sequence (repetition time (TR)/inversion time (TI)/echo time (TE): 1900/900/2.26 ms, field of view (FOV) 256x256 mm², 160 slices, 1x1x1 mm³ voxel size);
- field map with two echo times for distortion correction; and
- two blood oxygen level dependent (BOLD) fMRI sequences using a single-shot T2*-weighted EPI sequence (TR/TE: 3000/36 ms, 210x 210 mm², FOV, 2x2x4 mm³, voxel size, 24 slices). Interleaved slices were acquired parallel to the anterior commissure posterior commissure line with no gap.

In total, the experiment was completed in 15 min.

Images were preprocessed and analyzed using Statistical Parametric Mapping (SPM12; Wellcome Department of Imaging Neuroscience, University College London, London, UK [22]; revision 7487) implemented in MATLAB. Morphological images were segmented, corrected for bias, and normalized to Montreal Neurological Institute atlas space (MNI).

Slice timing, spatial realignment, distortion correction, coregistration to the morphological images, and normalization were applied, followed by 6 mm full width at half maximum (FWHM) isotropic Gaussian kernel smoothing. The canonical hemodynamic response function and its temporal derivative were used for model estimation, and three contrasts were evaluated: “SSA > control condition”, “SLB > control condition”, and “SLB > SSA”.

2.4. Statistical Modeling and Inference Analysis

Given that a large number of regions of interest are reported in the literature, we ran voxelwise analyses across the whole brain. A cluster extent of 25 voxels was determined by running a Monte Carlo simulation [23–25] using cluster threshold betas based on an individual voxel threshold of $p = 0.001$ and a corrected threshold of $p = 0.05$. The two tasks were compared using a paired t test with a cluster extent of 25 voxels.

To allow us to compare our results with those of previous studies [4,7,20,26–29], we converted the literature data into MNI coordinates using the MNI to Talairach application [30,31]. We visualized our results using SPM12 and the xjView toolbox (available online: <https://www.alivelearn.net/xjview> (accessed on 27 May 2021) and MRICroGL (available online: <https://www.mccauslandcenter.sc.edu/mricrogl/> (accessed on 27 May 2021). The interpretation was performed in MNI space, using the automated anatomical labeling atlas (AAL3) [32], Jülich brain cytoarchitectonic atlas [33–36], and brainnetome atlas [37] for cyto-myelo labeling. The latter, based on anatomical connectivity parcellation and containing 246 regions of the bilateral hemispheres (210 cortical and 36 subcortical sub-regions), was the most useful one for identifying activated regions reported in the results.

3. Results

Subjects responded within the standard to both tasks showing the reliability of the tasks. The SSA mean deviation was $\theta\text{-}4^\circ$, SD 1.3; the SLB mean deviation was 1° , SD 0.3. The mean response times of both tasks were not significantly different suggesting a similar complexity ($p = 1.17$).

3.1. Subjective Straight-Ahead Task (SSA)

The “SSA > control condition” contrast highlighted a parieto-occipital network shown in in Figure 3 and Table 1. We observed right-hemispheric dominance (74.3% of activated voxels).

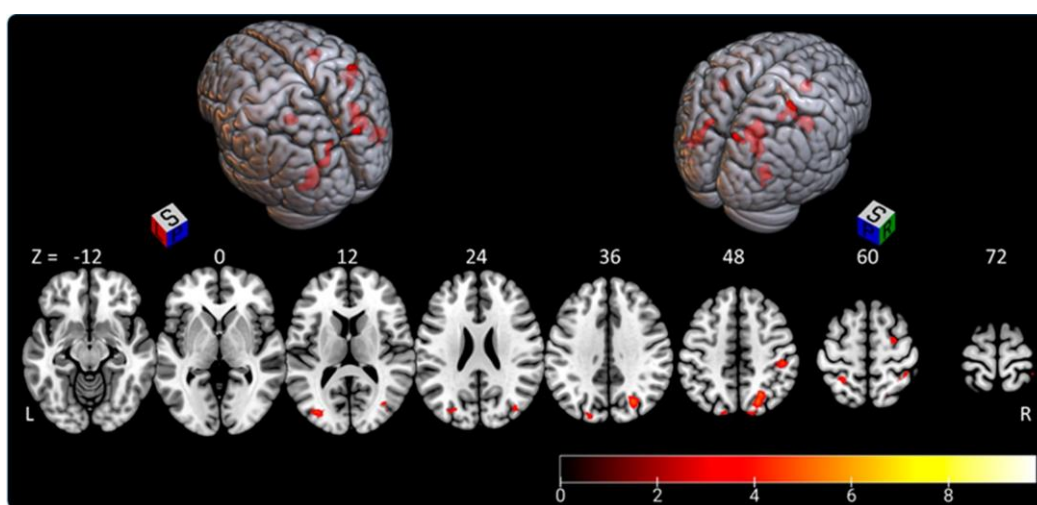


Figure 3. Rendered image of activated clusters highlighted by the “SSA > control condition” contrast. The color bar indicates t -values (BOLD); L—left, P—posterior, R—right, S—superior, Z coordinates in MNI atlas.

Table 1. Activated areas highlighted by the “SSA > control condition” contrast. The number of voxels is given for each cluster, together with the side (i.e., left or right hemisphere), the cluster composition (i.e., percentage of voxels in each area assigned using AAL3 and brainnetome atlas), MNI coordinates and t value of the peak. Only activated areas covering more than 10% of the cluster are shown.

Cluster voxels / side	AAL3 % in the area	Peak MNI coordinates (x y z) / T value	BRAINNETOME % in the area
226 / right	42.5 occipital sup	24 -62 46 / 5.630	31.9 lsOccg
	33.6 parietal sup		28.8 A7c
92 / left	96.7 occipital mid	-30 -84 14 / 5.023	44.6 mOccG
			35.9 A39c
81 / right	61.7 postcentral	46 -28 42 / 5.440	69.1 A40rd
	29.6 supramarginal		19.8 A2
66 / right	87.9 occipital mind	42 -80 18 / 5.471	54.5 A39c
			31.8 mOccG
58 / right	55.2 postcentral	38 -44 66 / 5.216	12.1 A7pc
	25.9 parietal inf		60.3 A5I
	19.0 parietal sup		19.0 A7ip
40 / right	72.5 frontal sup	26 -4 58 / 5.087	85.0 A6cdl
	17.5 precentral		10.0 A6dl
39 / left	76.9 occipital sup	-18 -86 38 / 4.506	10.3 msOccG
	23.1 parietal sup		79.5 lsOccG
31 / left	51.6 parietal sup	-26 -46 58 / 6.259	19.4 A7pc
	25.8 parietal inf		38.7 A5I
	22.6 postcentral		

-
- The activated voxels in the eight significant clusters were distributed as follows:
- the right parietal lobe (superior parietal lobule: A7c, A5l, A7pc; inferior parietal lobule: A39c, A40rd, A40rv; precuneus: dmPOS; postcentral gyrus: A2) representing 45.5% of activated areas;
 - the right lateral occipital cortex (msOccG, lsOccG, mOccG), representing 21.5% of activated areas;
 - the left lateral occipital cortex (V5/MT+, msOccG, lsOccG, mOccG), representing 16% of activated areas;
 - the left parietal lobe (superior parietal lobule: A5l, A7pc; and inferior parietal lobule: A39c), representing 9.5% of activated areas; and
 - the right premotor cortex (superior frontal gyrus: A6cdl), representing 7.5% of activated areas.

3.2. Subjective Longitudinal Body Plane Task (SLB)

The “SLB > control condition” contrast highlighted a fronto-parieto-occipital network extending to the temporal lobe and insula, with right-hemispheric predominance (75.5% of clusters located in right hemisphere). Activated clusters are shown in Figure 4 and Table 2.

Activated voxels were distributed as follows:

- the right parietal lobe (superior parietal lobule: A7r, A7c, A5l, A7pc, A7ip; inferior parietal lobule: A39c, A40rd, A40rv; precuneus: dmPOS; postcentral gyrus: A1/2/3ulhf, A2, A1/2/3tru), representing 27% of activated areas;
- the right lateral occipital cortex (V5/M+, msOccG, lsOccG, mOccG, iOccG), representing 22.5% of activated areas;
- the right frontal lobe (predominant in the precentral gyrus: A4hf, A6cdl, A4ul, A4tl, A6cvl; superior frontal gyrus: A8m, A6dl, A6m; inferior frontal gyrus: A44d, A44op; paracentral gyrus: A4ll), representing 21% of activated areas;
- the left lateral occipital cortex (V5/MT+, mOccG, iOccG), representing 8% of activated areas;
- the left frontal lobe (supplementary motor area: A6m; precentral gyrus: A4hf, A6cdl, A4ul, A4t; and paracentral lobule: A4ll), representing 7.5% of activated areas; and
- less than 5% in each of the following areas: left parietal lobe (superior parietal lobule: A5l, A7pc; inferior parietal lobule: A39c, A39rv; postcentral gyrus: A1/2/3ulhf, A2), right insular lobe (vIa, dIa, dIg, dId), left temporal lobe (middle temporal gyrus: A37dl; inferior temporal gyrus: A37vl; fusiform gyrus: A37lv), left cingulate gyrus, right temporal lobe (middle temporal gyrus: A37dl; inferior temporal gyrus: A37vl; fusiform gyrus: A37lv), and right cingulate gyrus.

Table 2. Activated areas highlighted by “SLB > control condition” contrast. The number of voxels is given for each cluster, together with the side (i.e., left or right hemisphere), the cluster composition (i.e., the percentage of voxels in each area assigned using AAL3 and brainnetome atlas), MNI coordinates and t value of the peak. Only activated areas covering more than 10% of the cluster are shown.

Cluster voxels / side	AAL3 % in the area	Peak MNI coordinates (x y z) / T value	BRAINNETOME % in the area
565 / right	25.3 occipital mid 25.1 temporal mid 18.9 occipital sup 13.3 temporal inf	44 -66 -6 / 10.448	16.6 mOccG 9.7 msOccG 8.5 lsOccG 38.1 V5/MT+
512 / right	59.4 postcentral 16.8 supramarginal 15.0 parietal sup	50 -22 42 / 6.4996	18.8 A2 24.2 A40rd 15.4 A5I 11.1 A40rv
240 / right	64.6 frontal sup 15.0 precentral 11.3 frontal mid	36 -6 58 / 6.921	56.3 A6cdl 22.5 A6dl
218 / left	59.2 occipital mid 20.2 temporal mid 18.4 occipital inf	-34 -78 10 / 6.0758	19.7 mOccG 45.4 V5/MT+ 11.0 A39c
152 / right-left	59.9 supp motor area L 31.6 sup motor area R	-4 -12 58 / 6.0816	51.3 IA6m 26.3 rA6m
107 / right	60.8 frontal inf oper 39.3 precentral	58 12 30 / 6.2155	92.5 A6cvl
78 / right	87.2 insula	44 20 -6 / 5.5758	34.6 dla 44.9 dld 11.5 A44op
55 / left	98.2 precentral	-40 -10 66 / 5.086	45.5 A6cdl 29.1 A4hf 18.2 A4ul
52 / left	73.1 postcentral 26.9 parietal sup	-40 -44 62 / 4.699	36.5 A7pc 38.5 A5I 19.2 A2
45 / right-left	53.3 cingulate mid L 31.1 cingulate mid R 11.1 sup motor area L	-2 6 42 / 6.001	57.8 IA24cd 35.6 rA24cd
31 / left	51.6 postcentral 48.4 precentral	-38 -18 46 / 5.1726	38.7 A1/2/3ulhf 41.9 A4hf

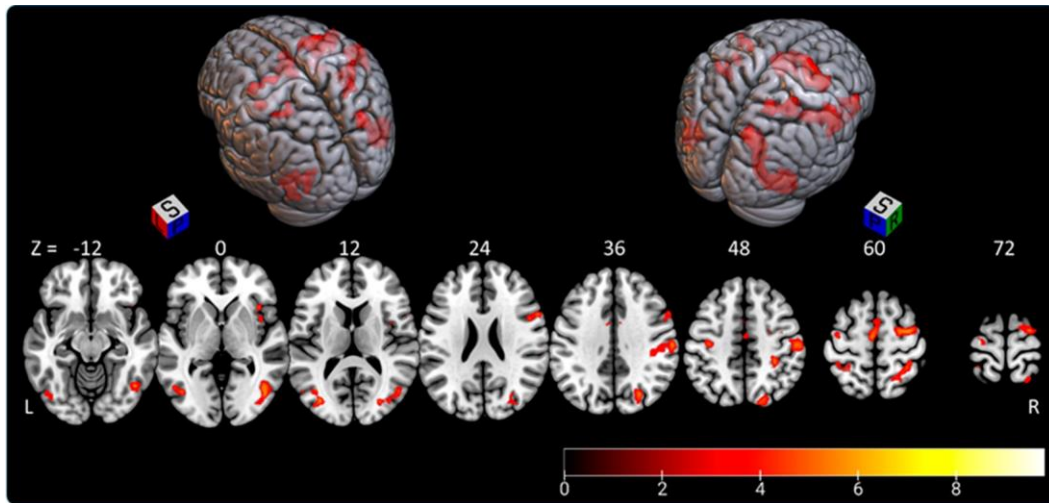


Figure 4. Rendered image of activated clusters highlighted by “SLB > control condition” contrast. The color bar indicates t -values (BOLD); L—left, P—posterior, R—right, S—superior, Z—coordinates in MNI atlas.

3.3. Subjective Longitudinal Body Plane Task versus Subjective Straight-Ahead Task

Subjects responded within the standard to both tasks showing the reliability of the tasks. The SSA mean deviation was 0.4° , SD 1.3; the SLB mean deviation was 1° , SD 0.3. The mean response times of both tasks were not significantly different suggesting a similar complexity ($p = 1.17$).

Both tasks elicited a parieto-occipital network that encompassed the superior and inferior parietal lobules, precuneus, and lateral occipital cortex. The “SLB > SSA” comparison revealed a larger activation area (2055 vs. 633 voxels) and higher intensity for the SLB task than for the SSA task. Moreover, the “SLB > SSA” contrast revealed activation in the left angular and precentral gyri (Figure 5, Table 3).

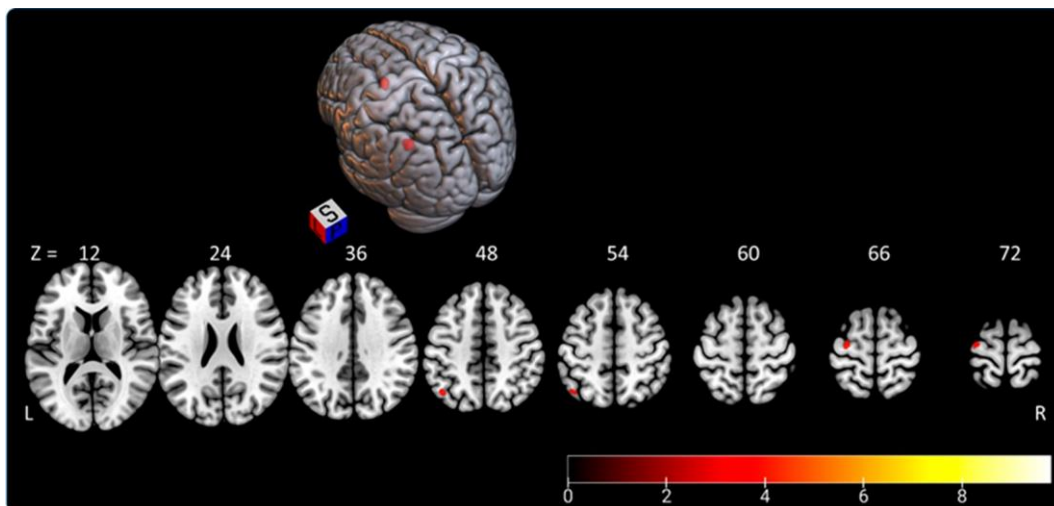


Figure 5. Rendered image of activated clusters highlighted by “SLB > SSA” contrast. The color bar indicates t -values (BOLD); L—left, P—posterior, R—right, S—superior, Z coordinates in MNI atlas.

Table 3. Activated areas highlighted by “SLB > SSA” contrast. The number of voxels is given for each cluster, together with the side (i.e., left or right hemisphere), the cluster composition (i.e., the percentage of voxels in each area assigned using AAL3 and brainnetome atlas), MNI coordinates and value of the peak. Only activated areas covering more than 10% of the cluster are shown.

Cluster voxels / side	AAL3	Peak	
		MNI coordinates (x y z) / T value	BRAINNETOME
28 / left	71.0 angular	-44 -66 50 / 4.9301	57.1 A39rd
	7.1 parietal inf		7.1 A39rv
25 / left	92.0 precentral	-30 -14 70 / 6.430	52.0 A6cdl
			40.0 A4ul

4. Discussion

Using fMRI, the present study investigated the neural bases of processes elicited by two different egocentric tasks in healthy participants: SSA and SLB. This was the first time that the SLB task had been implemented in fMRI, reproducing the clinical assessment setting in a supine position without visual clues. We demonstrated its feasibility and complementarity with the SSA task [20]. These tasks can both be administered to patients with spatial cognitive disorders following stroke. Our results will enhance understanding of the egocentric reference frame concept both in healthy participants and in patients with a brain lesion.

The SSA and SLB both activated a parieto-occipital network with right-hemispheric predominance. This is in agreement with previous human and animal studies reporting activation of a fronto-parieto-occipital network by spatial cognition tasks [3,4,7,20,26–29,38–40]. Studies in nonhuman primates have highlighted the involvement of the posterior parietal cortex, parieto-insular vestibular cortex, and parieto-occipital sulcus as multimodal integration areas [38–46]. In 2010, Galati et al. published a review of studies investigating egocentric and allocentric tasks in healthy participants. This review, similar to more recent articles in humans [4,7,18,20,26–29], described the crucial role of the bilateral fronto-parietal network for spatial tasks, with involvement of the posterior parietal cortex extending to the superior frontal region [7,20,27,29]. In particular, egocentric activity was related to the posterior parietal cortex including the precuneus [27,29], superior parietal lobule [7,20,27,28], and intraparietal sulcus [20]. In the right hemisphere, activation maps often extend to the supramarginalis gyrus and angular gyrus [7,20,27]. These areas involved in the integration and selection of multimodal sensory inputs may, therefore, support the elaboration of mental representations of the body in space [8,20]. Activated areas reported in the superior and inferior parietal lobules confirm the involvement of somesthesia and motor imagery in the egocentric reference frame.

We found strong activity in the right lateral occipital cortex implicated in visual perception, corroborating previous experimental findings [43]. As we used a moving bar instead of a static image, the motion may have increased occipital activity.

Along these lines, we found less extensive frontal activation in the superior and inferior frontal gyri than in previous studies [27,29]. However, these studies compared an egocentric task with an allocentric task in the same run. As the background required to perform the allocentric task is similar in both the SSA and SLB conditions, participants may engage attention and inhibition functions in order to be able to shift between the two tasks, thereby, increasing cognitive load and thus prefrontal activity. This may explain the lack of prefrontal activity in our study, in which we used a separate background for each task.

By analyzing and comparing two tasks involving the egocentric reference frame, our study represents a milestone in the comprehension of egocentric frame mechanisms. We found significant differences in fMRI activity between the corporeal and extracorporeal egocentric tasks. Interestingly, the SLB task activated additional areas in the left hemisphere, including the angular (A39rd, A39rv, A40c) and precentral gyrus (A6cdl, A4ul). The angular gyrus is a high-level cognitive area involved in attentional and memory processes [47,48], whereas the premotor cortex is engaged in movement selection and preparation [49]. The left lateralization of premotor cortex activity during the SLB task can be viewed from the perspective of motor imagery tasks that typically activate the left premotor cortex [50–52]. This sheds light on the complexity of corporeal task processes. Moreover, the SLB task appears to require mental spatial coordinate transformation, as participants have to mentally align the external cues (the light bar) with their body's midsagittal plane [53]. This view is supported by studies showing the implication of left parietal temporal occipital junction lesions in body schema disturbances, causing difficulties in spatial orientation [47]. Moreover, our results are consistent with the hypothesis of a functional interhemispheric connection involved in egocentric processing, particularly during corporeal tasks [15].

The present study had several limitations. First, the sample size is small and increasing sample sizes are desired. However, previous studies have included even smaller samples (fewer than 10 participants). Moreover, the age range is wide, but we do not expect variability in healthy controls as regards this kind of task [54–56]. Indeed, age has been reported to affect allocentric tasks while preserving egocentric strategies. Furthermore, we

did not observe any age effect on task performance. Second, we focused our investigation on the egocentric reference frame in particular. Given the lack of study on this subject, we aimed to improve knowledge of the elaboration of the egocentric reference frame. Thus, we implemented two egocentric tasks oriented toward corporal or extracorporeal spaces with a control condition when the bar changed direction. In order to verify how specific the MRI findings are in terms of brain processing of egocentricity, it would have been interesting to add an allocentric task and compare our results to previous works. Third, the 3 min runtime may have been too short to obtain reliable results. However, we used an AB block design to compensate for the short duration of the tasks, which was a requirement in this clinical setting involving patients with stroke.

5. Conclusions

This study investigated two egocentric tasks oriented toward either extracorporeal or corporeal spaces in 17 healthy participants. There was a large overlap between the SSA and SLB tasks, with a right fronto-parieto-occipital pattern of activity, showing that they share a common network. However, the SLB task elicited additional activity in the left angular gyrus and premotor cortex, suggesting greater complexity for SLB processes with functional interhemispheric connectivity. These results shedding light on the clinical dissociations reported for spatial cognitive disorders need to be confirmed in studies involving patients with spatial cognition disorders.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/brainsci11080963/s1>, File S1. Video of part of SSA in fMRI (gif). File S2. Video of part of SLBin fMRI (gif).

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Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author on request.

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Chapter 3. Egocentric spatial representation in case of stroke, an fMRI study. (*publication 2*)

Article in Progress

The reorganization of egocentric spatial representation in patients who had a right hemispheric stroke, an fMRI study.

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Abstract

Background: Spatial cognition disorders are a pejorative prognosis factor for postural balance and autonomy recovery after stroke. More specifically, the egocentric referential frame is used in the activity of daily living, and its impairment after stroke is detrimental. This study aimed to investigate, using neuroimaging, how patients with a right stroke perform two egocentric tasks. These tasks were the subjective straight-ahead task (SSA), exploring the extracorporeal space and the subjective longitudinal body plane task (SLB) involving the corporeal space.

Methods: Fourteen patients who had a right stroke within nine months underwent a 3T MRI scan, including anatomical and functional imaging. Data were analyzed in light of the results of seventeen healthy participants, previously published. In addition, we studied the regions activated during SSA and SLB according to the lesion location, spatial cognitive impairment and the time since stroke.

Results: Patients with a mean age of 61 years old (range 45-73) were included at 82 .3 days since stroke (range 18-195). Compared to group level activations obtained in healthy subjects, brain activations in patients were too heterogeneous to find significant results at the group level. At the individual level, we observed three kinds of activation patterns in decreasing rank: 1) patients with bilateral activations; 2) patients with only contralesional activations; 3) patients having predominantly ipsilesional activations despite the lesion. During SSA, we located activations in the right inferior frontal gyrus, post cerebellum, middle temporal gyrus,

middle occipital gyrus and PPC; and left cuneus and superior parietal lobule. During SLB, patients activated the right posterior cerebellum, middle temporal gyrus, precentral gyrus, angular and middle occipital gyrus. Left activations were found in the middle occipital gyrus, cuneus, middle temporal gyrus, precentral and superior frontal gyrus. Compared to areas involved during these tasks in healthy subjects, we found two additional locations: the cerebellum posterior and the middle and inferior temporal gyrus. Given the limited number of patients in each group, we could not statistically identify a lesion pattern or spatial ability. However, it seems that patients with a small lesion are more likely to activate ipsilesional areas.

Conclusion: Neuroimaging suggests different activation patterns in right stroke patients during egocentric tasks related to their lesion's characteristics. Studies of the networks underlying these egocentric activations and the study of a larger population could upgrade knowledge about the potential reorganization in high-level integration brain areas during spatial cognition tasks. Identifying reorganization profiles could allow adapting their rehabilitation program.

Keywords spatial cognition; egocentric reference frame; functional MRI; stroke

Introduction

After a stroke, spatial cognition disorders are pejorative for postural balance and autonomy recovery (Fong et al., 2001; Rousseaux et al., 2014; Bonan et al., 2015). More specifically, the egocentric impairments after stroke are highly detrimental. Because the egocentric reference frame encodes the spatial information centred on body coordinates. So, this referential is relevant to the initiation of all body and space-oriented actions. Indeed, egocentric updates are continuously involved in activities of daily living, such as postural control, walking or gripping (Burgess, 2008). The present work investigates egocentric referential frame adaptation after a stroke during two tasks. The first task, the subjective straight ahead task (SSA), has been investigated in fMRI in healthy subjects in several studies (Ventre et al., 1984; Chokron and Imbert, 1995). The second relevant task, namely the subjective longitudinal body plane (SLB), was adapted for use in an fMRI context device developed in clinical practice (Barra et al., 2007). SLB adaptation for fMRI has been used in our previous work (Leplaidier et al.,

2021). In healthy patients, we previously found that both tasks elicited a parieto-occipital network encompassing the superior and inferior parietal lobules and lateral occipital cortex, with a right hemispheric dominance. Additionally, the SLB activated the left angular and left premotor cortex. In patients, we hypothesized that different activation patterns could emerge depending on the lesion location, spatial cognitive impairment and the time since stroke.

Materials and Methods

Participants

This work was performed at the University Hospital of Rennes as part of a randomized control trial (RCT), including patients within nine months of a first right supratentorial ischemic or hemorrhagic stroke who presented a weight-bearing asymmetry. We included 14 patients in this ancillary fMRI study, as described in table 1. All patients gave their written informed consent to participate in this study, approved by the Poitiers-France III West institutional review board (no. 05/12/16; AVCPOSTIM study—clinical trial identifier NCT01677091). The exclusion criteria were any disorder that might have affected balance before the stroke (i.e., medical history of neurological, orthopedic, rheumatological or vestibular disorder) and a visual issue or behavioural impairment that might hamper assessment.

Experimental design

The SSA and SLB tasks were performed as described previously (Leplaideur et al., 2021). During the SSA, patients indicated when the moving bar would divide their extracorporeal space into two halves. During the SLB, the patients indicated when the rotating bar was aligned with a plane dividing their corporeal space into two equal parts.

The same stimuli were presented during the control condition, but participants pressed the button when the bar changed direction.

Each fMRI sequence lasted three minutes and followed a block design with alternating 30s-task and 30s-control conditions. The bar passed through the centre six times at a constant two degrees per second within each block. The process was similar for both tasks. The tasks were implemented using E-Prime 2.0 Professional software (Psychology Software Tools, Pittsburgh, PA, USA) and presented using goggles (NordicNeuroLab, Bergen, Norway) attached to the head coil to immerse participants in the task removing all spatial clues. The instruction was

presented via the goggles in different colours just before the task. While performing the tasks, participants reported their perception by pressing a button with their right index finger. Before the experiment, they practised outside the scanner until they were able to perform both tasks. They all confirmed they understood the instructions.

We controlled visually that patients performed the task as expected, but the task was not meant to measure precisely the deviation. Patients' SSA and SLB were evaluated previously in the seven days preceding the MRI scan.

MRI acquisition

MRI acquisition was performed on a 3 Tesla scanner (Magnetom Verio; Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil. The experimenter checked the alignment of the head, shoulders, trunk, and limbs before MRI acquisition. Foam pads maintained head and trunk.

The following MR sequences were acquired:

- sagittal morphological isotropic 3D T1 MPRAGE sequence (repetition time (TR)/inversion time (TI)/echo time (TE): 1900/900/2.26 ms, field of view (FOV) 256 X 256 mm², 160 slices, 1X1X1 mm³ voxel size);
- field map with two echo times for distortion correction; and
- two blood oxygen level-dependent (BOLD) fMRI sequences using a single-shot T2*- weighted EPI sequence (TR/TE: 3000/36 ms, 210x210 mm², FOV, 2X2X4 mm³, voxel size, 24 slices). Interleaved slices were acquired parallel to the anterior commissure posterior commissure line with no gap. In total, the scans were completed in 15 min.

Images were preprocessed and analyzed using Statistical Parametric Mapping (SPM12; Wellcome Department of Imaging Neuroscience, University College London, London, UK [22]; revision 7487) and MATLAB. Morphological images were segmented, corrected for bias, and normalized to the Montreal Neurological Institute atlas space (MNI).

Slice timing, spatial realignment, distortion correction, coregistration to the morphological images, and normalization were applied, followed by 6 mm full width at half maximum (FWHM) isotropic Gaussian kernel smoothing. The canonical hemodynamic response function and its temporal derivative were used for model estimation, and three contrasts were evaluated: "SSA > control condition", "SLB > control condition", "SSA>SLB".

Lesion delineation

A trained medical doctor (SL), supervised by an expert neuroradiologist (JCF), performed lesion delineation on FLAIR images informed by T1-weighted images using ITK-SNAP (Yushkevich et al., 2006). The following processing was performed: coregistration of FLAIR images on T1-weighted images and image normalization in the Montreal Neurological Institute (MNI) space. Finally, lesion maps were overlaid on a T1 template and visualized using MRICroGL (<https://www.mccauslandcenter.sc.edu/mricrogl/>).

Preliminary Results

Baseline data

Data were collected from 14 patients (6 women) with a mean age of 61.6 years old ($SD = 9.1$). Etiology was ischemic in seven cases and hemorrhagic in seven cases. Meantime since stroke at inclusion was 82.3 days ($SD = 57$). The results of the SSA were deviated in 78% and 43% for the SLB. Figure 1 shows the group, individual patient's characteristics and normalized lesion frequency maps on a T1-template in the standard MNI space with MNI Z-coordinates, i.e. on axial sections. The colour bar shows the number of patients with a lesion within a particular voxel.

The patients' lesion was presented in 37 % in the frontal lobe (precentral gyrus, middle and inferior frontal gyrus, SMA), 15% in the parietal lobe (supramarginal gyrus, inferior parietal lobule and postcentral gyrus), 13.7% in the temporal lobe (sup temporal gyrus), 12.8% in the occipital lobe, 4% in the limbic lobe, and 3.3% in the insula.

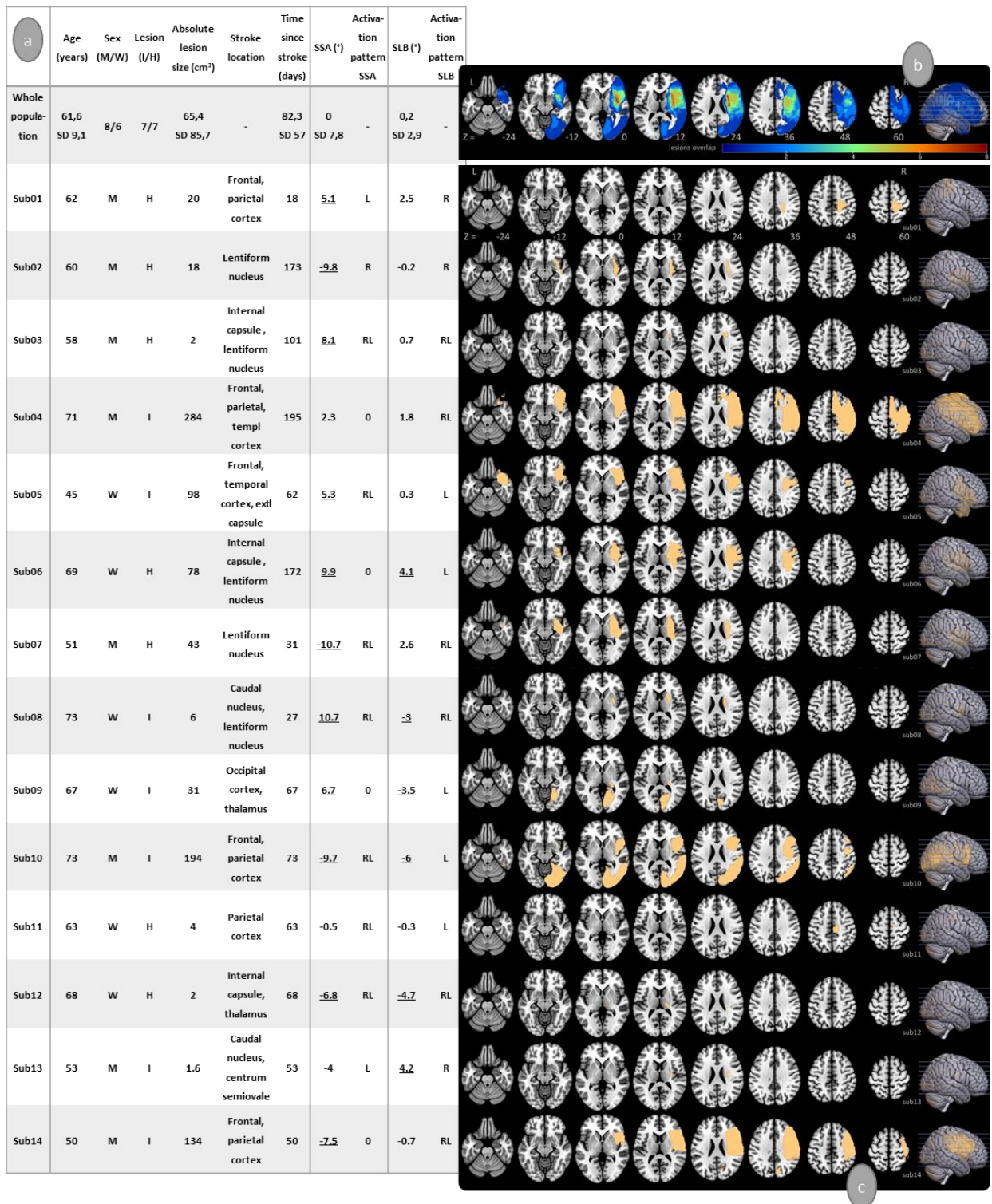


Table 1 – (a) Patients’ baseline characteristics (mean, SD), the outstanding results are underlined (Norms of SSA [-4.89° ; 4.59°], norms of SLB [-2.44° ; 2.92°]) M man, W woman, 0 no activation, R right, L left or RL bilateral activations ; (b) lesion frequency maps: the colour scale indicates the number of patients for whom the lesion extended to the voxel ; (c) individual brain lesions of the fourteen patients; Z coordinates in the MNI atlas. R = right; L = left.

fMRI activations

SSA

Individual analyses revealed heterogeneity in brain activations, suggesting various brain reorganization processes. No significant activations were observed in patients at the group level. Individual patient activations ($p = 0.001$, cluster > 25) are presented below. Four different patterns were observed.

Firstly, we did not detect any activations for four patients (sub04, sub06, sub09, sub14) during the SSA task, while visual monitoring ensured that the task was performed. Their lesions are shown in figure 1 (mean lesions size were 131 cm^3 (ranging from 31 to 282 cm^3), their meantime since stroke was 121 days (ranging 50 to 195 days), three out of four patients had SSA deviation (sub06: 9.9° , sub09: 6.7° , sub14: -7.5°).

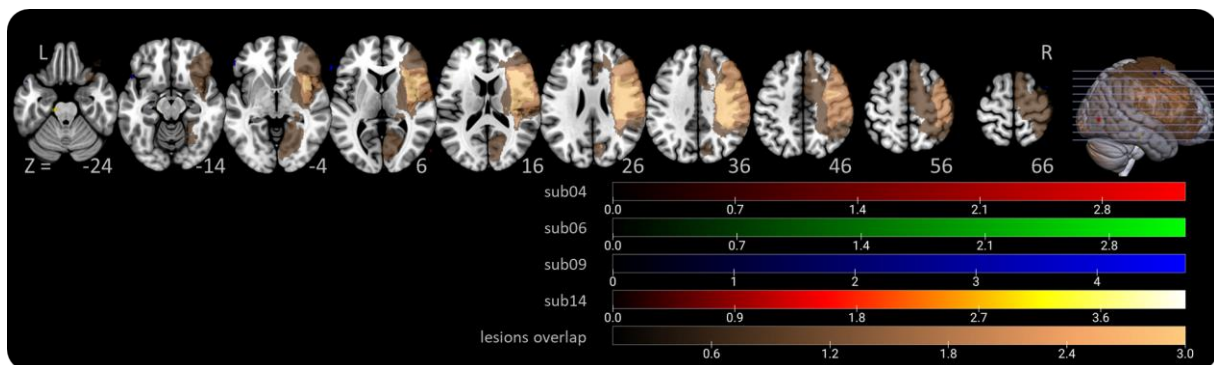


Figure 1 Lesion frequency map of sub04, sub06, sub09, sub14; Color scale: number of patients for whom the lesion extended to this voxel, Z coordinates in the MNI atlas. R right; L left. The analyses of brain activations of these patients during SSA did not detect any voxels activated.

Secondly, one patient (sub02) with a small subcortical lesion of 18 cm^3 presented an activation in the ipsilesional inferior frontal gyrus (figure 2). This area was not frequently activated in healthy subjects. This patient presented an SSA deviation (-9.8°) and was at 173 days from stroke.

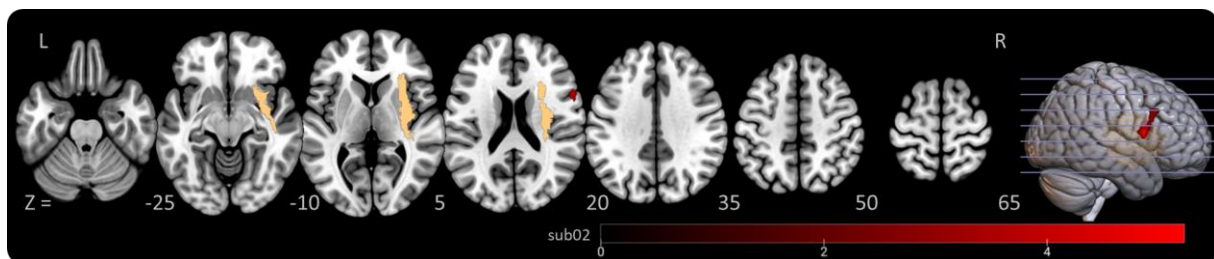


Figure 2. Rendered image of activated cluster highlighted by ‘SSA > control condition’ contrast in the sub2 who had only right activation during the SSA task. The colour bar indicates T-values (BOLD), Z coordinates in the MNI atlas, R_right; L_left.

Third, two patients (sub01:20 cm³, sub13: 1.6 cm³) only activated contralesional brain areas (figure 3), predominantly in the left occipital lobe (cuneus), postcentral gyrus, and SPL. These areas were frequently activated in healthy participants, yet with a right predominance. These patients presented an SSA deviation (sub01: 5.1°, sub13: -4°) and were 18 and 53 days from stroke.

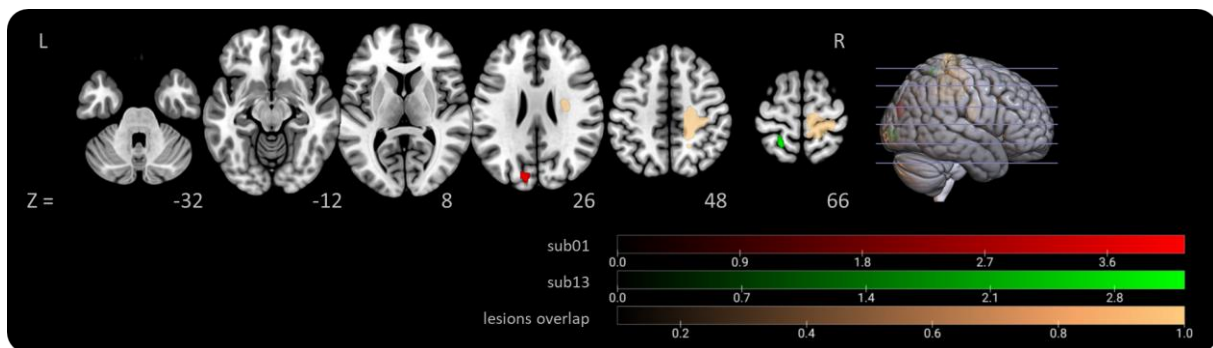


Figure 3. Rendered image of activated cluster highlighted by ‘SSA > control condition’ contrast of sub01, sub13 who had only left activations during SSA task. The colour bar indicates T-values (BOLD), Z coordinates in the MNI atlas, R_right; L_left.

Finally, 50 % of patients (7/14) activated bilateral clusters without the right predominance observed in healthy subjects. The lesions of these patients (sub03, sub05, sub07, sub08, sub10, sub11, sub12) are shown in figure 4 (mean lesions size were 49.8 cm³ (ranging from 2 to 194), their meantime since stroke was 60.7 days (ranging from 27 to 101), six patients had SSA deviation (sub03: 8.1, sub05: 5.3, sub07: -10.7, sub08: 10.7, sub 10: -9.7, sub 12: -6.8 °) Activations in the posterior cerebellum, middle temporal gyrus, occipital lobule, parietal lobule (postcentral gyrus, SMG, precuneus, superior parietal lobule), and frontal lobule (middle and inferior frontal gyrus, precentral gyrus) were also observed. These areas are frequently activated in healthy subjects except for the posterior cerebellum and middle temporal gyrus.

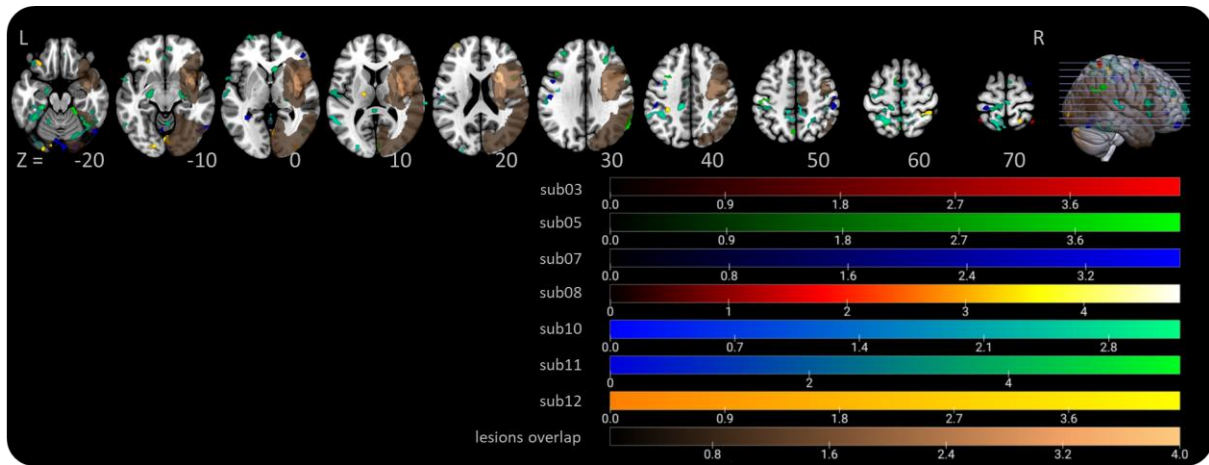


Figure 4. Rendered image of activated cluster highlighted by ‘SSA > control condition’ contrast of patients sub03, sub05, sub07, sub08, sub10, sub12 who had bilateral activations during SSA task. The colour bar indicates T-values (BOLD), Z coordinates in the MNI atlas, R = right; L = left.

SLB

During SLB, at the group-level, a cluster of 39 voxels was activated ($p = 0.001$, cluster > 25), with a peak in the contralesional cuneus (MNI coordinates -8 -84 30) (figure 5). This area was activated in healthy participants, but mostly on the ipsilesional side.

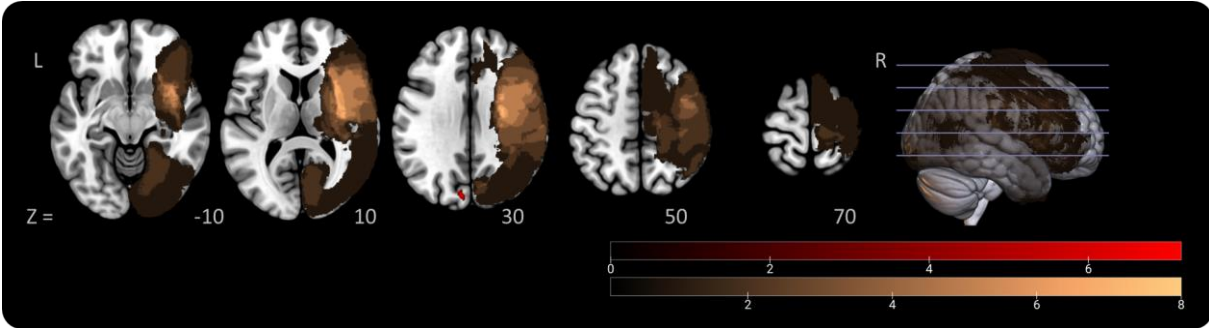


Figure 5. Rendered image of activated cluster highlighted by ‘SLB > control condition’ contrast for 2nd level analysis in 14 patients during SLB task. The red colour bar indicates T-values (BOLD), the second colour bar shows the lesion frequency map, Z = coordinates in the MNI atlas, R = right; L = left.

As during SSA, individual analyses are reported under the assumption that several brain reorganizations could emerge. Thereby, we observed three patterns of activation

Three patients (sub01, sub02, sub13) activated only ipsilesional areas: posterior cerebellum, middle temporal gyrus, median frontal gyrus, precentral gyrus, angular gyrus, SPL, precuneus,

cingulate gyrus, caudate nucleus. Except for cerebellum and temporal locations, these activations were frequently observed in healthy subjects. The cluster activations and lesions of these patients are shown in figure 6 (mean lesions size were 13.2 cm³ (ranging from 1.6 to 20), their meantime since stroke was 81.3 days (ranging from 18 to 173), only one patient had SLB deviation (sub13: 4.2 °).

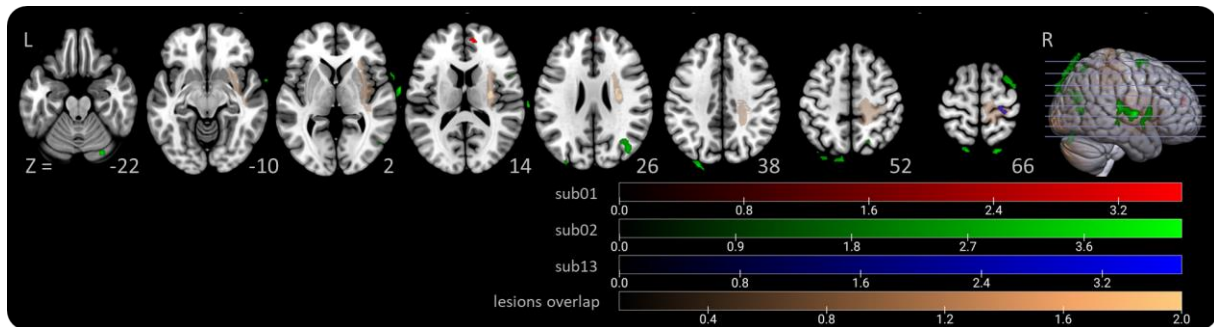


Figure 6. Rendered image of activated cluster highlighted by ‘SLB > control condition’ contrast. The colour bar indicates T-values (BOLD), Z coordinates in the MNI atlas, R=right; L=left.

Five patients (sub05, sub06, sub09, sub10, sub11) activated only contralesional areas: middle occipital gyrus, cuneus, middle temporal gyrus, middle frontal gyrus, superior frontal gyrus, precentral gyrus, postcentral gyrus, parietal inferior, insula. The lesions of these patients are shown in figure 7 (mean lesions size were 81 cm³ (ranging from 4 to 194), their meantime since stroke 8.4 days (ranging from 62 to 172), three patients had SLB deviation (sub06: 4.1, sub09: -3.5, sub10: -6).

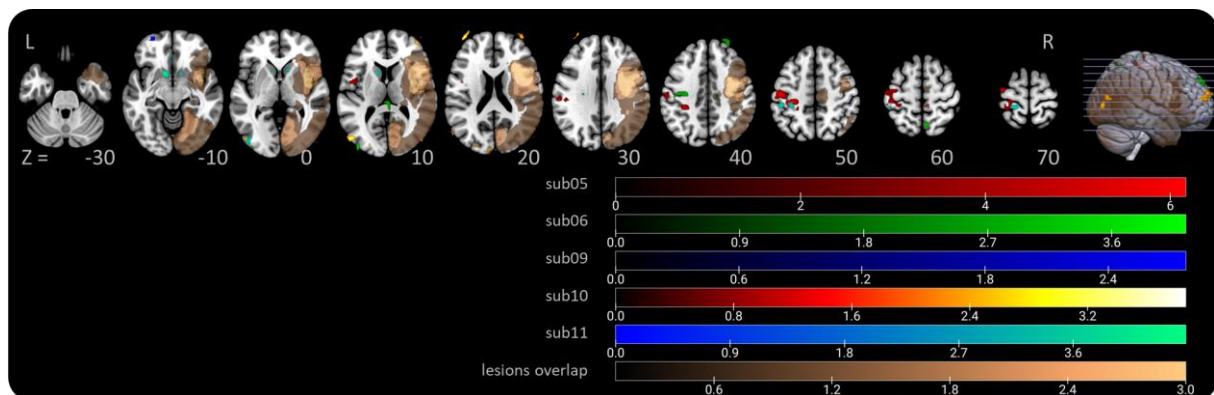


Figure 7. Rendered image of activated cluster highlighted by ‘SLB > control condition’ contrast. The colour bar indicates T-values (BOLD), Z coordinates in the MNI atlas, R_right; L_left.

Six patients (sub03, sub04, sub07, sub08, sub12, sub14) expressed bilateral activations in the cerebellum, middle and inferior occipital gyrus, cuneus, superior and middle temporal gyrus, superior and medial frontal gyrus, precentral gyrus, parietal inferior, postcentral gyrus, precuneus and angular. The activations and lesions of these patients are shown in figure 8. The mean lesion size was 89.5 cm³ (ranging from 2 to 134), their mean time since stroke was 78.6 days (ranging from 27 to 195). Two patients had SLB deviations (sub08: -3.5, sub14: -4.7).

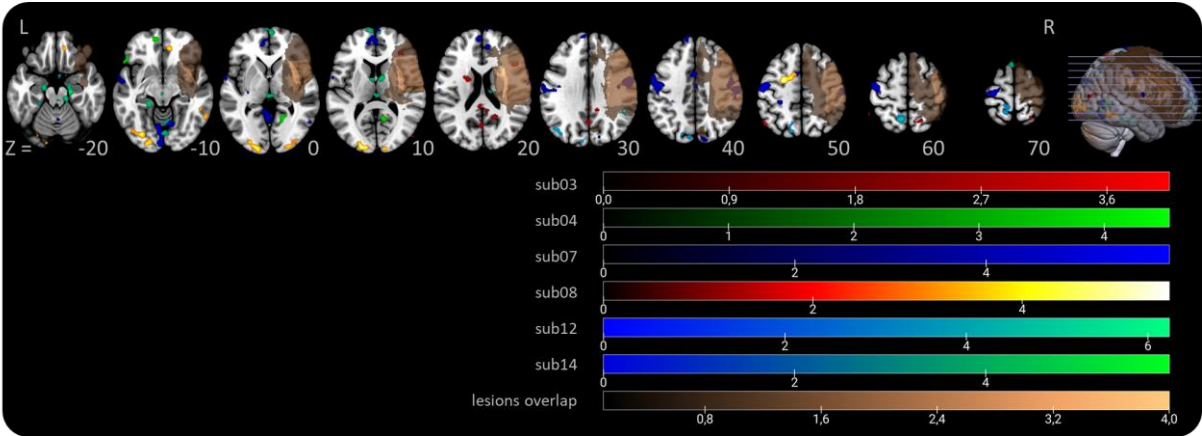


Figure 8. Rendered image of activated cluster highlighted by ‘SLB > control condition’ contrast. The colour bar indicates T-values (BOLD), Z coordinates in the MNI atlas, R_right; L_left.

Discussion

The present work investigated the activation during two egocentric tasks after a right stroke. We distinguished three different activation patterns, i.e. only ipsilesional, only contralesional, bilateral activations. We hypothesized that these different activation patterns could reflect the cortical reorganization after a stroke.

Interestingly, we observed activations in a fronto parieto occipital network. However, the right predominance was not respected compared to healthy subjects (Leplaidur et al., 2021). More activations appeared in the cerebellum, middle and superior temporal gyrus. Since the involvement of the cerebellum in high-level cognitive processes has been explored for a long

time (Petrosini, 1998; Passot, 2009; Rondi-Reig et al., 2014), its recruitment could reflect an adaptation of patients with spatial cognition disorders. Indeed, cerebellum activations were also found after PA during a spatial task by Saj et al. in 2019). Furthermore, the temporal gyrus implication in egocentric tasks after stroke could be related to the hypothesis of superior temporal gyrus (STG) implication in complex exploratory search tasks, developed in previous works (Karnath et al., 2001; Ellison, 2004). These results need to be interpreted with caution given our number of subjects and thresholds used.

Similarly to what occurred during motor tasks or language tasks in patients who had a stroke (Tombari et al., 2004; Wilson, 2017; Cirillo et al., 2020), we found three patterns of activations: 1) bilateral activations, 2) contralesional activations, 3) activations in the perilesional area. These different reorganization profiles have also been presented in USN cases (Umarova et al., 2016; Gammeri et al., 2020). After analysing the neglect evolution of 34 patients, the authors concluded that neglect recovery was correlated with right parietal and left prefrontal activations (Umarova et al., 2016). These different kinds of reorganisation are classically dependent on the time after the stroke or the severity of the functional impairment.

Even if the small lesion size seems to improve activation ipsilesional, we did not find any relation between the lesion localization and the reorganization profile. However, in this study, several factors explain our difficulty in analysing these data: 1) the number of patients per group is limited; 2) in this ancillary study, the inclusion time required the acquisition of standing balance (an inclusion criterion of the original study), and therefore the time between stroke and inclusion depended on the severity of balance disorders.

In some cases, we did not detect any activation. From our point of view, this lack of activation would not be due to an absence of the realization of the task because we carefully monitor during the fMRI that the patient performed the task. Preprocessing in case of stroke could explain this defect. Indeed, we choose to maintain a whole-brain analysis given that their lesion was located in the region of interest for these tasks. The integration of a lesion mask or an individualized HRF could improve the interpretation of these tasks.

Moreover, the delay in performing tasks needs to be considered. During these continuously moving bars, the reaction time is not distinguishable from the result of the task. Indeed, as

found in reorganization review in case of phasic disorders, the time taken to perform the task can impact the fMRI analysis (Wilson et al 2020).

Conclusion

For the first time to our knowledge, this work demonstrated reorganisation patterns in the case of right vascular lesions in patients with balance disorders. Three patterns emerge bilateral, ipsilesional and contralesional activations during egocentric tasks after a right stroke. The cerebellum posterior and the temporal gyrus, high-level integration areas allowing spatial cognition adaptations, could be a region of interest for future studies. These results need to be reproduced and extended to a larger group of patients.

KEY POINTS

SPATIAL COGNITION – NEURAL BASES OF EGOCENTRIC TASKS

Considering the repercussion of spatial cognition disabilities after a stroke, we focused our research on egocentric referential frame. SSA and SLB are tasks used to assess respectively the extracorporeal and corporeal part of this referential frame.

IN healthu subjects, neural correlates of egocentric tasks involve a bilateral fronto-parieto network with a right predominance, a major involvement of the PPC with extension to the superior frontal lobule. During the contrast SLB > SSA , added activation were found in the left angular and precentral. These results suggested a greater complexity of corporeal processes engaging body representation.

THE REORGANIZATION OF EGOCENTRIC REPRESENTATION AFTER STROKE

After a right stroke, patients could be divided in three groups according to their activations during SSA and SLB : ipsilesional activations, contralesional activations , and bilateral recruitment. Patients predominantly activated bilateral areas close to those of healthy subjects. However , the cerebellum and temporal gyrus could represent areas of adaptation for this high level spatial cognition tasks.

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Part 2. Neck Muscle Vibration

CHAPTER 1. Neck muscle vibration – Theoretical framework

What are the principles of action of NMV? What are the hypothesis underlying NMV effects?

CHAPTER 2. The clinical effects of neck muscle vibration

What are the impacts of NMV on postural orientation and spatial cognition in the literature?

Publication 3 The effects of neck muscle vibration on postural orientation and spatial perception: A systematic review

What are the effects of repetitive NMV on postural disturbances after a chronic stroke?

Publication 4 The effects of repetitive neck-muscle vibration on postural disturbances after a chronic stroke

Chapter 1. Neck muscle vibration – Theoretical framework

a. Sensory stimulations

As previously mentioned, spatial cognition disorders, especially in relation to the egocentric referential, impact the prognosis of patients after a stroke. However, the specific management of the cognitive part of these disabilities is not commonly performed in balance rehabilitation programs. Sensory stimulation appears to be an attractive option to improve patients' treatment. By increasing sensory inputs, these stimulations aim to recalibrate referentials (Andersen and Snyder, 1993). Indeed, different stimulations have shown immediate effectiveness in improving postural imbalance after stroke, especially in the case of RHL, even without neglect (Bonan et al., 2015). Pérennou et al. showed that the sitting balance was improved by proprioceptive transcutaneous nerve stimulation of the cervical region (Perennou, 2005). Rode et al. found a corrective effect of caloric vestibular stimulation on the asymmetry of the centre of pressure with a higher impact in RHL subjects (Rode et al., 1998). Optokinetic and galvanic vestibular stimuli modulated the hemiparetic subject's centre of pressure in stroke patients (Karnath, 1996; Bense et al., 2001; Bonan et al., 2016). An improvement of balance in standing position on a force platform and in sitting position was observed after PA (Tilikete et al., 2001; Nijboer T.C.W. et al., 2014; Hugues et al., 2015). Finally, encouraging results were obtained with vibratory proprioceptive stimulation of the neck muscles (Bottini et al., 2001; Leplaideur et al., 2016).

b. High-level transformations

The mechanisms underlying such postural effects are not totally understood (Hugues et al., 2019) but could be explained by a high-level impact on the body and spatial representation rather than a sensorimotor effect (Michel, 2016). This assumption comes from a variety of arguments. Firstly, the impact of sensory stimulations predominates in patients with RHL compared to patients with LHL, likely related to the spatial role of the right hemisphere. Secondly, several sensory stimulations effectively reduce postural bias, whatever their modalities, suggesting a supramodal brain action, as shown for optokinetic stimulation, galvanic vestibular stimulation (Bense et al., 2001) and NMV (Bottini et al., 2001). Third, a long

term balance modification was reported several minutes after stimulation (Wierzbicka et al., 1998; Karnath et al., 2002).

c. NMV mechanism of action

Several indications exist for focal vibration in rehabilitation: pain, tendinitis, spasticity, to modulate proprioception (Courtine et al., 2007; Murillo et al., 2014). Indeed, muscle vibrations induce activation of primary muscle spindle endings proprioceptive receptors. This generates activation of the proprioceptive afferent fibres Ia leading to a stretching illusion of the muscle vibrated (Goodwin et al., 1972; Roll and Vedel, 1982; Gilhodes et al., 1986; Roll and Gilhodes, 1995; Calvin-Figuere et al., 1999; Romaguère et al., 2003).

A historical example was presented by Lackner et al. in 1988, describing the Pinocchio illusion (Lackner, 1988). Fourteen blindfolded subjects received vibration on the brachial biceps while they were asked to grasp their nose (framed section of the figure 1). As a result, ten subjects experienced their arms moving, and half of them felt like their nose was elongating. This experiment highlighted that vibration modifies proprioceptive inputs and distorts body perception and body orientation in space. The integration of these components is involved in the adaptation of the reference frame.

















	Test configuration A	Experienced pattern	Test configuration B	Experienced pattern
1				
2				
3				
4				

Figure 1 – Image from the publication of ‘Lackner JR, Some proprioceptive influences of the perceptual representation of body shape and orientation. Brain 1988’. Representation of

different test configurations (with vibration position indicated by the arrow) and predominant patterns experienced during vibration.

d. NMV and egocentric referential frame

NMV provides an afferent proprioceptive input to the central nervous system due to the stimulation location between the head and the trunk. Indeed, with visual and vestibular inputs, the neck muscles are mainly involved in perceiving the head position relative to the body (Lackner and Levine, 1979; Biguer et al., 1988; Karnath et al., 2002; Pettorossi and Schieppati, 2014).

NMV was first tested on USN. In 1993, Karnath et al. tested NMV on three neglect patients and reported that their left deviation on neglect assessment was improved by up to 15 degrees. In 2002, Schindler et al. performed a cross over study with NMV and visual exploration in 20 left neglect patients, demonstrating an SSA deviation to the neglected side at two months. In 2003, Johannsen et al. included six left neglect patients. Repeated sessions of NMV induced spatial neglect improvement on Bells test and letter cancellation test, which were stable more than one year later (Karnath et al., 1993; Schindler, 2002; Johannsen et al., 2003). Karnath described an enlarged exploration to the side vibrated (Karnath et al., 1993). Even if these observations must be interpreted with caution because of the limited number of subjects, the neglect improvement was suggested to be due to a “re-centring” of the egocentric referential frame using an illusory modification of afferent kinesthetic information relative to the position of the head from the trunk. Indeed, their neck proprioceptive receptors play a crucial role in the process of the egocentric referential frame (Jeannerod and Biguer, 1989; Chokron et al., 2004; Naito et al., 2016). A large part of studies evokes the illusion of head movement to the opposite side of the vibration. However, patients could also report an illusion of trunk rotation to the side vibrated relative to the stationary head (Saevarsson et al., 2010; Guinet and Michel, 2013). This kinesthetic illusion induces an egocentric referential frame shift towards the vibrated side. This is supported by previous studies where NMV influenced the deviation of the SSA towards the side of vibration (Biguer et al., 1988; Karnath et al., 2002; Chokron et al., 2004). An interesting study showed that NMV does not seem effective on object size judgments, unlike optokinetic manipulation, suggesting that NMV may not act on the allocentric references (Schindler and Kerkhoff, 2004).

e. Brain activations during NMV

In 2001, Bottini et al. carried out a Positron emission tomography Scan (PETscan) on six healthy volunteers during NMV and caloric vestibular stimulation (CVS) (figure 2 - Bottini et al., 2001). They applied a vibration at 80 Hz with an amplitude of 0.4mm on the left posterior neck. The vibrator position was adjusted to induce a horizontal illusion of deviation of a light spot to the right, in darkness. They found that NMV activated the right insula, the right somatosensory area S2, parietal operculum, corpus callosum, and the left superior temporal region.

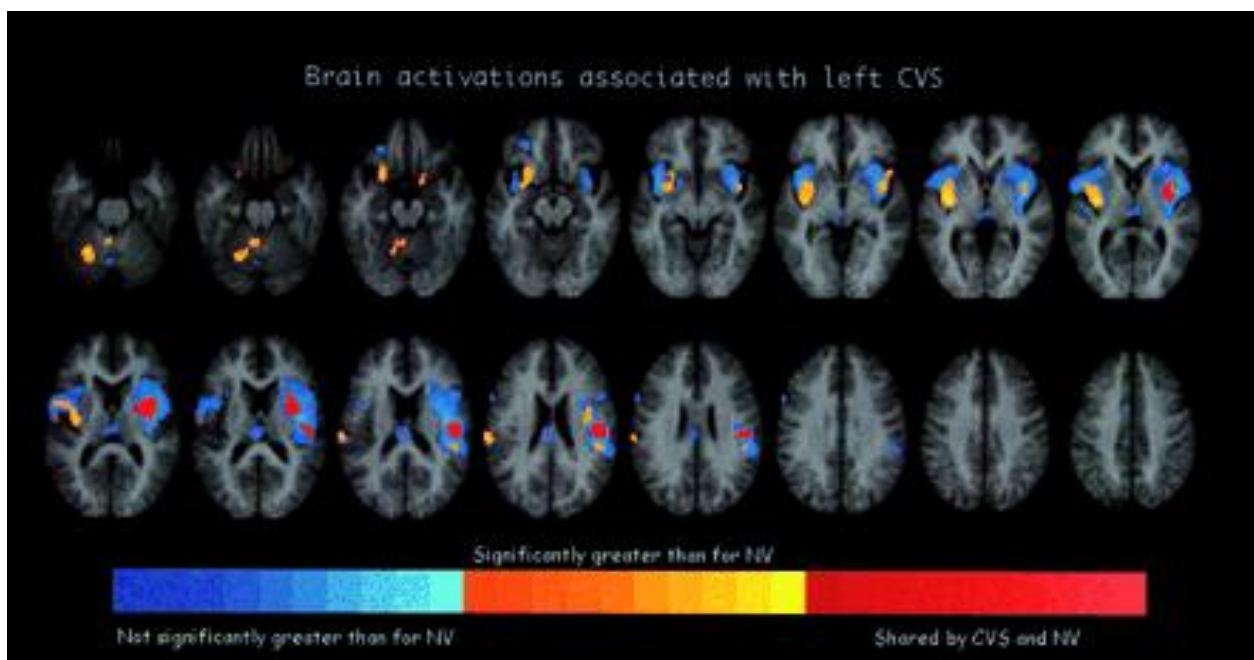


Figure 2 from (Bottini et al., 2001). Brain areas were activated by the left CVS and by the left NMV. All coloured voxels are areas activated by left CVS; blue = not significantly greater for CVS than for NMV; yellow = greater activation for CVS than NMV; red = shared by CVS and NMV.

In 2008, Fasold et al. (Fasold et al., 2008) analysed regions contributing to egocentric space perception using NMV during fMRI (figure 3). Sixteen healthy participants experienced vibration on the right trapezoid, bordering the splenius, with frequencies between 100 and 200 Hz. fMRI was conducted while the subjects maintained their eyes closed. A network of primary and secondary cortical areas was identified: 1) areas 3a, 2, S2 and the parieto-insular vestibular cortex (PIVC), 2) the intraparietal sulcus, motor and premotor areas, and the frontal

eye field (FEF). The activation of these areas during NMV confirmed their involvement in sensory integration and proprioception process.

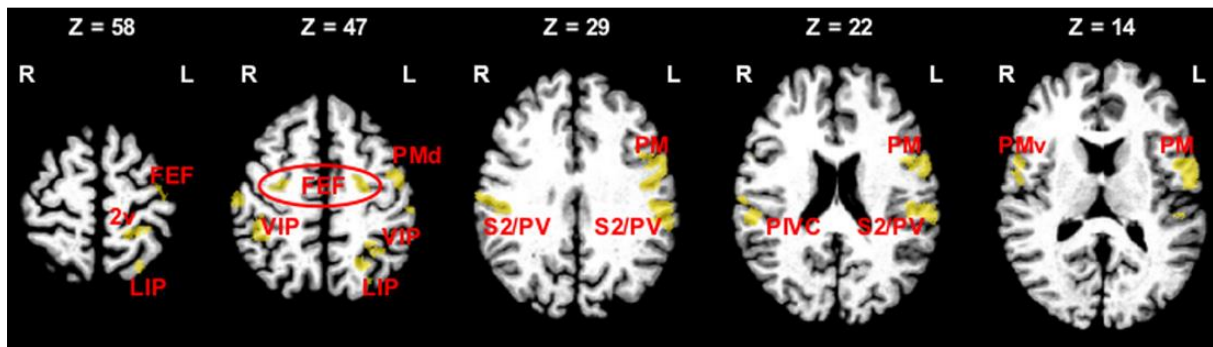


Figure 3. From (Fasold et al., 2008). Results from group analysis. Cortical areas activated by right NMV ($p < 0.001$). FEF=frontal eye field. LIP lateral intraparietal area. M1=motor area 1. PIVC=parieto-insula vestibular cortex. PM=premotor cortex. PMd=premotor dorsal cortex. PMv=premotor ventral cortex. PV=parietal ventral area. S2=somatosensory area 2. VIP=ventral intraparietal area.

f. Individual adaptations during NMV

Reaction to vibration is individually variable. For example, in the case of peripheral vibration, subjects resist differently to displacement illusion induced by the stimulation (Wierzbicka et al., 1998). In the case of wrist vibration, Romaguère et al. compared the cortical activities arising in subjects during wrist vibration, with or without an illusion of movement. The illusion of movement specifically activated the contralateral sensorimotor and premotor and the parietal cortices in which the representation of the body in space is elaborated (Romaguère et al., 2003). However, the literature is divided on the predictive effectiveness of visual susceptibility induced by NMV, i.e. the illusion during NMV of a light deviation toward the opposite side of the vibration. Near to 70% of the population reports a visual susceptibility (i.e. a deviation of the visual environment toward the opposite side of the vibration) during NMV (Karnath et al., 2002; Schindler and Kerkhoff, 2004; Leplaideur et al., 2016; Jamal et al., 2020b). Individual sensorial preferences for proprioceptive input rather than visual input could explain this variability (Vibert et al., 2006; Kluzik et al., 2007).

g. Clinical application of NMV

An interesting characteristic of NMV is that it is minimally dependent on patient cooperation. Since the final objective of this work is to adapt rehabilitation protocols, the easiness of use is

crucial. With a bottom-up action, they require minimal participation of the patients and can be used early after stroke.

Chapter 2. The review on effects of neck muscles vibration on postural orientation and spatial perception (*publication 3*)

Sensory stimulation by NMV appears as a promising pathway for treating balance disorders related to spatial cognition disorders. They are thought to decrease the distortion of the perception of the body in space by restoring the symmetry of sensory inputs.

In the following article (Jamal et al., 2020a), with Karim Jamal, we reviewed articles investigating NMV effect on postural orientation and spatial perception in healthy subjects and in patients who had distorted body orientation perception. After screening 290 references, 67 articles were included with a total of 1522 participants (958 healthy subjects, 235 patients with vestibular lesions and 159 who had a stroke).

Unfortunately, the studies were very heterogeneous, so the evidence is poor. Firstly, our review concluded that in healthy participants, NMV produces an illusion of a visual environment moving to the opposite side of vibration and an SSA deviation to the vibrated side. Secondly, in patients who had a stroke, NMV seems to modulate both spatial and postural bias.

To simplify the reading, the tables of the article are provided in appendix 4.



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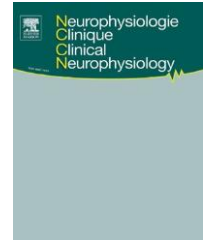
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COMPREHENSIVE REVIEW

The effects of neck muscle vibration on postural orientation and spatial perception: A systematic review



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KEYWORDS

Neck muscle vibration;
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Summary

Background. — Neck muscle vibration (NMV) is increasingly used for its modulation of body orientation and spatial perception, but its mechanisms of action are still not well known.

Objectives. — To describe the effects of NMV on postural orientation and spatial perception, in both healthy people and patients with disturbed balance potentially related to distorted body orientation perception.

Methods. — Following the PRISMA guidelines, a systematic search was performed using the databases MEDLINE, EMBASE, Cochrane library and PEDrO with the key words ((Postural balance) OR (Spatial reference)) AND (Neck muscle vibration) for articles published through to July 2016.

Results. — A total of 67 articles were assessed; these exhibited wide heterogeneity and generally poor quality methodology. In healthy subjects, under bilateral NMV, the body tilts in the anterior direction (Level of Evidence LoE II). Under unilateral NMV, the visual environment moves towards the side opposite the vibration (LoE II) and the subject's experience of "straight ahead" is shifted towards the side of the vibration (LoE II). NMV also modulates both spatial and postural bias between stroke and vestibular patients.

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Discussion. — NMV modulates both spatial and postural bias and could thus be proposed as a tool in rehabilitative therapy. However, due to the heterogeneity of published data and the various significant shortfalls highlighted, current research does not allow clear guidelines to be proposed.

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Introduction

Postural orientation requires integration of vestibular, visual, and somatosensory information in order to develop perception of the body in space and thus both maintain a position and allow the body to move [3,28]. This postural orientation can be altered by nervous system pathology, especially stroke or vestibular disease. By modulating one or more of the sources of input information, sensorial stimulation is known to manipulate the subject's posture [6].

Focusing on proprioceptive input, muscle vibration has been extensively used in two different approaches. The first is vibration applied to a specific tendon or muscle, termed "focal vibration", and the second is global stimulation of the body based on a vibrating platform referred to as "Whole body vibration" [84]. This review will focus on the former approach.

Several postural muscles, such as muscles of the trunk and the lower limbs, have been subjected to vibration in order to modulate postural orientation [20,25]. The neck muscles are unique for their localization between the head and the trunk. Their proprioceptive receptors play a crucial role in the detection of the position of the head in relation to the trunk [65]. Together with visual and vestibular inputs [5], the neck muscles are particularly involved in the perception of the body in space [5,40,44,65]. This perception of body in space can be captured by measuring the perception of allocentric space representation such as the vertical misperception (Subjective Visual Vertical) [7,66] and the egocentric space representation such as the body midsagittal misperception (Subjective Straight Ahead) [19]. By vibrating the neck muscles, a shift of the visual environment is observed, expressed clinically as the illusion of movement of a visual target [41]. As a consequence of this anatomical configuration, neck muscle vibrations (NMV) are used not only for their postural effect but also for their action on spatial perception. It is therefore essential to gather in-depth qualitative information on the effects of NMV on the perception of space as well as the effect on posture, in order to understand its action. Our objective was to conduct a systematic review of the characteristics and findings of these studies, and to assess the effects of neck muscle vibration (NMV) on postural orientation and spatial perception in both healthy people and patients with disturbed balance, in order to understand the potentially corrective effect of NMV in the patient population.

Methods

This review followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [55]. Details of the protocol for this systematic review were registered on PROSPERO (CRD42016045392). Studies were only considered eligible if they involved the effect of NMV on either balance or spatial perception, with or without comparators. Studies in which the primary outcome was postural orientation evaluated by posturography in standing or sitting position were included, as were those with assessment of spatial perception (subjective straight ahead (SSA), subjective visual vertical (SSV), subjective haptic vertical (SHV), longitudinal body axis (LBA), pointing task or visual target). A systematic search was performed using the databases MEDLINE, EMBASE, the Cochrane library and PEDrO. The keywords used in the search were ((postural balance*) OR (Spatial reference*)) AND (Neck muscle vibration). With the exception of reviews and meta-analyses, only studies published in French and in English up to July 2016 were considered. Lastly, a manual search was carried out on Google Scholar, Research Gate and clinical trial.gov for on-going studies. The reference lists of manuscripts and the bibliography of relevant reviews and meta-analyses were also searched.

After having eliminated all duplicates, an eligibility examination for the remaining studies was performed independently by two researchers (KJ and SL) on the basis of titles and abstracts. In the event of divergence between them, this was resolved by a third reviewer (IB). Data extraction was assessed by one reviewer (KJ) and then evaluated by a second (SL) for final validation. Any disagreement between them was resolved by a third reviewer (IB). Valid information was extracted from each eligible study on the basis of the following criteria:

- characteristics of the study — authors, year of publication and the type of design;
- characteristics of the trial participants — age, number of people involved in the analysis and the population analyzed;
- type of intervention — muscle vibrated, the side treated, duration and frequency;
- outcome measure: postural orientation, evaluated by posturography in standing or sitting position, and spatial perception (subjective straight ahead [SSA]), subjective

visual vertical [SSV], subjective haptic vertical [SHV], longitudinal body axis [LBA], pointing task and visual target; status of the main results – the effect of the vibration; under vibration, the immediate effect as soon as the vibrator stops and the lasting effect at a distance from the vibration.

The methodological quality of both the randomized control trials (RCTs) and the crossover trials (CO) was assessed using the PEDro scale [21,51]. This scale is based on 11 items scored out of 10: namely, eligibility criteria, randomization, concealed allocation, blinding (subjects, therapists, and assessors), follow-up, intention-to-treat analysis, between-group comparisons, point estimates and variability [57,63]. This scale gives a classification of quality with different cut-off score possibilities whereby 9 to 10 is considered excellent; 6 to 8 good; 4 to 5 fair; and < 4 poor quality [54,57,63]. Other studies were assessed by way of the Quality Assessment Tool for Before–After (Pre-Post) Studies with No Control Group [61] based on 12 items: objective clearly stated, eligibility criteria described, representative patient population, all eligible participants enrolled in the study, adequate sample size, intervention described, outcome measure specified, outcome assessors blinded, loss to follow-up, statistical analysis of outcome measure before and after intervention, interrupted time-series design and individual data used for group effects. According to the guidelines, the rating quality was considered to be good, fair or poor. The efficiency of NMV was scored according to the level of evidence (LoE) following the Sackett et al guidelines [14,70] for each outcome. For LoE I: large RCTs with clear results (only RCTs with a PEDro score of 6/10 or more), for LoE II: small RCTs with unclear results (poorer quality RCTs with a PEDro score under 6/10), for LoE III: cohort and case-control studies, for LoE IV: historical cohorts or case-control studies, for LoE V: case series, studies with no controls [54]. The quality of methodology was assessed independently by two researchers (KJ and SL) and in the event of a disagreement between them, this was resolved by a third reviewer (IB).

Results

In this systematic review, 290 references were identified, to which 15 references were added thereafter by way of a manual search (Fig. 1). Only 92 articles met the eligibility criteria and their full texts were requested. In the end, 67 articles, published between 1979 and May 2016, were included in this review, divided into 41 articles concerning postural orientation, 27 articles on spatial perception, and one article was included in both categories. These 67 articles covered a total of 74 experimental sessions, of which 56 (75%) were related to cross-over designs with median quality on the PEDro scale of 5/10 [min = 3/10; max = 6/10] (Table 1) and 18 (25%) to other study designs (Quality Assessment Tool for Before–After (Pre-Post) Studies with No Control Group), most of these being studies of fair to poor quality (Table 2). A total of 21 out of 75 were of good quality (i.e. above the PEDro cut-off of 6/10), among which 4 experimental sessions were based on spatial perception and the others (17) on postural orientation (Table 1).

A total of 1522 participants [min = 4; max = 104] were included in this systematic review, among whom 958 were

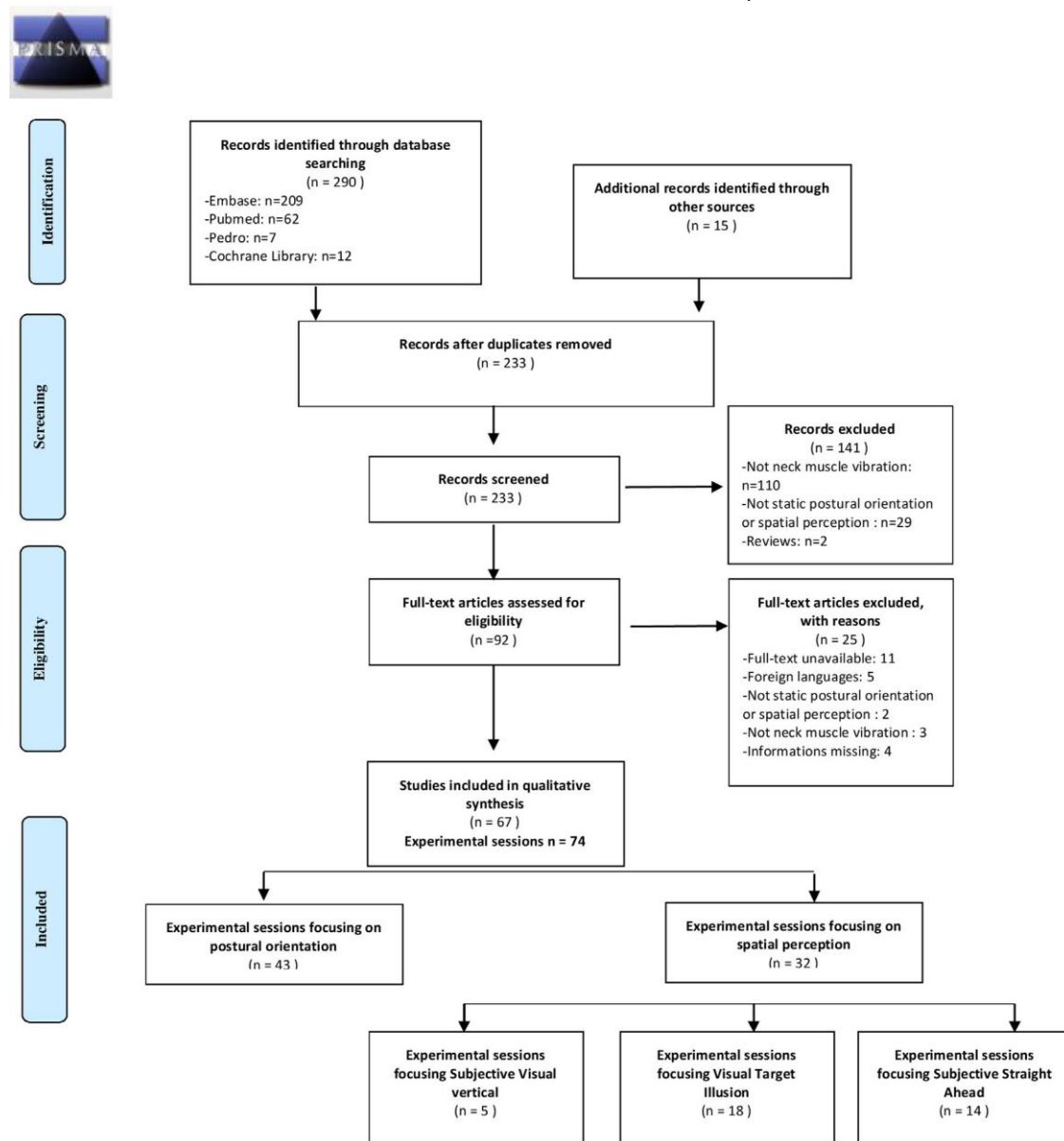
healthy subjects, 235 were patients with vestibular lesions and 158 were stroke patients (Table 3). All the characteristics of the interventions are presented in Table 4. The median frequency and amplitude applied by the vibrator was 90 Hz [min = 20; max = 140] and 0.8 mm [min = 0.13; max = 1.4]. The most common muscle sites were the dorsal neck muscles for 23 studies (31%) with the identification of posterior or paravertebral or paraspinal neck muscles. Vibration was performed on one side (either right or left) for 20 studies (27%) and bilaterally for 21 (28%) studies. In most cases, muscle tracking was either not performed (46%) or established by anatomical location (40%) for the studies on postural balance; for spatial perception, however, most authors used the illusion of movement of a visual target to position the vibrator (59%). The median duration of the vibration was 20s [min = 1 s; max = 28min].

Postural orientation

The results for the effect of NMV on postural orientation are presented in Tables 5 and 6. Concerning bilateral NMV in healthy subjects, authors were in agreement, and many good-quality studies reported that the body tilted in the anterior direction (LoE II) [50,56,58,62,75,81]. Further to this, two studies (one of fair quality and the other of poor quality) described body tilt as soon as the vibrator was switched on, within the first milliseconds of onset of the vibration, generating first a backward body tilt and only thereafter a forward tilt at 250 ms [1,80]. One fair-quality study described a vectoral additive effect when vibrating back and oblique neck muscles: the body tilted in both the antero-posterior and the medial-lateral direction and when the vibrators were placed on two antagonist muscles; the effect vanished and no displacement was found [42].

Unilateral NMV applied to healthy subjects tilted the subject either in the anteroposterior plane or in the medial-lateral plane, depending upon which muscle was vibrated or the manner in which the vibrator was placed on the back of the neck (LoE IV). In the medial-lateral plane, bearing in mind that studies were only of fair quality, most of them found that subjects usually tilted in the direction opposite the vibrated side [11,20,42]. Only three studies of poor quality found that subjects could also tilt forward in the anteroposterior plane [46,69] (Table 5).

With regard to the retention effects after the vibrator was switched off, the systematic review highlights some disagreement. Only one study, albeit of good quality, did not observe any retention effect as their test subjects returned to their initial position after a short-duration bilateral NMV (1 s–4 s) [13]. In the case of unilateral NMV, three fair-quality articles found variability from one subject to another after stopping the vibration [16,22,82]. The length of the effect after stopping NMV was dependent on each individual experiment, for example, Wierzbicka et al. [82] described a retention effect between 3 minutes up to 3 h, while this was attained for at least 5 min for Leplaideur et al. [16] and 13 min for Duclos et al. [22]. Besides this, a variability was also observed in the direction of the retention effect as Duclos et al. [22] found a long lasting effect which was a tilt towards the NMV side for half of the healthy subjects while the other half, the tilt was in the opposite direction.



systematic reviews showed some disagreement. Among

Figure 1 Prisma flow diagram.

This being said, three studies of fair to poor quality observed that when vibrating with different eye, head or trunk orientations, the body tilted towards the orientation of gaze rather than head or trunk orientation [29,33,34]. Five studies of good quality showed that vibrating with the eyes open had little or no effect on postural orientation (LoE II) [26,56,62,64,81] and one study (good quality) showed that the effect of vibration can be reduced or even suppressed by finger contact on a stable surface [10]. One good-quality study described an increase in the effect after successive sessions [13]. Magnusson et al. [50] (good quality) found that the amplitude of the tilt was related to the amplitude of the vibration, with a greater effect when the vibration amplitude was

studies on patients with unilateral vestibular lesions, two studies of fair to very poor quality put forward the idea that unilateral NMV on the contra-lesional side tilted the body forward, whereas uni-lateral NMV on the ipsi-lesional side tilted the body in the medial plane towards the side of the lesion [45,67]. Controversially, one study of fair quality did not find any effect, and this is possibly due to a longer time-lapse since the lesion, to which they refer in their article [24]. Focusing on bilateral NMV in the case of unilateral vestibular lesions, two studies of fair to poor quality found that the body tilted towards the side of the lesion (LoE V) [79,83]. In the case of bilateral vestibular lesions, only one study of fair quality found no effect [45]. Regarding the retention effect, only one study of fair quality [83] focused on the effect after 15 s of vibration and found

that patients moved gradually back to their initial position. Therefore, on the basis of these studies, this systematic review provides a low level of evidence (LoE V) for the efficacy of NMV on unilateral and bilateral vestibular lesions. For stroke patients, three studies of fair quality observed that unilateral NMV on the contralesional side resulted in a medial-lateral tilt towards the contralesional side, i.e. the hemiplegic side, in both right and left brain damaged groups [17,18,48] with a greater body tilt among the stroke patients who experienced the illusion of movement of a visual target under vibration [48]. On the other hand, only one study of good quality showed that bilateral NMV in standing position led to a forward tilt [58]. This systematic review revealed the absence of studies focusing on the retention effect amongst stroke patients.

Spatial perception

Illusion of movement of a visual target (VT)

Sixteen articles focused on VT with a total of 304 subjects, of whom 92 were patients, for the most part stroke patients (n = 72) (Tables 7 and 8). The six articles, of fair quality, without exception all found that during unilateral NMV in healthy subjects, the VT shifted towards the direction opposite to the vibrated side (LoE II) [31,37,41,47,52,68]. This systematic review found two means of assessing the illusion of movement of a VT; the first was to ask the subject to give a self-report on whether there was an illusion of movement of the VT and to define its direction [37] and the second was the administration of a pointing task [52]. One poor quality study found that the illusion of motion was consistent whether the subject was pointing towards it or just viewing it [5]. Two studies of fair to poor quality observed that in a few cases the illusion could also move on the vertical plane [5,41].

Four studies of poor quality highlighted that this illusion was not consistent [5,38,74,77]. Biguer et al. [5] specified that whatever the side of vibration, only 78% of the healthy subjects were found to be susceptible to visual illusions. A greater amplitude of deviation was found when the vibration amplitude was increased [5]. Regarding the effect after the cessation of the vibration, the most relevant studies were found to be of poor quality with authors in disagreement on the topic; some authors stated that the VT could reverse its direction to return to its initial position [5,74], while others claimed that for some subjects [31] the VT continued in the same direction after the vibration was switched off. The same effect was observed in both sitting and supine positions [68] (fair quality).

Concerning stroke patients, apart from the poor quality of most studies, 3 authors reported a frequency of illusion of movement of the VT (LoE IV) identical to the proportion found among healthy subjects [35,37,48] (Table 8). Unilateral spatial neglect did not influence this proportion [37,38]. In the vestibular lesion population, no studies on the effect of NMV on the illusion of VT movement were found.

Mid-sagittal plane perception: Subjective Straight

Ahead(SSA)

Eleven articles focused on SSA with a total of 271 trial subjects, of whom 60 were patients, stroke patients for the most part. Two good quality articles and the others of fair to poor quality found that the SSA shifted towards the vibrated side whatever the method used (visual or haptic condition), in both healthy subjects (LoE II) (Table 7) [15,40] and stroke patients, independently from the side of the brain damage [39,48,72,73] (LoE II). Only one study of fair quality focused on patients with vestibular lesions and found a shift towards the side of the vestibular lesion [76] (Table 8). In addition, some studies of fair quality [30,41] found that the healthy subjects who deviated on SSA were those who were susceptible to the illusion of movement of the VT.

Biguer et al. [5] reported that increasing the amplitude of vibration led to a greater amplitude of SSA deviation. Karnath et al. (fair quality) showed that the duration of the vibration resulted in an effect maintained over time [40]. The same effect was found when vibrating in both upright and sitting positions, but when the body was maintained tilted in the roll plane, the SSA deviation was greater (fair quality) [15].

Gravitational perception: Subjective Vertical (SV)

Five articles with a total number of 140 subjects were included in the analysis, 76 of whom were healthy subjects (Table 7) and the rest vestibular patients (Table 8). There was one good quality study [53]. Regarding the healthy subjects, unilateral vibration on either the sternocleidomastoid (SCOM) or other dorsal neck muscles induced a tilt in the roll plane of Subjective Visual Vertical (SVV) towards the vibrated side [53] as compared to the subjective visual horizontal (SVH) where the effect was absent (fair quality) [4,36]. NMV with the head-roll tilt to the opposite side induced a greater tilt of the SVV towards the side of the vibration (the Müller effect) [53]. This result, found in the sitting position, was also found in the standing position [27] (fair quality). This systematic review revealed the absence of studies focusing on the retention effect. Similarly, this systematic review pointed out, that no studies provided evidence on evaluating the effect of NMV on the SV in the stroke population.

Among patients with vestibular lesions, three studies of fair quality showed that, independently from the time-lapse since the lesion, both contralesional and ipsilesional NMV increased the abnormal ipsilesional SV tilt with a greater effect when vibrating the ipsilesional side (LoE IV) [4,36,43]. In addition, compared to healthy subjects, this effect was influenced by the head orientation in the roll plane, given that it increased when the head was tilted towards the contralesional side, but not towards the ipsilesional side (fair quality) [4].

Discussion

To our knowledge, there have been only a limited number of reviews on the subject of neck muscle vibration [59,65]. In the perspective of moving towards better understanding of the mechanism of action of NMV

on postural orientation and body perception in space, this review differs from others: first by its systematic methodology, secondly, the fact that it takes both postural orientation and spatial perception into account, and thirdly, the fact that it includes both healthy subjects and patients with a disturbed balance, in order to evaluate the potentially corrective effect of NMV in the patient population.

This review highlights the fact that the effect of NMV has been studied extensively, with literature on this research going as far back as 1979 and continuing to be substantial. It can be noted that the effect of NMV on postural balance has been studied more widely than its effect on spatial perception. It must however be recalled that only 56 experimental sessions out of 74 were based on cross-over trial designs, while the remaining 25% were experimental designs, translating into poor methodological quality for these studies. The Pedro Scale and the Quality Assessment Tool for Before–After (Pre-Post) Studies with No Control Group also confirmed this conclusion. Consequently, some results should be interpreted with caution. This being said, our findings could help get a better understanding of the mechanism of action of NMV on postural muscles.

This systematic review has outlined some general points for healthy subjects, with a good level of evidence; first under bilateral NMV, the body tilts in the anterior direction, and secondly, under unilateral NMV, the external visual environment (VT) has repeatedly been found to move towards the side opposite the vibrator whereas the subject's experience of straight ahead was found to be shifted towards the vibrated side, so that the environment appears to move relative to the body mid-sagittal plane. Furthermore, albeit to a lesser extent, a body tilt is produced under unilateral NMV, but the direction is not always the same. This can be explained by the very heterogeneous methodologies used for the localization of the vibrated muscle. Moreover, the muscle is not always clearly identified, which could confuse the postural results. Therefore, the method of muscle location should be carefully defined in future studies. Some authors have suggested the use of the illusion of displacement of a visual target [41,48]. This method can be used to identify the muscle that causes the most marked environmental-lateral shift. In addition, the patients who perceived the illusion of the displacement of a visual target responded better on both spatial perception and postural balance, with an adequate level of evidence [30,41,48]. However, this method does have some limitations: firstly, the illusion is inconstant (78% in both healthy subjects and patients) and secondly, the link between a visual illusion and postural effects is still under discussion in the literature [78].

With regards to the effect once the vibration was switched off, no clear consensus was found in the literature. A retention effect had been identified only in healthy subjects for postural orientation. Karnath et al. showed that increasing the duration of the vibration resulted in an effect maintained over time [40]. However, the duration of the effect was subject-dependent and the direction of the effect after end of vibration was variable. The retention effect on the

spatial perception seems to stop after its use. Regrettably, due to the limited number of studies which dealt with the topic of the retention effect and in particular, rehabilitation of patients with postural disorders, it is difficult to draw any noteworthy conclusion. A second retention effect was observed after several sessions as a cumulative effect. This retention effect appeared more intensive as the sessions progressed repeated. Indeed, Bove et al. described an increase in the effect after successive sessions [13], which suggests the implication of chronic vibration use in future studies involving patients with postural disorders in rehabilitation. This should however be confirmed by experimental studies. In order to gain a better understanding of the specificity of neck muscle vibration, we chose to highlight the specificities of neck muscle vibration compared to vibration of other muscles. Interestingly, some points differ. First, the direction of the body tilt under bilateral neck muscle vibration is in the opposite direction to that obtained under

back postural lower limb vibration (triceps surae) [82]. Moreover, unlike lower limb vibration in the sitting or the upright position [2], the effect of NMV is constant regardless of the position. Indeed, the reaction to vibration of the triceps surae results in a backward tilt in upright position [23,62] and a forward tilt in sitting position [82] whereas the forward shift is produced regardless of the body position for NMV [62,82]. This is also the case for space perception under NMV; the same effect was repeatedly obtained whatever the position, sitting or standing [68]. This difference between NMV and lower limb muscle vibration supports the notion of a different frame of reference involved in the perception of body in space, i.e. body-referenced for lower limb vibration, and head-referenced for NMV [68]. In our opinion, this is due to the particular configuration of the neck muscles between the head and the trunk and their close relationship with other sensory receptors. In the case of NMV, the forward tilt is the response to the illusion of the body tilting backwards relative to the head, due to the absence of stimulation of the vestibular receptor, since the head is the reference [34,65]. This explanation is further supported by the fact that the effect of NMV was found to be influenced either by the orientation of the head or by the direction of gaze [33] which was found for postural balance [32,33], spatial perception (SSA [15], SVV [27,53] and VT) [68]. An additional point is, as expected, that NMV modulates body orientation and also the perception of space. When compared to other forms of sensorial stimulation such as vestibular or visual stimulations, the modulation of NMV on body mid-sagittal plane perception (SSA) [37,72], on external environment perception (VT) [38] or on gravitational environment perception (SV) [36], was similar. In addition, the effect of NMV can also be altered by external sensorial information [10], which shows with a fair level of evidence that it is more relevant to carry out vibration either with eyes closed or

in a dark room [5,12,13,68,80]. In general, this suggests that NMV, like any other stimulation, acts on supramodal cerebral centers, and especially in areas where the representation of the body in space is elaborated [49,60,71]. Indeed, Bottini et al., who studied NMV during position emission tomography scans, confirmed brain activity particularly in the areas of multisensory integration where the egocentric representation of space is involved [9]. Therefore, our hypothesis is that the interconnected information by way of the neck or oculomotor muscle proprioceptive receptors and/or vestibular receptors is probably processed in addition to the proprioception information contributed by NMV.

This modulation of both body orientation and space perception therefore supports the use of this modulation among patients with altered postural and spatial perception. In fact, for stroke patients, both postural orientation and spatial perception shift towards the side opposite the vibrator and more precisely towards the contra-lesional side, with good evidence for SSA. Therefore, the findings of this review are in favor of the application of vibration to the contra-lesional side of the neck in order to correct the ipsi-lateral bias in both postural and spatial perception. Interesting results were found for the correction of misperceptions of the body in space for subacute patients [37,48], but no articles have confirmed these results relating to either long-term studies or for stroke patients at a chronic stage. Similarly, vestibular patients are of particular interest, as their asymmetrical behaviors could be at least partially due to body misorientation in space in acute disorders, as a result of imbalance of left and right vestibular inputs [8]. For unilateral vestibular patients, unilateral NMV induces a body tilt either in the antero-posterior plane or towards the lesional side, translating into the misinterpretation of vestibular information, which is not corrected [45,67]. In the case of bilateral vestibular or compensated vestibular lesion, no effect was found. Regrettably, the small number of studies, often of low quality and with small numbers of patients, does not enable us to firmly conclude to the interest of NMV.

There are several limitations to this review. Although this review yielded interesting results with an adequate level of evidence, some results need to be confirmed with better quality designs and larger population samples. These limitations open a new avenue for further studies, especially since this review has highlighted the small number of studies on the subject in relation to studies entailing comparisons of NMV with other muscles and also the very small number of studies on stroke and vestibular lesions. The findings require confirmation by way of better quality studies. Therefore, the effect of NMV on both postural orientation and spatial perception still remains a subject for research and for future studies.

Conclusion

The strength of this original review is that it highlights the specific characteristics of NMV for modulating both postural orientation and spatial perception in healthy subjects and patients, in that NMV induces body shifts and deviations in spatial perception. This review has provided some interesting results with an adequate level of evidence, but some results need to be confirmed with better-quality designs and larger populations. As a consequence, the effect of NMV on postural orientation and spatial perception remains a subject for further research studies with improved methodological quality.

Disclosure of interest

The authors declare that they have no competing interest.

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Chapter 3. The effects of neck muscle vibration on postural disturbances - Initial studies (*publication 4*)

Our working hypothesis was that proprioceptive stimulation by neck muscle vibration could reduce balance disorders associated with cognitive impairment after stroke using a high-level spatial process.

Thus, in a preliminary study, we performed one session of NMV on 31 patients who had a recent stroke (Leplaideur et al., 2016, Appendix 5). We reported that the session of NMV decreases the mediolateral (ML) deviation of the patient centre of pressure (CoP) position. This effect seemed to be higher in case of sensitivity deficit of the hemiparetic body and visual illusion toward the NMV contralateral side of the displacement of the environment during vibration. Additionally, the correction of the ML deviation of the CoP was modulated by the vision.

After these encouraging results, we investigated cumulative NMV sessions on the balance disabilities in chronic stroke patients. Results are presented in the following publication (Jamal et al., 2020b).



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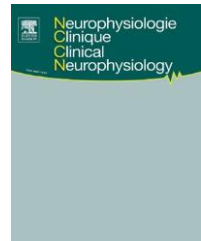
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ORIGINAL ARTICLE

The effects of repetitive neck-muscle vibration on postural disturbances after a chronic stroke

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KEYWORDS

Neck muscle vibration; Postural asymmetry; Spatial representation; Stroke

Abstract

Objective. — We aimed to test a repeated program of vibration sessions of the neck muscles (rNMV) on postural disturbances and spatial perception in patients with right (RBD) versus left (LBD) vascular brain damage.

Methods. — Thirty-two chronic stroke patients (mean age 60.9 ± 10 yrs and mean time since stroke 4.9 ± 4 yrs), 16 RBD and 16 LBD, underwent a program of 10 sessions of NMV over two weeks. Posturography parameters (weight-bearing asymmetry (WBA), X_m , Y_m , and surface), balance rating (Berg Balance Scale (BBS), Timed Up and Go (TUG)), space representation (subjective straight ahead (SSA), longitudinal body axis (LBA), subjective visual vertical (SVV)), and post-stroke deficiencies (motricity index, sensitivity, and spasticity) were tested and the data analyzed by ANOVA or a linear rank-based model, depending on whether the data were normally distributed, with lesion side and time factor (D-15, D0, D15, D21, D45).

Results. — The ANOVA revealed a significant interaction between lesion side and time for WBA ($P < 0.0001$) with a significant shift towards the paretic lower limb in the RBD patients only ($P = 0.0001$), whereas there was no effect in the LBD patients ($P = 0.98$). Neither group showed

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a significant modification of spatial representation. Nonetheless, there was a significant improvement in motricity ($P = 0.02$), TUG ($P = 0.0005$), and BBS ($P < 0.0001$) in both groups at the end of treatment and afterwards.

Conclusions. – rNMV appeared to correct WBA in RBD patients only. This suggests that rNMV could be effective in treating sustainable imbalance due to spatial cognition disorders.

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Introduction

One of the causes of disability in patients following a stroke is postural imbalance, characterized by increased postural sway and weight-bearing asymmetry (WBA) as evaluated on a force-platform [1–3]. WBA is recurrent and long-lasting, with a prevalence of 50% in chronic stroke patients [4], even higher in those with right brain damage [3,5]. WBA is often associated with level of independent self-care and length of hospital stay [6]. Thus, there is an interest in correcting WBA.

Apart from sensory and motor deficit [1,6,7], WBA may also be at least partially due to a bias in body orientation in space [8,9]. Spatial bias, such as neglect or biased subjective vertical (SV), subjective straight ahead (SSA) and longitudinal body axis (LBA) parameters, are common after stroke and related to poor balance [7,10–12]. These spatial biases are more frequent and longer lasting in RBD patients, probably because spatial cognition, in particular the central process of the representation of the body in space, is located within the right cerebral hemisphere [9,10,13,14]. This could explain why patients with right brain damage (RBD) have an excessive WBA compared to patients with left brain damage (LBD) and have poorer prognosis in terms of balance [3,5,10].

A previous study conducted by our group showed encouraging results after one session of neck muscle vibration (NMV) in patients with acute stroke [15]. Our hypothesis is that the stimulation of sensory information reduces WBA, probably through reduction of bias in orientation [8]. No study has yet examined a program of repeated vibration sessions on the neck muscles of chronic stroke patients.

The first objective of the study was to compare the effect of a program of repeated vibration sessions on the neck muscles on WBA in patients with RBD versus those with LBD. We hypothesized that repeated sensory stimulation would be effective in the treatment of imbalance due to body orientation bias and consequently lead to a greater reduction of WBA in RBD patients, due to the correction of body orientation disorders, which correspond at least partially to the WBA of these patients. We also studied the effect of the program on other spatial biases of our patients in order to better understand the mechanism of action of such stimulation.

Methods

Patients

Stroke patients were recruited from a list of patients who were treated in the Department of Physical Medicine and

Rehabilitation (PMR) at the University Hospital of Rennes. From March 2017 to February 2018, patients who fulfilled the inclusion criteria were contacted by telephone and those who immediately responded were included in the study. All patients received information concerning the protocol and gave their signed consent. The inclusion criteria were as follows: right or left brain supratentorial vascular damage, more than one year since the stroke, and age < 80 years. Chronic patients were considered, as they may show little or no evolution of their balance and may still have a postural imbalance dating from the time of their stroke. As WBA was the principal criteria, selected patients had to be able to maintain an upright position for at least 30 s with their eyes closed for the force-platform test. Previous studies [4] have defined the normal range of weight bearing as between 47 and 53%; patients who were within this range were considered to be symmetrical and were therefore excluded. Patients who had either an ischemic or hemorrhagic brainstem stroke, bilateral hemispheric stroke, an orthopedic and/or rheumatological history affecting the distribution center of pressure when standing, a visual history that did not allow assessment of their vision, and those with major comprehension disorders were also excluded. The sample size calculation was based on a result obtained during a program of repetitive prism adaptation, i.e. the percentage correction of WBA

+3.5% (1) in the chronic RBD group with initial WBA of 30.4% (10.6) [11]. The goal was to achieve the same benefit. We determined that subgroups of 16 patients would ensure 95% power, with an alpha risk of 5%. This study was approved by the local Ethics Committee of Rennes University Hospital, number 16.23, and registered (Clinicaltrial.gov NCT03112616).

Evaluations

Posturography parameters

Postural assessment of the patient was performed using a double force platform (FP) (PostureWin V143 TechnoConcept©). Patients stood on the platform in their bare feet with their feet 14 cm apart, with the instruction to stand as straight as possible with their arms alongside the body while looking straight ahead. The percentage of the weight on the nonparetic limb (WBA), mean mediolateral (X_m), and anterolateral (Y_m) position of the center of pressure (COP) (mm) and surface (mm²) were calculated as the mean of four trials, each lasting 30 s: two with opened eyes (OP) and two with closed eyes, with the patient wearing a blindfold (CE).

Evaluation of spatial representations

Subjective Straight Ahead (SSA) [16]. Evaluation of the SSA was carried out on a measuring table (Fig. 1). Patients were instructed to point “straight ahead”, so as to divide the space into two parts, with no imposed time limit in 10 starting positions in a randomized sequence with the right arm for RBD and the left arm for LBD patients. A positive sign corresponded to the ipsilesional side. The value (in degrees up to 0.5°) obtained consisted of the mean (M) and standard deviation of 10 measurements (SD).

Longitudinal Body Axis (LBA) [17]. Evaluation of the LBA was performed using a light strip in front of the patient in a supine position, in complete darkness, with the head, trunk, and lower limbs aligned and maintained by cushions (Fig. 2). The patient was given the task of indicating when the strip was parallel to the axis of his body. No visual reference other than the wand was available and there was no time limit. A

positive sign corresponded to the ipsilesional side. The value (in degrees up to 0.5°) obtained consisted of the M and SD of 10 measurements.

Subjective Visual Vertical (SVV). Evaluation of the SVV was performed in a sitting position with the head fixed, using a virtual reality helmet (Oculus®, Virtualis). From an imposed starting position, the patient was presented with a blue background with an oblique red line with

10 different starting positions in a random sequence ($10^\circ/5^\circ/15^\circ/10^\circ/30^\circ/5^\circ/20^\circ/15^\circ/30^\circ/20^\circ$). No visual reference, other than the red line, was available and there was no time limit. The patient was given the task of

indicating when the line was aligned with the vertical axis and the position of the head was monitored throughout the exercise task. A positive sign corresponded to the ipsilesional side. The value (in degrees up to 0.5°) consisted of the M and SD of 10 measurements.

Assessment of post-stroke deficiencies

A lower limb motricity test (motricity index) with a score of 100 [18]; a spasticity test (Ashworth modified MAS) [19], which targets the sural triceps, quadriceps, and adductors; and a sensory test, consisting of two clinical examinations and the sum of the obtained results were conducted. The first test consisted of tactile localization on the lower limb and the second, an arthrokinetic sensitivity test on the knee, ankle, and toes. Four tests of visuospatial neglect were also conducted: the bell cancellation test [20], 20-cm line bisection [20], the Fluff test [21], and the OTA test [22]. Visuospatial neglect was considered if the patient had at least three out of four positive tests. Finally, the presence or absence of homonymous hemianopia was clinically tested with a confrontation visual field test on each quadrant with a ball.

Balance Rating

Evaluation of functional impact of balance disorders was carried out using the Timed Up and Go (TUG) [23], and the Berg Balance Scale (BBS) [24].

Protocol

The intervention consisted of NMV in a dark room without a session per day, five days per week, for two weeks.

Evaluations were performed two weeks before the intervention (D-15), just before the first intervention (D0), at the end of the intervention (D15), one week later (D21), and one month later (D45) (Fig. 3). Vibration was carried out in a sitting position using a VB 115® vibrator (TechnoConcept, France) at a frequency of 80 Hz and an amplitude of 0.4 mm. The examiner manually positioned the vibrator on the left side of the neck muscle for RBD patients and on the right for patients with LBD. The position of the vibrator was individualized by looking first at the position in which the subject perceived a maximum deviation of a visual target placed in front of them and moving to the opposite side of the vibrated muscle side. If there was no deviation, the vibrator was placed under the occiput. In this position, vibration was applied above the semispinalis and splenius. Then the patient was blindfolded, and the intervention applied for 10 min. In addition to repetitive NMV (rNMV), all patients received their usual rehabilitation treatment.

Statistical analysis

Statistical analysis was performed using SAS 9.3 Software. The clinical data between the patients with RBD and LBD were compared using Student's t-test or the Mann-Whitney test (normality of the distribution was assessed using the Kolmogorov-Smirnov test). A comparison of the posturography parameters (WBA, X_m , Y_m , Surface) and Balance rating (TUG and BBS) at D-15 and D0 in both groups (RBD and LBD) was performed using a Student's t-test for paired data in order to verify the absence of evolution under their usual rehabilitation. Posturography parameters (WBA, X_m , Y_m , and surface), spatial reference data (SSA, LBA, and SVV), and characteristics of hemiplegia (motricity and sensitivity) were separately analyzed using ANOVA for repeated measures (rmANOVA) for normally distributed data and a generalized linear model with the gamma law or ranks for non-normally distributed data, with a between subjects factor, “lesion side” (RBD and LBD), and within subject factor, “time” (D0, D15, D21, D45). Tukey's post-hoc test was performed for all significant results. All tests were conducted at a significance level of $P = 0.05$.

Results

Forty-two patients from the list of chronic stroke patients followed by the physicians of the department were contacted by telephone, based on the inclusion criteria. All patients provided their approval, except two who refused to participate and one who died. After informing the patients and obtaining their consent, 39 were enrolled in the study. Five RBD patients and two LBD patients were excluded at D-15, as they did not show any signs of WBA on the force platform. Thirty-two patients, 26 men and six women, with an average age of 60.9 ± 10 years and an average time since their stroke of 4.9 ± 4 years, divided between two groups of 16 RBD and 16 LBD, were included (Fig. 4). Patients were similar in age ($P = 0.55$), time since stroke ($P = 0.7$), motricity ($P = 0.7$), sensitivity ($P = 0.1$) and balance ratings (BBS $P = 0.79$, TUG $P = 0.78$) (Table 1). WBA was different between the RBD and LBD patients (WBA RBD = $65.95\% \pm 9.4$ versus $60.6\% \pm 4.5$ LBD $P = 0.05$). There was no difference in any of

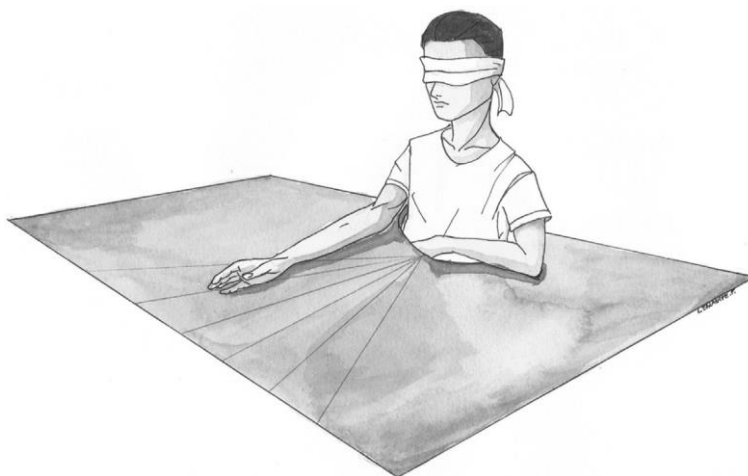


Figure 1 Experimental set-up of the Subjective Straight Ahead (SSA). Evaluation of the SSA was carried out on a measuring table on which the patient was required to move his hand while blindfolded. The table was graduated, and a one-degree angle corresponded to one linear cm. The midsagittal line coincided with the middle of the table with the head and trunk of the patient placed in strict alignment. From a starting position, with 10 starting positions, in a randomized sequence ($-10^{\circ}/5^{\circ}/-15^{\circ}/10^{\circ}/30^{\circ}/-5^{\circ}/-20^{\circ}/15^{\circ}/-30^{\circ}/20^{\circ}$) in which the arm of the patient was placed by the examiner, the patients were instructed to point “straight ahead”.

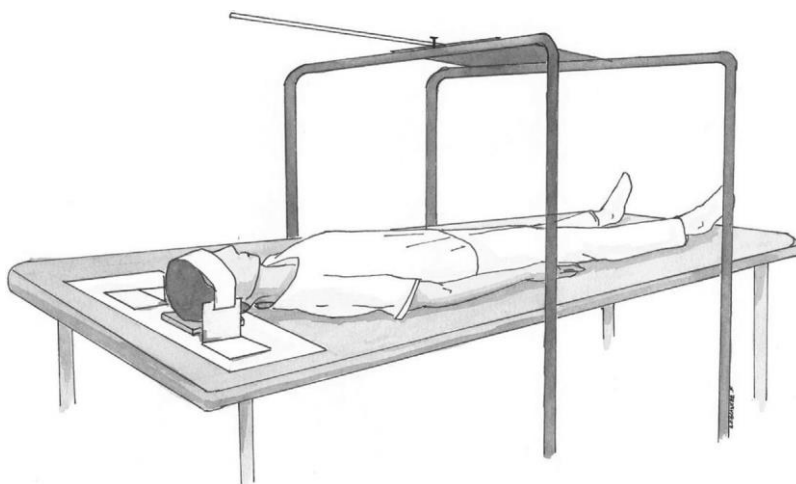


Figure 2 Experimental set-up of the Longitudinal Body Axis (LBA). Evaluation of the LBA was performed using a light strip in front of the patient in a supine position, in complete darkness, with the head, trunk, and lower limbs aligned and maintained by cushions. The rotation center of the light wand was aligned with the patient’s navel and the plumb line. The light wand was moved around its axis of rotation by the examiner from a starting position, with 10 starting positions, in a randomized sequence ($-10^{\circ}/5^{\circ}/-15^{\circ}/10^{\circ}/30^{\circ}/-5^{\circ}/-20^{\circ}/15^{\circ}/-30^{\circ}/20^{\circ}$). The patient was given the task of indicating when the strip was parallel to the axis of his body.

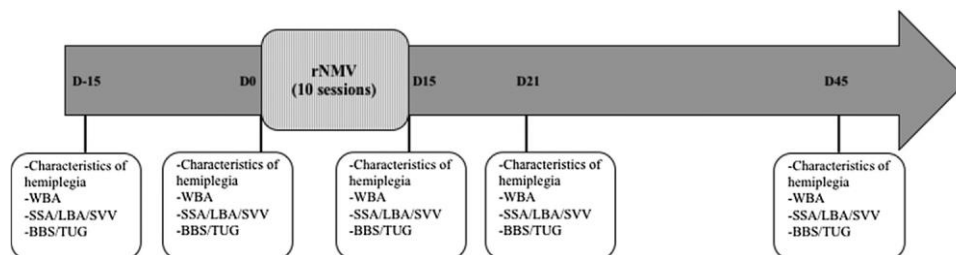


Figure 3 Protocol with evaluation time and neck muscle vibration intervention. (Berg Balance Scale (BBS), Longitudinal Body Axis (LBA), Repetitive Neck Muscle Vibration (rNMV), Subjective Straight Ahead (SSA), Subjective Visual Vertical (SVV), Timed Up and Go (TUG), Weight Bearing Asymmetry (WBA)).

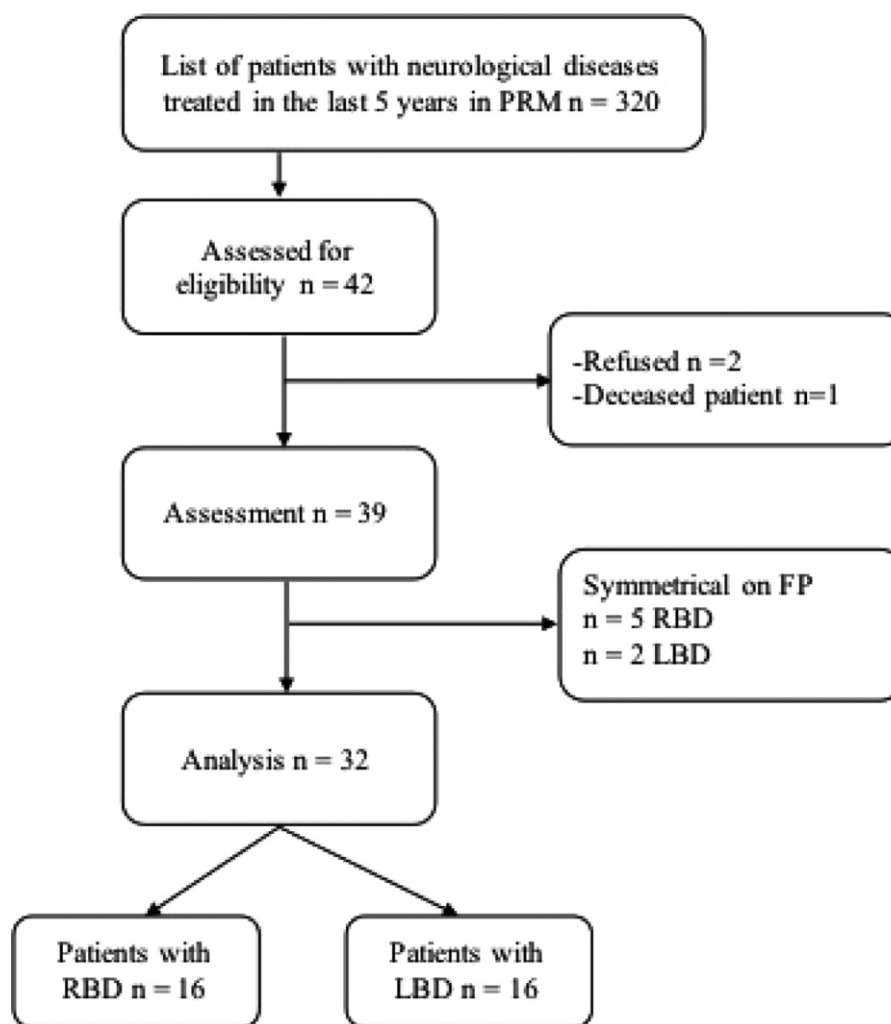


Figure 4 Flowchart of participants (RBD: right brain damage; LBD: left brain damage; FP: Force Platform).

Table 1 Clinical data, patients with right brain damage (RBD) and patients with left brain damage (LBD).

	RBD (n = 16)	LBD (n = 16)	P
Male/Female	14/2	12/4	—
Ischemic/hemorrhagic	9/7	12/4	—
Age (years)	62.1 (11.3)	59.8 (10.2)	0.55
Delay-post (years)	5.27 (4)	4.71 (4)	0.7
Motricity (/100)	69 (16)	71 (17)	0.77
Sensitivity (/6)	4 (1)	5 (1)	0.15
Visuo-spatial neglect	11/16	0/16	—
Hemianopia	0/16	0/16	—
WBA (%)	65.95 (9.4)	60.6 (4.5)	0.05
LBA M (°)	-0.81	-0.54	0.1
LBA SD (°)	2.73	1.76	0.01
SSA M (°)	-1.1	1.54	0.1
SSA SD (°)	2.59	3.27	0.1
SVV M (°)	0.94	0.57	0.5
SVV SD (°)	3.21	2.26	0.0005
TUG (s)	26 (17)	24 (18)	0.78
BBS (/56)	43 (8)	42 (11)	0.79

BBS: Berg Balance Scale; LBA: Longitudinal Body Axis; SSA: Subjective Straight Ahead; SVV: Subjective Visual Vertical; TUG: Timed UpAnd Go; WBA: Weight Bearing Asymmetry.

the posturography parameters (WBA, Xm, Ym, Surface) and Balance rating (TUG and BBS) between D-15 and D0 showing the absence of evolution (WBA RBD $P = 0.38$; LBD $P = 0.09$; Xm RBD $P = 0.6$; LBD $P = 0.4$; Ym RBD $P = 0.6$; LBD $P = 0.9$; surface RBD $P = 0.8$; LBD $P = 0.5$; TUG RBD $P = 0.9$; LBD $P = 0.8$; BBS RBD $P = 1$; LBD $P = 0.1$).

The rmANOVA revealed a significant interaction between lesion side and time for WBA ($F[4;120] = 5.25$, $P < 0.0001$) with a reduction of WBA only in the RBD patients and only at D15 (4.4% 3.5), confirmed by the post-hoc test (D0 vs D15 $P = 0.0001$ and D0 vs D21 $P = 0.43$). The results were similar when accounting for Xm (lesion side \times time $F[4;120] = 12.45$; $P < 0.0001$), with a significant shift in the RBD group (D0 vs D15 $P < 0.0001$). The rmANOVA revealed no effect or interaction between lesion side and time for Ym ($F[4;120] = 0.51$; $P = 0.72$) and the Surface ($F[4;120] = 0.42$; $P = 0.79$) (Table 2). Difference between the mean for RBD and LBD patients were found only between the standard deviation for SVV SD $P = 0.005$ and LBA SD $P = 0.01$ (Table 1). The rmANOVA revealed no effect or interaction between lesion side and time (SSA $F[4;120] = 1.46$; $P = 0.21$; SVV $F[4;120] = 1.83$; $P = 0.09$; LBA $F[4;120] = 0.93$; $P = 0.44$) (Table 2).

Vibration did not induce any change in sensitivity test values over time ($F[4;120] = 2.25$; $P = 0.07$) or by group ($F[1;30] = 1.67$; $P = 0.2$). Motricity improved for both groups of patients over time ($F[4;120] = 3.25$; $P = 0.02$), independently of lesion side ($F[1;30] = 0.02$; $P = 0.89$). The post-hoc test revealed an improvement at D15 ($P = 0.02$) and D21 ($P = 0.02$). The TUG of the patients improved at D21 ($F[4;120] = 6.9$; $P = 0.0005$) ($P = 0.003$) and D45

($P = 0.01$), independently of the lesion side ($F[1;30] = 0.17$; $P = 0.68$). The BBS of the patients also improved over time ($F[4;120] = 9.23$; $P < 0.0001$), as revealed by the post-hoc test at D15 ($P < 0.0001$), D21 ($P < 0.0001$), and D45 ($P < 0.0001$), independently of lesion side ($F[1;30] = 0.11$; $P = 0.74$) (Table 3).

Discussion

We obtained a reduction in WBA after NMV as expected. This effect was only observed in the group of RBD patients. Surprisingly, balance ratings and motricity improved for patients of both groups (RBD and LBD) after the program, with a long-lasting effect.

WBA was higher in RBD patients before rNMV, even though the same time had elapsed since the stroke for both patients with RBD and LBD [3,5,10]. This disparity, repeatedly found in the literature, has been assumed to be due to body mis-orientation in space, which occurs mostly in RBD patients [8,9]. Following rNMV, the degree of WBA of RBD patients moved closer to that of the LBD patients before the program (Fig. 5). RBD patients shifted in the medio-lateral plane towards the hemiplegic leg without any change in the antero-posterior plane, whereas there was no significant effect on the posturography parameters for LBD patients. These results strongly suggest that the effect of NMV on RBD patients may be due to correction of the component of the WBA that is due to spatial cognition disorders. Indeed, the right hemisphere is thought to be responsible for spatial cognition [9,14]. Additionally, stimulation of sensory information, i.e. prism adaptation, vestibular

caloric stimulation, or galvanic vestibular stimulation, modifies the postural asymmetry of the subject, irrespective of the sensorial modality [11,15,25], with a close relationship between the effects of different sensory modalities [25]. This suggests that sensory stimulation affects supramodal sensorial cerebral structures in the right hemisphere [8], as already shown by Bottini et al. [26], who studied the effects of proprioceptive sensory stimulation by vibration on regional cerebral blood flow, measured using positron emission tomography.

Neck muscles are directly linked to the vestibular and oculomotor systems and may play a crucial role in egocentric perception of the body in space [27]. The information obtained from proprioceptive receptors of the neck muscles, together with that of the oculomotor muscles and vestibular system, is involved in the location of objects relative to the body. NMV produces a subjective perception of deviations of the axis of the body [28], suggesting that NMV could act on the relative position of the body in space and consequently displace the position of CoP towards the paretic limb. We would thus expect a change in both aspects of egocentric spatial representation, i.e. SSA and LBA. However, our chronic post-stroke patients had normal spatial bias deviation with the exception of a greater uncertainty in the perception of SVV and LBA. We also observed no significant change for either SSA or LBA. A slight change in SSA could be viewed as a mirror image of the change in WBA (Fig. 6). Our results differ from those of two previous studies [11,28]. The first reported an SSA shift towards the vibrated side during NMV [28] and a pilot study established an association between both the shift in SSA and WBA with another form of sensorial stimulation (prism adaptation) [11]. However, our study did not initially focus on SSA and our calculation of the number of patients to be included was based on WBA and not the assessment of spatial representation. Another possible explanation for the absence of the effect of NMV on spatial representation could be related to the cortical dissociation between the different evaluations already mentioned in the literature [14,29,30] and particularly when considering the posture and the modality assessed. Indeed, Pérennou et al. [31], when investigating the perception of verticality by different modality in a group of patients with hemispheric and brain stem stroke, did find a dissociation between postural verticality (PV) and SVV and this was possibly due to different brain regions involved in this spatial process. Therefore, it could be of interest when investigating the perception of verticality to assess the PV in addition to the SVV in further studies.

The reduction of WBA was obtained without decreasing postural stability, as shown by the stability of the surface of the displacement of the CoP, which is a platform parameter that expresses bodily stability. This is an additional argument that suggests that the part of WBA corrected by rNMV is not a compensatory behavior to postural instability, but rather due to a primary disorder, in this case, a spatial cognition disorder. Therefore, WBA can be considered not only as an adaptation to postural disturbance due to motor and sensitivity weakness, but also the reflection of a disturbance in spatial cognition, at least in RBD patients [1,32]. As a result, it may be beneficial to correct at least this aspect of WBA. This result merits exploration of the possibility of obtaining an effect at an early stage after stroke. NMV is

Table 2 Mean and Standard deviation of posturography parameters and spatial representation after rNMV.

	D0	D15	D21	D45
Posturography parameters				
RBD				
% on none-paretic limb	65.1 (9)	60.7 (9) ^a	63.4 (10)	63 (8)
Xm (mm)	38.6 (23)	26.1 (24) ^a	33.6 (25)	32.9 (22)
Ym (mm)	35.5 (21)	35.5 (18)	35.8 (21)	39.4 (21)
Surface (mm ²)	320 (228)	358 (199)	322 (147)	308 (176)
LBD				
% on none-paretic limb	59.4 (5)	58.9 (5)	57.9 (5)	58 (6)
Xm (mm)	-21 (12)	-20.5 (15)	-19.2 (15)	-18 (18)
Ym (mm)	34.6 (9)	38.4 (9)	36.8 (10)	37.5 (8)
Surface (mm ²)				
Spatial representation				
RBD				
LBA (°)	-1 (2)	-1.1 (2.7)	-1.2 (1.3)	-0.5 (2.1)
SSA (°)	0.1 (3.8)	-1.4 (4.4)	-1.4 (3.9)	-0.2 (3.1)
LBD				
LBA (°)	-0.5 (2.6)	-0.1 (1.9)	-0.1 (2)	-0.7 (1.9)
SSA (°)	0.9 (3.6)	1.3 (3.9)	0.8 (3.4)	0.1 (2.4)

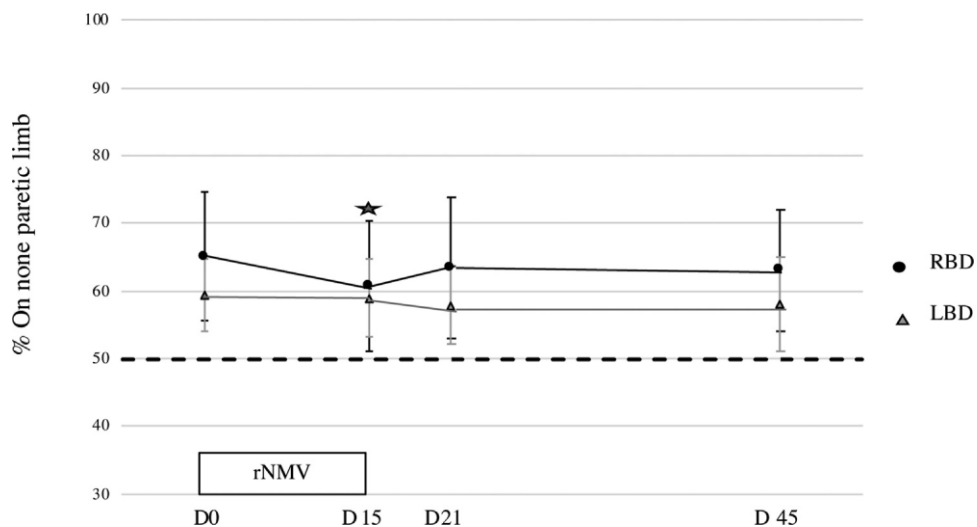
LBA: Longitudinal body axis; LBD: Left brain damage; RBD: Right brain damage; SSA: Subjective straight ahead; SVV: Subjective visualvertical.

^a Significant effect.

Table 3 Mean and Standard deviation of the assessment of post-stroke deficiencies; sensory testing, motricity index, TUG andBBS of patients with left and right brain damage.

	D0	D15	D21	D45
Severity of hemiplegia				
Motricity Index (/100)	70.1 (16)	73 (18) ^a	73.6 (17) ^a	73 (17)
Sensitivity (/6)	4.7 (1)	5 (1.7)	4.9 (1.5)	4.8 (1.6)
Balance rate				
Berg Balance Scale (/56)	43 (10)	44.4 (10) ^a	44.5 (10) ^a	44.6 (10) ^a
Timed up and Go (s)	24.4 (16)	23.3 (16)	23.1 (16) ^a	23.6 (17) ^a

^a Significant effect.

**Figure 5** Evolution of Weight Bearing Asymmetry (WBA) of patients with Right brain damage (RBD) and patients with Left brain damage (LBD) Repetitive neck muscle vibration (rNMV). (★) significant effect.

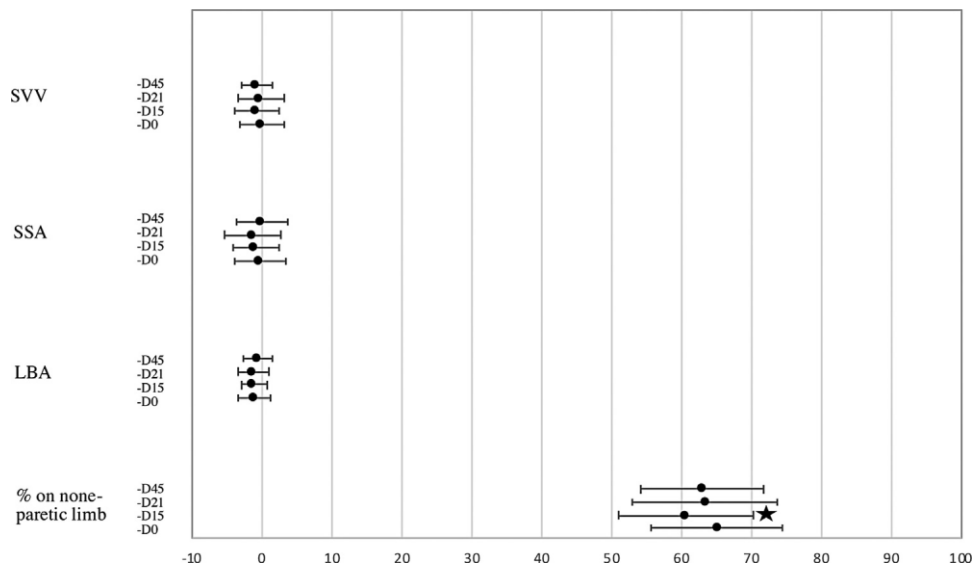


Figure 6 Evolution of both weight-bearing asymmetry (WBA) and spatial representation assessment. Longitudinal body axis (LBA), Subjective straight ahead (SSA), Subjective visual vertical (SVV) in Right brain damage patients. (★) significant effect.

a clinical technique that does not require active participation of the patients, unlike top-down techniques, and is easy to implement and inexpensive. This creates new treatment possibilities early after stroke, when spatial cognition disorders are very troublesome, especially in RBD patients, with the hope to more rapidly improve balance in these patients. The effect induced by rNMV was evident at the end of the program but was not maintained one week later. In this regard, our program may have been insufficient in terms of intensity, duration or number of sessions. Indeed, Karnath et al. [33] showed that increasing the vibration time resulted in a more stable effect with regards to SSA. It will therefore be necessary in future work to further investigate this sustained effect by increasing the intensity and duration of stimulation. It was also revealed that sensorial stimulation such as neck muscle vibration combined with another stimulation [34] or standard rehabilitation exercises [35] is more effective than a sensorial stimulation on its own and this could possibly be another additional investigation in order to enhance the effect.

Surprisingly, rNMV improved lower-limb strength and dynamic balance (TUG and BBS) in both LBD and RBD patient groups. This unexpected outcome suggests that there may be other mechanisms simultaneously at work aside from the effects on body orientation observed in the RBD patients. However, its direct influence is not evident. It has been hypothesized that there is a close interconnection between the sensory and motor cortices, initially recognized in animals [36]. Fasold et al. [37], by functional MRI, showed that NMV stimulated cerebral activity in both motor and multisensory integration areas in healthy subjects. It is therefore possible that sensory stimulation by NMV can improve motor recovery. The improved motor control in both RBD and LBD patients following rNMV may involve central activation of the motor areas. However, the observed improvement favors the hypothesis of an effect remote from the stimulation site. It is therefore important to determine the mechanism of NMV and compare it to another

type of sensory stimulation, such as transcutaneous electrical stimulation (TNS), to gain a better understanding of its effects. Similar to NMV, TNS equally improves both lower-limb strength and postural balance [38]. Moreover, TNS may modulate the sensory-motor cortex, which is stimulated [39]. In addition, Pérennou et al. [40] reported an improvement in postural balance in stroke patients with neglect when TNS was applied to the neck muscles. Nonetheless, no study has been carried out to assess lower limb strength after TNS of neck muscles. The results of these authors [40] are in accordance with ours and support the interest of stimulating the neck muscles. Neck muscles have a specific role in postural control through their direct link with the vestibular system and could also act on tonus regulation of lower limbs.

Our study had several methodological limitations. Our primary choice was to exclusively include chronic patients. Caution was taken to ensure that there was no modification of WBA or spatial representation during a period of 15 days before the intervention to avoid a confounding bias. In this study, the effect of neck muscle vibration was compared in patients with RBD versus those with LBD without any sham group. Therefore, this design does not allow us to be certain of the real effect of NMV and should as a consequence be repeated with a sham control group in order to confirm our result. Concerning our selection criteria, patients were recruited based on their ability to maintain an upright position for at least 30 seconds with their eyes closed, to allow performance of the force-platform test. As a consequence, the generalizability of our results is limited to patients who are not severely disabled and further studies need to be undertaken with more patients who are at an acute stage and with more marked spatial cognition disorders.

Conclusion

In conclusion, repeated NMV may be effective in treating postural disorders caused by spatial cognition disorders. There was a non-significant trend towards maintaining the positive effect longer term. A possible reason for lack of significant long-term effect in our study is that the stimulation

may have been insufficient, either in its intensity or duration. This also raises the issue of whether such stimulations should be started at an early stage of stroke. Further studies are necessary to investigate other NMV protocols and the effect of duration. Our second result was an improvement in lower limb strength, as well as the dynamic balance (TUG and BBS) in both LBD and RBD patient groups. This result suggests an effect remote from the stimulation site, highlighting the relevance of vibrating the neck muscles in the course of stroke rehabilitation.

Disclosure of interest

The authors declare that they have no competing interest.

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KEYPOINTS – THE BASES OF NECK MUSCLE VIBRATIONS

Sensorial stimulation are a promising approach to improve balance disorders after stroke. Indeed, they could have a high-level effect inducing an egocentric referential frame recalibration.

NMV induce an illusion of muscle stretching. It is a potent proprioceptive stimulus The literature reported brain activations in areas related to multisensory integration (insula, Parietal operculum, superior temporal gyrus) and somatosensory areas .

These preliminary studies on effect of NMV on WBA after stroke were promising. A larger RCT was necessary to confirm these results.

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Part 3. A randomized control trial protocol combining neck muscle vibration and prism adaptation on postural recovery after a right stroke

CHAPTER 1. Presentation of the experimental research – the randomized control trial Protocol AVCPOSTIM

What are experimental processes used to investigate the clinical effect of NMV on balance disorders after a stroke?

CHAPTER 2. Results of this multicenter study combining PA and NMV on postural recovery after stroke (*Publication 5*)

Chapter 1. Experimental research – Randomized control trial Protocol AVCPOSTIM

As previously described, stroke induces postural asymmetry and postural instability, impairing patient recovery. These balance disabilities can be related to motor or sensitivity weakness, but also spatial cognition. This cause of balance disability have been less studied than motricity or spasticity and thus less targeted in balance rehabilitation programs, impacting balance abilities and functional prognosis. As discussed in the previous chapter, sensory stimulations are promising therapeutics. However, further explorations are required to improve knowledge about the influence of spatial cognition and evaluate the effect of sensory stimulation on balance disabilities in case of stroke. Thus, we performed a multicenter research protocol to study the impact of NMV and PA, separately and in combination, on WBA after a right stroke. To provide clues for a complete understanding of the study, complement chapter 2 dedicated to NMV and the paper submitted presenting the study results; I will present below the PA, the second sensory stimulation evaluated in this study and could not be presented in detail in the paper. I will also explain the support briefly to combine NMV to PA.

PA has been extensively studied on USN (Saevarsson et al., 2010; Guinet and Michel, 2013; Petit et al., 2018; Rossetti et al., 2019; Li et al., 2021). Benefits on neglect rehabilitation were demonstrated (Luaute et al., 2006; Michel, 2016; Li et al., 2021). However, the transposition of this improvement on daily living abilities was not proved (Longley et al., 2021).

Typically, during PA sessions, the patient sits at a table, the chin placed on a support, not looking at his/her arm. PA is carried out using glasses with a 10° right optical deviation of the visual field. During the session, the instruction is to point 50 times with the right hand on spots alternatively located to the left or the right side in front of him/her. The mechanism of action of PA includes two steps. The short-term effect consists of a visuomotor shift that reflects a rapid adjustment at the level of the visuomotor loop. This visuomotor shift is followed by a slower effect: the spatial recalibration consisting of a spatial realignment of the egocentric referential of the patient to the visuomotor shift (Petit et al., 2018). Previous studies have shown that the entire PA effect is present after one session, and cumulative sessions have a long-lasting impact on visuospatial bias (Jacquin-Courtois et al., 2013). Concerning the

postural bias, some pioneering studies, studying the effect of PA in patients who had a chronic stroke, yet in a limited number of patients, showed an improvement of sitting or standing asymmetry in the short term (Tilikete et al., 2001; Nijboer T.C.W. et al., 2014; Hugues et al., 2015).

Several functional imaging studies supported the assumption of a high-level effect of PA (Luaute et al., 2009; Chapman et al., 2010; Bédard and Sanes, 2014; Küper et al., 2014; Michel, 2016; Schintu et al., 2020). Using an event-related task design, Luaute et al. report activations successively in the anterior intraparietal sulcus, detecting the error's deviation, parieto occipital sulcus to correct for this error and cerebellum activities for spatial realignment (Luaute et al., 2009). Saj et al. detected an activity enhancement in bilateral parietal, frontal and occipital cortex during visuospatial tasks just after PA. Studying stroke patients, they found variations in activated areas depending on the lesion location.

Within the context of balance bias, we questioned the effect of sensory stimulations combination. Indeed, Karnath et al. tested the association of two sensory stimulations on spatial tasks (figure 1): the impact of proprioceptive (NMV) and vestibular (caloric stimulation) stimulations on SSA in 17 healthy subjects. They found addition of the deviation obtained by each stimulation, i.e. an increased left SSA deviation when using left caloric and left NMV stimulation together (Karnath, 1994).

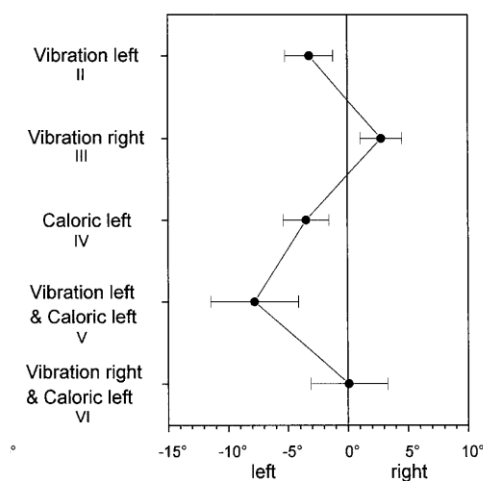


Figure 1 – From Karnath HO. Subjective body orientation in neglect and the interactive contribution of neck muscle proprioception and vestibular stimulation. *Brain*. 1994;117 (Pt 5):1001–1012. This figure presented the SSA deviation (in degree) in the nine subjects who reported an illusion of motion during left and right stimulations.

Later, Saevarsson et al., in 2010, carried out a study on 12 patients who had chronic neglect. They investigated the effect of a combining program with NMV and PA versus sessions of PA alone and NMV alone. The combination of NMV and PA improved the neglect symptoms better than NMV or PA applied on their own, concerning visual search and pencil neglects tests (Saevarsson et al., 2010). In light of these studies, we hypothesized that the combined NMV+PA program could have a cumulative effect on balance disability related to spatial cognition disorders following a right hemispheric stroke.

In this study, we used body weight asymmetry (BWA) as a marker of balance disability related to spatial cognition disorders. We, therefore, selected right lesioned patients with increased WBA and evaluated the effect of the sensory stimulations on the improvement of the postural asymmetry in standing position. We additionally assessed the SSA and SLB as other markers of spatial cognition.

Thus, the main objective of the AVCPOSTIM RCT study was to investigate the effect of NMV and PA separately or in combination with PA on the WBA in stroke patients. The second objective was to understand better the mechanisms involved in spatial cognition and sensory stimulations using neuroimaging.

The clinical results are presented in chapter 2 as an article in submission.

Chapter 2. Clinical results – Randomized control trial Protocol AVCPOSTIM (*publication 5*)

Combining prism adaptation and neck vibration for postural recovery after stroke: a multicenter randomized study

Authors

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in submission

ABSTRACT

Background and Objectives

The purpose of this multicenter randomized, controlled, single-blind trial was to investigate the cumulative effects of prism adaptation (PA), neck muscle vibration (NMV), and PA+NMV sessions on postural asymmetry after a recent right-hemisphere stroke. We hypothesized that the combination of PA and NMV would have a synergistic effect.

Methods

Patients attending eight rehabilitation centers were screened within 9 months of their first right-hemisphere supratentorial stroke. They were included if their paretic limb supported less than 40% of their body weight. Patients were randomized into four groups: sham intervention, PA, NMV, and NMV+PA, and underwent 10 sessions over 2 weeks. The primary outcome was the mean deviation of the center of pressure on the mediolateral axis (ML), evaluated on a force platform at the end of the intervention (Day 14). Secondary outcomes included changes in ML immediately after the first session, and at Days 90 and 180.

Results

Eighty-nine patients were randomly allocated to one of four groups : sham ($n = 22$), PA ($n = 23$), NMV ($n = 22$), or NMV+PA ($n = 22$). For our primary outcome at Day 14, we did not observe any differences in ML change between the groups. Secondary analyses revealed 1) immediately after the first session, a higher short-term reduction in ML in the eyes-open condition for the NMV group, compared with the sham group (median difference: ML = -8.3 mm vs. 0.5 mm, IQR = 27, effect size (Cohen's d) = 0.56, $p = 0.04$), 2) in the longer term (Days 90 and 180), a smaller reduction in ML for the NMV and PA+NMV groups, compared with the sham and PA groups (Day 90: $p = 0.013$; Day 180: $p = 0.002$).

Discussion

The present study produced Class II evidence of a lack of a beneficial effect of repetitive unimodal or combined sessions of NMV and PA on postural asymmetry after stroke. For future studies, we suggest selecting patients earlier after stroke, and more specifically those with spatial cognition disorders, and adding dynamic tasks to the sensory stimulation.

INTRODUCTION

Balance disorders after stroke are a negative factor for autonomy, recovery of transferring, and walking recovery, adding to the repercussions of stroke from both personal and socioeconomic perspectives ¹. Additionally to motor weakness, sensory disorders and spasticity, the distortion of spatial perception contributes to an excessive postural bias toward the side of the lesion, resulting in a weight-bearing asymmetry (WBA) ²⁻⁴. Indeed, WBA prevails after a right-hemisphere stroke, probably because the lesion can impair the brain regions that are primarily involved in spatial cognition processing ^{5,6}. Even though this is a crucial issue, no treatments that explicitly address the cognitive component of imbalance are currently implemented. Sensory stimulation is one potential treatment, as it is believed to reduce the distortion of internal representations of the body in space ². It was initially tested on visuospatial neglect ⁷, with a focus on combinations of techniques ⁸. Given that the brain mechanisms leading to biases in neglect and postural impairment are very similar, sensory stimulation may also have a positive effect on balance disorders related to spatial cognition impairment ^{2,9}. Prism adaptation (PA) and neck muscle vibration (NMV) are viewed as possible options, as their bottom-up action requires minimal participation from patients, allowing them to be used early after stroke.

The present multicenter randomized controlled trial investigated the cumulative effect of sessions of PA, NMV, or a combination of the two on postural asymmetry in patients after right-hemisphere stroke. We hypothesized that the combination of PA and NMV has a synergistic effect.

METHODS

Participants

In eight rehabilitation centers, all consecutive patients aged between 18 and 80 years and who attended within 9 months of a first right supratentorial ischemic or hemorrhagic stroke were screened between 2013 and 2018. The first eligibility criterion was hemiplegia, where the patients' paretic limb supported less than 40% of their body weight, as measured on a force platform ¹⁰ as soon as they could stand alone. CT or MR scans confirmed the vascular lesion. As WBA was the primary outcome, selected patients also had to be capable of remaining upright for 30 seconds with their eyes closed. The exclusion criteria were any disorder that might have affected balance before the stroke (i.e., medical history of neurological,

orthopedic, rheumatological or vestibular disorder), and a visual issue or behavioral impairment that might hamper assessment.

Trial design

The AVCPOSTIM study was a multicenter, randomized, controlled, single-blind study. Center eligibility depended on the number of stroke patients managed each year and the team's ability to carry out recruitment. The coordinating center trained the care providers during implementation visits. Data were collected via an electronic case report form. Monitoring visits were regularly conducted.

Patients were assigned to one of four groups (sham, PA, NMV, NMV+PA) in order of randomization number, using a centralized randomization method implemented in Ennov Clinical® software (Groupe Ennov, Paris, France). The randomization list was stratified by center. A computer program generated blocks of varying sizes. The order of block sizes and the order of rehabilitation techniques in each block were randomly generated. Outcome assessors and investigators were blind to the intervention group. Stimulation sessions were carried out with distinct therapists. No change in rehabilitation programs was introduced once the trial had started.

Standard Protocol Approvals, Registrations, Patient Consents

The Institutional Review Board of Poitiers-France III West No. 05/12/16 approved the study (ClinicalTrials.gov identifier NCT01677091). All the patients gave their written informed consent before enrolment.

Interventions

Patients performed 10 sessions of their assigned intervention over 2 weeks. The intervention consisted of one stimulation session (unimodal or bimodal) per day, 5 days a week, in a dedicated experimental room. The care provider reported the course of each session (i.e., achievement according to protocol and tolerance). All patients continued to receive their usual rehabilitation treatment, excluding posturography exercises.

During PA sessions, patients sat at a table, with their chin placed on a chinrest, and did not look at their arm. PA was carried out using glasses (Optique Peter®, Lentilly, France) with a 10° right optical deviation of the visual field. During each session, patients were instructed to point 50 times with the right hand to dots alternately displayed on the left or right side in front of them. PA has been shown in many clinical studies to reduce neglect¹¹⁻¹⁴. It acts in two steps. Its short-term effect consists of a visuomotor shift that reflects a rapid adjustment at

the level of the visuomotor loop. This visuomotor shift is followed by a longer-term effect, namely spatial recalibration, which consists of a spatial realignment of the patient's egocentric reference frame with the visuomotor shift¹⁵. The effect of PA on visuospatial bias after one session and after cumulative sessions is long-lasting¹⁶. Concerning postural bias, some pioneering studies in a limited number of patients or with chronic stroke have reported an improvement in standing asymmetry in the short term¹⁷⁻¹⁹.

NMV was carried out in a sitting position using a VB 115[®] vibrator (TechnoConcept, Manosque, France) with a frequency of 80 Hz and an amplitude of 0.4 mm²⁰. The therapist manually positioned the vibrator on the left side of the neck muscle (i.e., contralesional side), where patients perceived a maximum illusion of a right deviation of a light point in front of them. If patients did not describe this illusion of deviation, the vibrator was placed under the occiput (between the semispinalis and splenius muscles). Patients were then blindfolded and the vibration was applied for 10 minutes. During stimulation, patients did not perform any specific activities. They were authorized to converse with the therapist. NMV is believed to work by sending a proprioceptive signal of neck muscle stretching to the central nervous system, thereby inducing an illusion of trunk displacement relative to the head in the direction of the vibrated side. As a consequence, the body's reference system is shifted toward the vibrated side (here, to the left). This theory was supported by the results of previous studies where NMV induced a shift in the egocentric reference frame, as demonstrated by the deviation of the subjective straight-ahead position^{21,22}. NMV has been shown to be efficient in reducing neglect symptoms^{20,23}. Furthermore, when tested on balance after either a single session following a recent stroke or cumulative sessions in the case of chronic stroke, results suggest that it has a positive effect on balance disorders^{24,25}.

In the NMV+PA group, patients practiced NMV first, followed by PA. The sham group performed a pointing sequence, as did the PA group, but without any sensory manipulation.

Outcomes

Evaluations were performed at five timepoints: before stimulation (baseline; Day 0), just after the first session (short-term effect), at the end of the intervention (Day 14), and 3 months (Day 90) and 6 months (Day 180) after the end of the intervention.

The postural assessment used a double force platform (PostureWin V143TechnoConcept© Manosque, France), with feet placed parallel, 14 cm apart. Participants were instructed to remain in as stable a standing position as possible, with their arms alongside their body. We

recorded the WBA (in %), the mean mediolateral deviation (ML, in mm) and mean anteroposterior deviation (AP, in mm) of the center of pressure (CoP), and the standard deviation of the CoP displacement (sway; in mm²). Results were reported as the mean of two 30-s trials with eyes open and then eyes closed.

For the clinical balance assessment, we administered the Postural Assessment Scale for Stroke (/36)²⁶, the Scale for Contraversive Pushing (/6)²⁷, the Berg Balance Scale (/56)²⁸, and Timed Up and Go (in s)²⁹. Post-stroke disabilities were assessed with Motricity Index for lower extremities (/100)³⁰, and the Modified Ashworth Scale³¹ on the sural triceps, quadriceps, and adductors. A test of epicritic and arthrokinetic sensitivity was administered. Patients scored 0 if they had no sensitivity, 1 if sensitivity was present but weak, and 2 if they had normal sensitivity. The Barthel Index (/100)³² evaluated functional abilities.

Five tests assessed visuospatial neglect: the Bells Test³³, Horizontal Line Bisection Test³⁴, the Fluff Test³⁵, the Ota Test³⁶, and the Catherine Bergego Scale³⁷.

Patients performed two body-centered spatial cognition tasks: Subjective Straight Ahead (SSA), and Subjective Longitudinal Body Plane (SLB). For the SSA, patients were blindfolded and seated in front of a measuring table. They were required to point straight ahead and divide the space in front of them into two parts³⁸. SLB was assessed using a light strip in front of the patient lying in supine position, in complete darkness, with the head, trunk, and lower limbs aligned³⁹. The light strip's center of rotation was aligned with the patient's navel. Patients had to indicate when the strip crossed the axis of their body (i.e., line passing through the midpoint between their shoulders and the midpoint between their ankles).

The primary outcome measure was a change in ML (eyes closed) after the interventions (Day 14). This measurement is assumed to partly reflect a balance disorder related to cognition impairment, especially in right-hemisphere stroke patients. Other assessment timepoints and other platform data (eyes open data, AP, and sway), clinical balance assessments, post-stroke disabilities, and visuospatial assessments were secondary outcomes.

Brain imaging

All patients underwent an MRI scan (or a CT scan in the case of an MR contraindication) at least 2 months after the stroke. All scans were centralized using the Shanoir server⁴⁰ as a prerequisite for lesion delineation and thence for stroke location and extent analysis. A trained medical doctor performed lesion delineation using ITK-SNAP⁴¹, supervised by an expert neuroradiologist. The following processing was then performed: coregistration of FLAIR

images on T1-weighted images, lesion reslicing on the other images, image normalization in Montreal Neurological Institute (MNI) space. Finally, lesion maps were overlaid on a T1 template and visualized using MRICroGL (<https://www.mccauslandcenter.sc.edu/mricrogl/>).

DATA and STATISTICAL ANALYSIS

Sample size

Based on previous studies, we expected to observe an improvement of 50% in the spontaneous ML of 27 mm (+/- 16 mm), corresponding to 13.5mm¹⁷. We thus determined that groups of 30 patients would ensure 90% power, with an alpha risk of 5%.

Statistical analysis

The statistical analysis was performed using SAS statistical software V9.4 (SAS Institute, Cary, NC) and R version 3.6.3 for visualization. Follow-up timepoints were the same for all participants. Patients lost to follow-up were included in the analysis in intention to treat.

The descriptive data at inclusion and confounders were compared using a one-factor analysis of variance (ANOVA) for quantitative values and a chi² test for qualitative data.

The primary outcome (ML at Day 14) was analyzed using an ANOVA with a two by two factorial design (PA effect , NMV effect).

For secondary outcomes, additional analyses were conducted for each of the other timepoints (short term, Day 90, and Day 180) and each of the two assessment conditions (change in baseline ML, eyes open and eyes closed). For this purpose, we fitted a linear model with the factor group (sham, NMV, PA, and NMV+PA) without correction, because of the absence of multiple comparisons. In addition, other factors, including data from force platforms, clinical balance, autonomy outcomes, neglect, spatial cognition tasks, stroke severity, and time since stroke were tested for their influence on the effect of the interventions. Median, interquartile range (IQR), effect size (Cohen's *d*), and *p* values for a null effect are reported. For all analyses, *p* values below 0.05 were considered statistically significant.

Data Availability

The data used and analyzed in the present study are available from the corresponding author on request.

RESULTS

Participant flow diagram

A total of 89 patients were randomly allocated to the four groups. Figure 1 presents the flow chart, based on the modified CONSORT flow diagram for individual randomized controlled

trials of nonpharmacological treatments⁴². Seven patients were excluded from the analyses ahead of any intervention. Three of them did not meet the initial inclusion criteria (two had weight-bearing symmetry, and one had a cognitive issue and was unable to perform the protocol). A fourth patient had a stroke recurrence, and three other participants withdrew their consent between the inclusion and the beginning of any assessment. Baseline values were not available for two patients at Day 0 because of technical problems, and could not therefore be included in the analysis. Eight participants were lost to follow-up at Day 90 and eight at Day 180, as they did not respond to the assessment requests despite several calls. They were included in the analysis in intention to treat.

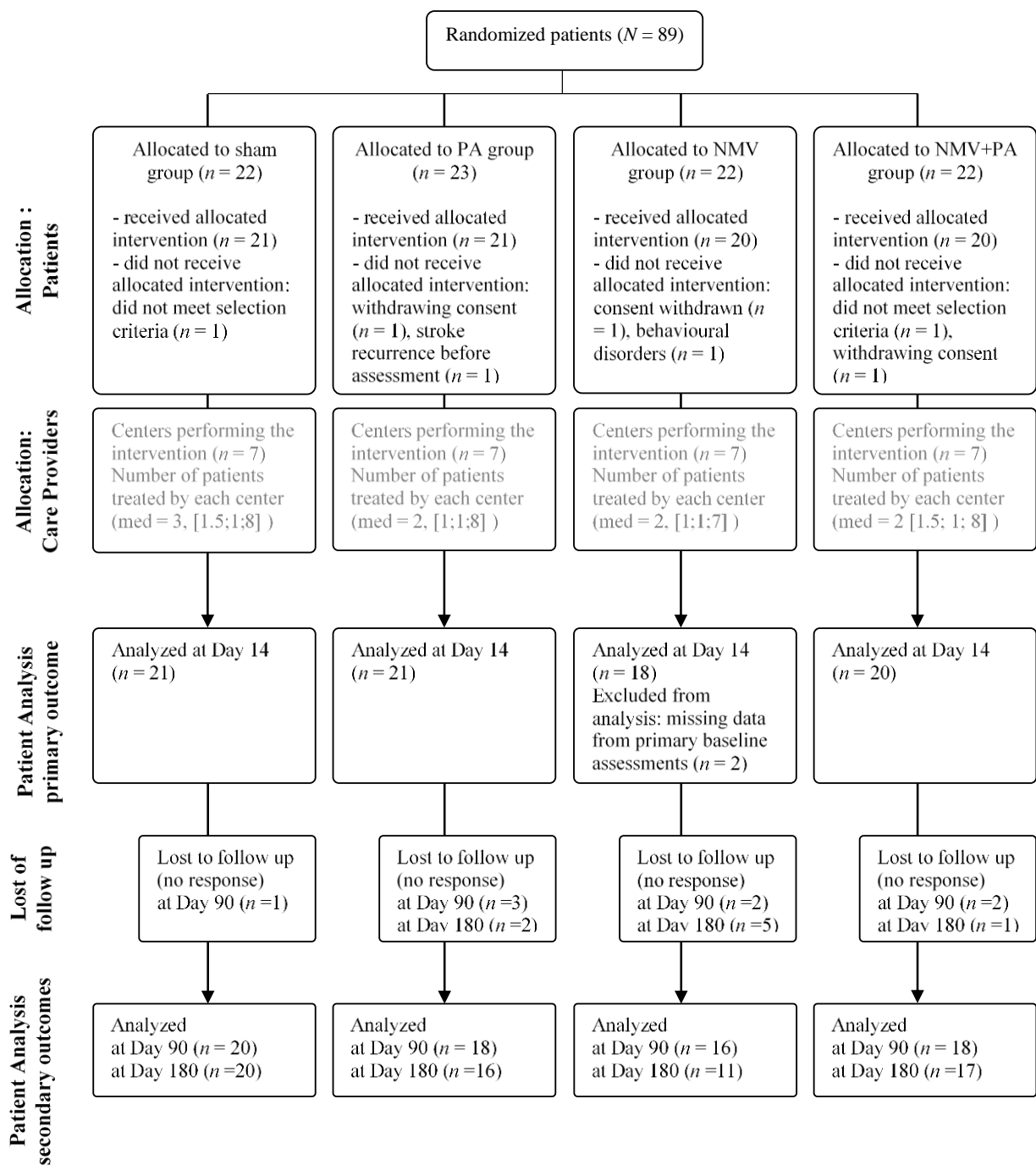


Figure 1. Flow diagram, with the number of patients treated by each center (med = median, [Interquartile range; min; max])

Baseline data

Data were collected from 80 patients (55 men, 25 women) with a mean age of 59.2 years ($SD = 10.2$). Etiology was ischemic in 51 cases and hemorrhagic in 29 cases. Mean time since stroke at inclusion was 94 days ($SD = 60.9$), with 55% early subacute (7 days to 3 months), 35% late subacute (3 to 6 months post-stroke), and 10% chronic patients (6 to 9 months after stroke). Table 1 shows the patient characteristics, principal confounders, and their distribution in each group. No statistically significant differences were found between groups.

	Whole population ($N = 80$)	sham group ($n = 21$)	PA group ($n = 21$)	NMV group ($n = 18$)	NMV+PA group ($n = 20$)
Age (years)	59.2 ± 10.2	60.2 ± 8.1	56.3 ± 11.8	56.4 ± 10.8	63.7 ± 8.6
Sex (M/F)	55/25	15/6	15/6	10/8	15/5
Lesion (I/H)	51/29	14/7	16/5	8/10	13/7
Time since stroke (days)	94.0 ± 60.9	115.1 ± 78.7	76.6 ± 52.9	91.9 ± 46.2	91.9 ± 56.5
Unilateral spatial neglect	69.7%	70.0%	63.2%	72.2%	73.7%
Epicritic hyposensitivity	59.9%	65.0%	52.3%	50.0%	60.0%
Ankle hypokinesia	36.7%	30%	38.1%	35.4%	45%
Lower limb motricity index (/100)	54.4 ± 21.1	52.9 ± 25.7	53.3 ± 20.6	52.7 ± 16.9	58.6 ± 20.9
PASS (/36)	28.9 ± 4.4	28.6 ± 4.8	30.4 ± 3.3	28.3 ± 4.4	28.4 ± 4.8
BBS (/56)	35.1 ± 11.1	33.5 ± 10.4	36.6 ± 9.6	36.7 ± 13.0	33.5 ± 11.7
Timed Up and Go (s)	47.5 ± 33.2	64.7 ± 44.8	41.0 ± 22.2	38.8 ± 28.8	47.7 ± 31.9
Barthel Index (/100)	67.7 ± 19.1	64.5 ± 19.9	69.7 ± 16.4	73.3 ± 201.0	63.3 ± 18.8
SLB (degree)	-0.2 ± 3.6	-0.3 ± 4.2	-0.7 ± 2.7	0.9 ± 2.8	-0.8 ± 4.6
SSA (degree)	-2.3 ± 8.0	-0.8 ± 11.9	-3.8 ± 7.6	-1.0 ± 6.6	-3.5 ± 4.5

□

Table 1- Participants' baseline characteristics (mean \pm SD or percentage of the whole population). Epicritic sensitivity (% hypoesthesia tested with a light touch on the foot) and posturography data were obtained with eyes closed. NMV = neck muscle vibration; PA = prism adaptation; M = males; F = females; I = ischemic; H = hemorrhagic; PASS = Postural Assessment Scale for Stroke; BBS = Berg Balance Scale; SLB = Subjective Longitudinal Body Plane; SSA = Subjective Straight Ahead.

MRI and CT

We analyzed 70 scans: 66 T1-weighted or FLAIR MRI scans, and four CT scans for patients with MRI contraindications. For 10 patients, data were missing or of low quality and could not be processed. Figure 2 presents the lesion maps. Lesioned voxels were most frequently located in the frontal lobe (precentral gyrus, middle and inferior frontal gyrus; 49%), 19% in the parietal lobe (inferior parietal lobule and postcentral gyrus), 9% in the superior temporal gyrus, and 7% in the insula. Other regions below 5% are not listed.

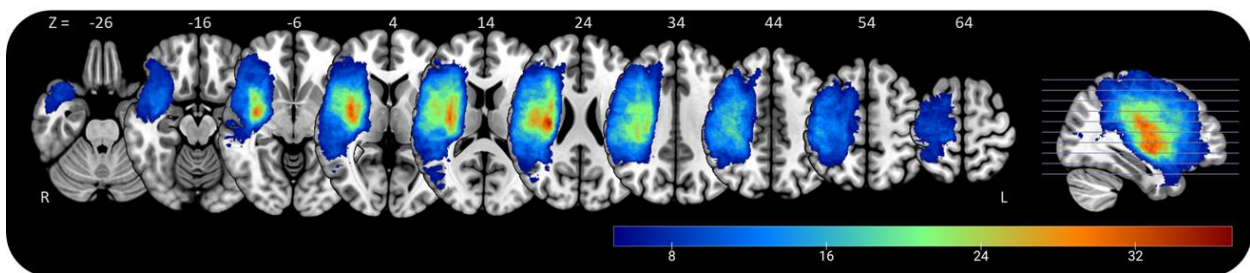


Figure 2. Lesion overlay maps; Color scale: number of patients for whom the lesion extended to this voxel, z coordinates in the MNI atlas. R = right; L = left.

Outcomes and estimation

➤ Primary outcome: End of intervention (Day 14)

Table 2 and Figure 3 report the change in ML compared with baseline for each of the four groups, including the primary outcome at Day 14. We did not find any evidence of differences between the changes observed in each group.

	Sham group (<i>n</i> = 21)	PA group (<i>n</i> = 21)	NMV group (<i>n</i> = 18)	NMV+PA group (<i>n</i> = 20)
ML EC (mm) day0	46.8 ± 44.3	43.3 ± 38.3	38.6 ± 34.6	40.4 ± 31.7
ML EO (mm) day0	58.9 ± 49.6	47.6 ± 28.7	52.9 ± 40.1	44.4 ± 38.1
Change in ML (mm)				
Day 1 EC	0.4 ± 19.4	-5.4 ± 18.9 <i>p</i> = 0.15	-1.1 ± 20.7 <i>p</i> = 0.81	-0.2 ± 30.7 <i>p</i> = 0.65
Day 1 EO	0.5 ± 24.2	-7.1 ± 18.4 <i>p</i> = 0.28	-8.3 ± 27 <i>p</i> = 0.03	-1.5 ± 22.9 <i>p</i> = 0.94
Day 14 EC	-8.2 ± 20.1	-10.9 ± 22.7 <i>p</i> = 0.69	-3.4 ± 22.5 <i>p</i> = 0.40	0.5 ± 24.7 <i>p</i> = 0.25
Day 14 EO	-4.6 ± 24.5	-10.7 ± 25.8 <i>p</i> = 0.53	-9.4 ± 21.7 <i>p</i> = 0.98	2.3 ± 27.4 <i>p</i> = 0.35
Day 90 EC	-15.3 ± 26.3	-18.0 ± 34.8 <i>p</i> = 0.66	2.0 ± 36.3 <i>p</i> = 0.04	10.7 ± 23.5 <i>p</i> = 0.01
Day 90 EO	-9.6 ± 25.5	-12.7 ± 41.6 <i>p</i> = 0.88	-9.3 ± 25.6 <i>p</i> = 0.28	5.9 ± 22.8 <i>p</i> = 0.09
Day 180 EC	-18.3 ± 36.6	-30.7 ± 22.3 <i>p</i> = 0.10	-1.9 ± 38.2 <i>p</i> = 0.04	6.2 ± 24.3 <i>p</i> = 0.13
Day 180 EO	-18.6 ± 32.8	-23.6 ± 31.5 <i>p</i> = 0.42	-14.6 ± 26.9 <i>p</i> = 0.15	10.8 ± 22.9 <i>p</i> = 0.12

Table 2- Results of mediolateral deviation (ML, median \pm interquartile range, mm) and difference between each timepoint and baseline. A negative change reflected a decrease in asymmetry. *P* values are reported for each group versus the sham group. EC = eyes closed; EO = eyes open.

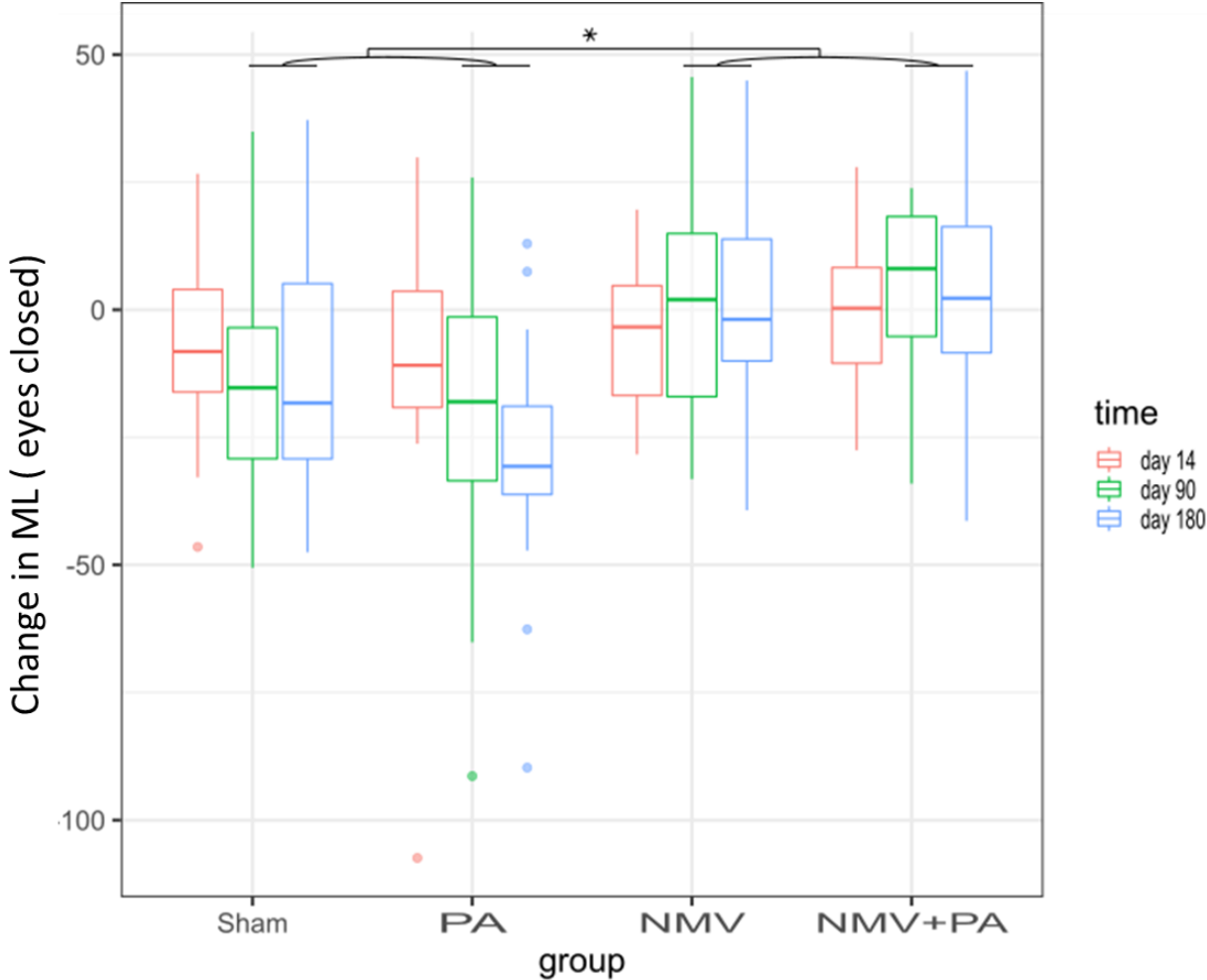


Figure 3 – Change in mediolateral deviation (ML, eyes closed; in mm) in each group (sham, PA, NMV, NMV+PA) at Day 14 (red), Day 90 (green), and Day 180 (blue), compared with baseline. A negative change reflects a decrease in asymmetry. * *p* = 0.013 at Day 90 and 0.002 at Day 180 for the difference in change between the NMV+PA and NMV versus PA and sham groups

➤ Additional analyses

Long-term assessments (Days 90 and 180)

We observed smaller ML reductions in the NMV and PA+NMV groups, compared with the sham and PA groups (Day 90: $p = 0.013$; Day 180: $p = 0.002$) (Fig. 3). The smallest reduction was observed with eyes closed in the NMV+PA group at Day 90 (median ML change = 10.7 vs. -15.3 mm, IQR = 23.5, $d = 0.86$, $p = 0.01$). Eyes closed assessments also revealed a smaller change in the NMV group than in the sham group (Day 90: median ML change = 2 vs. -15.3 mm, IQR = 36.3, $d = 0.72$, $p = 0.04$; Day 180: median ML change = -1.9 vs -18.3 mm, IQR = 38.2, $d = 0.65$, $p = 0.04$). However, this difference was not observed in the eyes open assessments. More generally, although we did not collect the necessary amount of statistical evidence, we observed a systematically harmful effect of the NMV*PA interaction on ML change (at all timepoints, with both eyes open and eyes closed).

Short-term effect

Figure 4 sets out results for the short-term effect of stimulation. After the first session, with eyes open, we observed a greater reduction in ML for the NMV group than for the sham group (median ML change = -8.3 vs. 0.5 mm, IQR = 27, $d = 0.56$, $p = 0.04$).

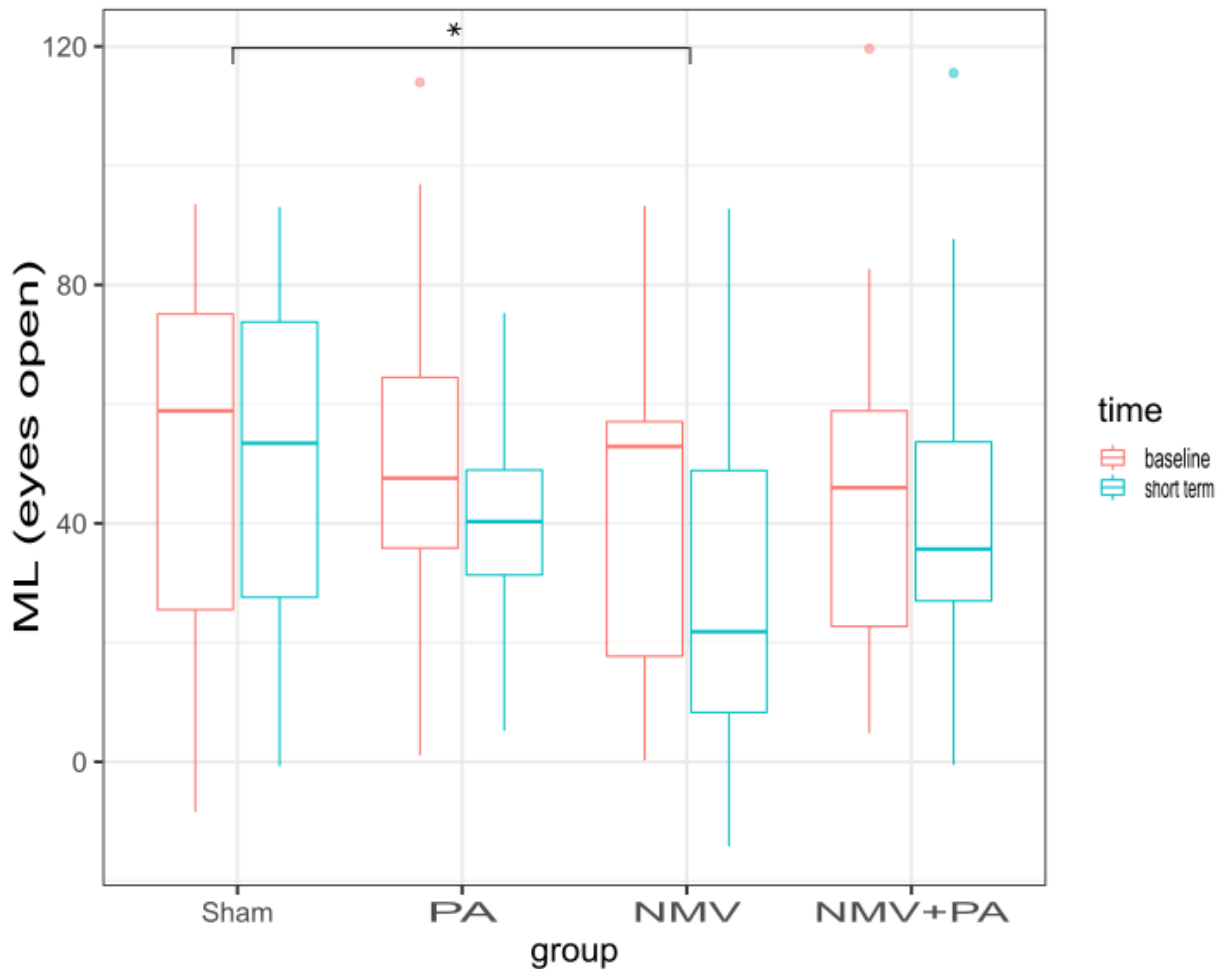


Figure 4 – Change in the mean deviation of the center of pressure on the mediolateral axis (ML, mm) eyes open in each group: sham, PA, NMV, and NMV+PA, at baseline Day 0 (red), and just after the first session (blue).

Other outcomes

No effect of the intervention was found for either force platform outcomes (i.e., AP, sway), clinical balance data, or autonomy outcomes. In addition, neglect, spatial cognition tasks, stroke severity, and time since stroke did not influence the effect of the interventions.

Harms

Patients did not describe any adverse events. In addition, we noted good compliance during assessments and interventions.

DISCUSSION

Sensory stimulation is believed to decrease the distortion of internal representations of the body in space ², and could have a positive impact on balance disorders related to spatial cognition impairment ^{2,9}. It represents a potential treatment for this specific balance disorder. The main objective of the present study was therefore to test the efficacy of repetitive sessions of sensory stimulation (i.e., PA, NMV, or both) on postural bias in patients who had recently experienced a first stroke. Given the extensive involvement of right-hemisphere brain networks in spatial cognition ⁴³, we limited our population of interest to patients who had a right-hemisphere stroke.

Our study failed to show any beneficial effect of repetitive unimodal or combined sessions of NMV and/or PA on postural asymmetry after stroke. Several considerations may explain this result and open up perspectives for future research. First, as postural asymmetry is considered to be a marker of body misperception in space, we selected patients with WBA, and therefore only included patients when they could stand alone on a force platform and whose paretic limb supported less than 40% of their body weight, up to 9 months after the stroke ¹⁰. It would be interesting to test the effect of NMV and PA earlier after stroke, when patients are probably more receptive to stimulation. Second, earlier and more specific spatial cognition markers would be useful. SSA and SLB could be discriminant to select patients earlier and more accurately identify spatial cognition disorders. These tests are not influenced by other deficiencies (i.e., motricity or sensitivity) besides WBA. Third, we postulate that performing an active postural task during the sensory stimulations could enhance the power of these stimulations to decrease spatial distortion by forcing patients to challenge their postural control. Previous studies have shown encouraging results when combining sensory stimulation with grasping tasks to improve neglect ^{23,44,45} or with dynamic tasks to improve balance ^{46,47}, suggesting both top-down and bottom-up benefits of therapeutic combinations. Thus, performing postural motor tasks during sensory stimulation could enhance the impact on balance by facilitating and stabilizing the process of realignment between visual and egocentric references needed to obtain a longlasting effect. More specifically, we suggest replacing the pointing task with a dynamic postural task during PA, and administering the same type of postural task (e.g., sit to stand task) during NMV.

Several additional considerations could explain these negative results, including 1) the limited number of patients per group at the end of the trial, 2) the extensive range of postural measurements, and 3) the variability of individual reactions to the sensory stimuli.

Our main research hypothesis was that the association of two different types of sensory stimulation would have a synergistic or at least an additive effect. We therefore expected that adding NMV would enhance the shift of the body obtained by PA. Previous combinations of sensory stimulation (NMV, PA, or vestibular) had been shown to have a beneficial impact on spatial bias^{8,48,49}. Surprisingly, the combination of our two interventions did not have a synergic effect, and even seemed to have a negative impact on postural asymmetry. There are three possible explanations for this result. First, even if these interventions are mostly passive, if a patient has impaired attention abilities, a combined program may be too demanding and fail to improve balance. Second, the adjustment sequences for PA and NMV differ. NMV induces an illusion of a proprioceptive shift to the left, and then an alignment of the visual reference frame with the shift in the egocentric one. The opposite mechanism occurs during PA. The latter induces a left deviation of the visuomotor environment first, followed by an alignment of the egocentric reference frame with the visual environment. Third, the right temporoparietal lobe may be overwhelmed by the multiplication of stimuli. This high-level area must simultaneously integrate multiple sensory inputs, elaborate, and continuously update the change in different spatial reference frames⁵⁰. The time needed to performing the coordinate transformations and the various changes in reference frames induced by each type of sensory stimulation may overwhelm this supramodal process.

We supplemented the results with secondary analyses. The latter should be interpreted with caution, owing to the lack of statistical power. We nevertheless believe that these additional analyses allowed us to improve our understanding of the mechanisms behind these types of sensory stimulation.

We observed a short-term effect of NMV on postural asymmetry assessed with eyes open²⁴. Furthermore, a shift in the body's reference frame only seemed to take place after NMV, when patients could see the environment, suggesting that the egocentric shift is related to the shift in the visual reference frame. This assumption is supported by previous studies showing that when the instruction to point to a target is given under NMV, with available visual control, patients point to the left of the target⁴⁸.

No effect was found for cumulative NMV sessions, and our results suggested negative changes at Days 90 and 180. This long-term effect is complex to interpret, given that there was no additive effect of sessions. Moreover, the smaller change in ML bias, compared with the sham and PA conditions, was only present in the eyes closed assessments.

Limitations

First, we did not manage to include the expected number of patients in time, probably owing to the highly selective criteria at inclusion. Second, there was a variable time between stroke and inclusion, as patients could only be included when they could stand alone on a force platform and if their paretic limb supported less than 40% of their body weight¹⁰. However, our population was functionally homogeneous in terms of balance abilities, and we did not detect any effect of this interval on the efficiency of the treatment.

CONCLUSION

Our results did not show any beneficial effect of repetitive unimodal sessions of either NMV or PA on balance abilities after a stroke. Moreover, the combination of the two was not beneficial in this population over the long term. Nevertheless, the present study provides hypotheses for future studies. Adding dynamic tasks focused on balance during sensory stimulation could induce a more robust recalibration of spatial references. Also, using earlier and more specific markers of spatial cognition disorders could promote the selection of receptive patients.

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KEY POINTS – NMV EFFECT ON POSTURAL RECOVERY AFTER STROKE

This study did not find significant long term effect of NMV on mediolateral bias of patients within nine months after a right stroke. Combining PA and NMV did not come out beneficial on WBA.

During NMV or PA , adding balance motor tasks could decrease distortion of reference frames coordinates. Moreover, using earlier and on patients with more specific spatial cognition disorders (SSA or SLB deviations) would select receptive patients.

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Part 4. Discussion and perspectives

CHAPTER 1. MRI considerations

CHAPTER 2. Clinical questions about the markers of spatial misperception

CHAPTER 3. Perspectives

The overall aim of this work was to understand better the part of postural disorders related to spatial cognition disorders in right stroke patients. And test proprioceptive sensory stimulation as a specific rehabilitation program for them. Improving the knowledge about the egocentric referential was an essential step because it is involved in several daily life abilities, such as grip, personal care, and balance. Moreover, the egocentric space contains classically two portions, the corporeal and extracorporeal areas.

Firstly, we conducted an original study to understand the neural basis of perception in these two portions of space. The analysis of healthy subjects fMRI data highlights common activations during two egocentric tasks, namely SSA extracorporeal and SLB corporeal. They activated a shared bilateral parieto-occipital network (involving the superior and inferior parietal lobules and lateral occipital cortex, with a right hemispheric dominance. The SLB > SSA contrast revealed additional activation on the left angular and premotor areas. These differences suggest that corporeal egocentric tasks (SLB) engaged attention and process close to motor imagery, whereas the extracorporeal (SSA) did not engage these areas. These differences in activation explain specific divergent clinical results suggesting differences in extracorporeal and corporeal information processing, as is the case in USN.

Secondly, we studied activation during tasks involving the representation of egocentric space after a stroke. We found that the patients presented three main activation patterns to realize egocentric tasks: perilesional activation, contralesional or bilateral. These three patterns are similar to the reorganization found for motor or language tasks. Additionally, at the difference to healthy subjects, activations were found in cerebellar and temporal regions suggesting their possible involvement in post-stroke spatial cognitive reorganization processes. Finally, from a technical point of view, we will discuss below challenges of fMRI analysis in case of a stroke.

The third purpose of this work was to test a sensory stimulation by NMV on postural disability related to spatial cognition disorders after right stroke. As these disorders impact the balance symmetry after stroke, we chose to investigate the effect of NMV on WBA. The NMV provided significant results after one session in subacute patients and a repetitive program of sessions in chronic patients who had a stroke. However, we did not demonstrate any effect in post-stroke patients with WBA within nine months of a right stroke. We will discuss which factors could explain the results. Unlike expected, the association with another sensory stimulation (PA) had a deleterious effect on WBA. We hypothesized concurrent adaptation processes or an overload of sensorimotor integration that did not allow for adequate processing.

Finally, I will suggest perspectives to continue this work and improve our understanding of the neural basis of egocentric spatial cognition.

Chapter 1. MRI Considerations

a. Stroke lesion delineation challenges

The first step for image data analysis in the case of stroke patients is segmenting the lesion. It comes to use for diagnosis of acute stroke outcome to identify lesion core, penumbra and oligemia, and research purposes to relate lesion extent to clinical outcomes. Between 2015 to 2018, segmentation challenges were organized (ISLES challenge, <http://www.isles-challenge.org>). Since the development of deep learning approaches has prevailed on other systems (Ito et al., 2019). In 2020, Karthik et al. have nicely reviewed 113 papers proposing deep learning methods to segment ischemic or hemorrhagic, acute or subacute stroke lesions (Karthik et al., 2020). They concluded that despite advancements in deep learning for detecting and segmentation stroke lesions, there were still limitations. Among the difficulties is the image database they rely on in terms of availability of annotated data and data heterogeneity (CT or MRI, conventional MRI (T1, T2, Diffusion) or advanced (perfusion) imaging. Whether ischemic or hemorrhagic, most methods address acute or sub-acute stroke rather than chronic lesion segmentation. Besides, the number of available labelled datasets to train and validate these methods are limited. To our knowledge, the ATLAS (Anatomical Tracings of Lesions After Stroke) data is the only collection available (Liew, 2018). This open source dataset of 304 T1-weighted MRIs, with stroke lesions manually segmented was used for my manual delineation training. For our dataset of 80 subacute and chronic stroke patients, we tested an automatic segmentation solution to avoid tedious manual segmentation and intersubject variability issues. We tested the solution of a team with expertise and interest in lesion segmentation (Doyle, 2017). Unfortunately, the previously trained model did not apply well to our data. More than half of automated segmentation needed manual correction that were as time consuming as direct manual segmentation (figure 1).

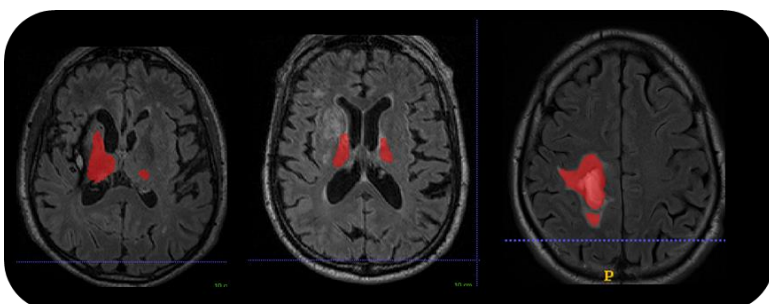


Figure 1 – Examples of automatic delineation failure.

These errors could be explained by the diversity of lesions (36.5% haemorrhagic or 63.5% ischemic), the various time between stroke and MRI (from 2 to 9 months) and above all, the fact that scans were acquired in eight different centres. Even though we attempted to harmonise the scans recommended by the ENIGMA stroke recovery working group (Liew et al., 2020), the data were acquired on clinical scanners. As part of the AVCPOSTIM study, sequences (T1, FLAIR, Diffusion), sequence parameters (2D, 3D, resolution, contrast), and quality were disparate. In the end, we decided to manually segment the data, which was time-consuming but provided reliable segmentations with a single reader. Besides, we tried to train the software on this segmented data and apply it to another local dataset, but the results were still disappointing.

Our research group has been participating for several years in the considerable effort to develop tools to segment multiple sclerosis (MS) lesions for clinical and research purposes. Indeed, the repetition of neuroimaging in MS patients is standardized to monitor the evolution of the lesion load and adapt treatment. Neuroimaging thus has a therapeutic impact on lesion evolution. Besides, the availability of training datasets warrants sufficient data to train models. In France, this is encouraged by the OFSEP PIA Cohort (<http://www.ofsep.org/en/cohort/cohort-description>), funded in 2011, which standardizes the imaging protocol and organizes the collection of imaging data at the national level. In the case of stroke, to date, the extension and location of the lesion are seldom used to discuss therapeutics. The clinical outcomes remain the primary evaluation. This may evolve if stroke lesions are taken as a predictive factor (Stinear and Ward, 2013; Imura et al., 2021), requiring segmentation not routinely done by clinicians. Moreover, these delineations allow to compare lesion location and extension with clinical outcomes, qualitatively, and also to use approaches such as Voxel Lesion Symptom Mapping.

b. Considerations regarding fMRI processing in stroke patients

Functional group-level analysis requires spatial normalization to register image data in a standardized template. In the case of stroke, the normalization process can be disturbed by intensity changes or spatial deformations. The first challenge is to account for the presence of a lesion when calculating the transformation. Several approaches were proposed to address this issue of spatial normalization in the case of a brain lesion. Cost-function masking can

exclude the lesioned voxels when deriving the normalisation parameters (Brett et al., 2001). The unified segmentation approach involves a model combining segmentation, bias correction and spatial normalisation in the inversion of a single unified model (Ashburner and Friston, 2005). The enantiomorphic method replaces the lesioned area with the homologous contralateral brain (Nachev et al., 2008). There is currently no consensus on the best approach (Crinion et al., 2007; Pappas et al., 2021). Because of its prevalence in the stroke literature, we choose the SPM unified segmentation. This method normalizes images to the MNI space by performing tissue matching based on tissue probability maps included in the SPM package. Normalization was visually controlled, and we did not observe any significant distortion.

Secondly, the standard average adult brain template used is the MNI-ICBM152 template (MNI), based on 152 normal young adults (18.5-43.5 years) (Fonov et al., 2011; Manera et al., 2020). However, stroke patients are generally older, and atlases based on healthy controls in a matched age range could be more appropriate. For example, the *Clinical toolbox* could be helpful for future works (<https://www.nitrc.org/projects/clinicaltbx/>; website visited the 24th Sept 2021). This toolbox uses a template based on healthy individuals with a mean age of 65 years old (Rorden et al., 2012) and proposes a unified segmentation approach.

Another discussion concerns the estimation of brain activity. The hemodynamic response function (HRF) is related to blood flow, blood volume, and blood oxygenation and varies across subjects and brain regions (Handwerker 2012). SPM proposes a canonical HRF that can be combined with spatial and temporal derivatives. Although this allows to better model subject response at the individual level, its use at the group level remains discussed (Calhoun et al., 2004). In stroke, since blood flow, volume, and oxygenation are potentially modified in perilesional areas as well as globally, using the canonical hemodynamic response function (HRF) is questionable (Veldsman et al., 2015; Siegel et al., 2017). Besides, decreased signal to noise ratio in fMRI data performed in the elderly was reported. Thus, Veldsman et al. suggest taking into account spatiotemporal modifications and relying on a patient-specific HRF to improve results. However, since we were using a block design, we could not extract the individual HRF and assumed that sensitivity to the HRF was less pronounced than with an event-related design. Thus, in our preliminary analysis, we used the canonical hemodynamic response function.

Chapter 2. Clinical questions about the markers of spatial misrepresentation.

In our clinical trial, we chose the WBA as a marker of postural disorder related to spatial misrepresentation, and our criteria of selection of patients was a WBA > 40%.

This was based on previous work that found a link between SLB and WBA (Barra et al., 2009; Jamal et al., 2018). WBA is associated with postural instability and the severity of the post-stroke disability (Pérennou, 2005; Kim and Kim, 2015). However, WBA is impacted by spatial cognition and weakness, sensitivity, and spasticity. Additionally, there is a debate whether WBA is a valuable adaptation to instability or the reflection of spatial misperception or both of them. One assumption is that WBA could be an adaptation limiting the solicitation on the paretic lower limb and diminishing the falling risk. However, it exists several arguments to support the hypothesis of responsibility of spatial misperception. First, balance asymmetry is linked to spatial cognition disorders (Barra et al., 2009). Secondly, previous Second, no adverse effects on postural stability were found in studies decreasing WBA (Jamal et al., 2020), which is an argument against the compensatory characters of WBA. However, the multiple factors impacting the WBA may explain the low responsiveness to change in our study.

The second drawback of this marker is that we have to wait until the patient can stand-alone. This point leads to two consequences. First, this delay induced heterogeneity of time between stroke and inclusion. Secondly, spatial cognition disorders may have delayed the recovery of standing balance abilities and at the time at which we applied sensory stimulation, the spatial cognition disorders could have greatly diminished. Precisely, the sensory stimulation interest may be used early before the obtention of a stable standing balance.

One way to improve the study of the effect of NMV on spatial cognition would be to use more specific and more sensitive biomarkers. Indeed, the interest of this sensory stimulation is the early use, at a time when spatial cognition disorders are prevalent. Thus, the SSA and SLB would be the markers of choice, measurable before acquiring standing balance and independent of the other factors involved in posture.

Chapter 3. Perspectives

a. Analyses of brain activation during NMV

During the RCT AVCPOSTIM, we carried out spatial cognition tasks (SSA and SLB) under fMRI with NMV. These results would be innovative because, to our knowledge, the brain activation under NMV has never been analysed during spatial cognition tasks. Moreover, the interpretation would be challenging in the population who had a stroke due to the lack of activation found during SSA and SLB. However, we hypothesis that NMV would be lateralized in the perilesional area. In our next work, we will explore brain activations during NMV in healthy subjects and patients during spatial cognition tasks or not.

b. The interest of lesion behaviour mapping on egocentric tasks

We have in mind to use lesion-behaviour mapping to assess the effect of damage to each voxel on the performance scale. The VLSM (voxel-based lesion-symptom mapping) is a mass-univariate analysis that uses an independent statistical test on every voxel (Karnath et al., 2019). Using VLSM maps for SSA and SLB could be another way to identify the involvement of regions in the process of spatial representation. Our project is to process lesion behaviour mapping on groups of patients with and without egocentric tasks deviation. Considering the limited functional modules searched, we should choose a region-of-interest approach instead of a voxelwise analysis. The MLBN (multivariate lesion behaviour mapping) could be an alternative (Karnath et al., 2019; Bowren et al., 2020). This method is based on multiple variables such as the lesion status of multiple voxels or ROI and behaviour variables. However, the analyses need a larger sample of patients (100 to 200 subjects).

c. The interest in works about network and connectivity

Previous work shows that brain activations during egocentric tasks in healthy subjects were located in bilateral fronto-parieto areas with a right predominance. In addition, we observed a significant involvement of the PPC and extension to the superior frontal lobule. However, it would be fascinating to assess the egocentric spatial frame regarding structural and functional

connectivity. Using diffusion-weighted imaging (DWI) structural connectivity could help to characterize the connections involved in the egocentric referential frame network.

Our fundamental results about the reorganization of brain activations after stroke (*publication 2*) may provide the background for further studies on the network of spatial cognition because stroke decreases activations and disconnects areas (Sporns et al., 2005; Thiebaut de Schotten et al., 2020). The analyse of connections modifications due to brain lesions may improve the understanding of the cerebral plasticity mechanisms for the recovery of spatial cognition (Grefkes and Fink, 2014; Silasi and Murphy, 2014; Su and Xu, 2020). Depending on the lesion location and the connections/disconnections, the rehabilitation protocol could be personalised. In such a way, spatial cognition recovery after a stroke could follow three main paths: 1) redirection connections; 2) inhibition of intact hemisphere; 3) plasticity in the perilesional network.

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Conclusion

The egocentric referential frame, often involved in spatial cognition disorders after stroke, needs to be considered in assessment and rehabilitation programs. Two biomarkers are usually used in clinical practice to test spatial representation in egocentric referential, i.e. SSA (extracorporeal space) and SLB (corporeal space). Both investigated using fMRI in healthy controls, they elicited a fronto-parieto-occipital network with a right predominance (superior and inferior parietal lobule, precuneus, postcentral gyrus, lateral occipital cortex, precentral cortex). The SLB appears to be an exciting biomarker involving additional areas, the left angular and left precentral areas suggesting a greater complexity of corporeal processes engaging g body representation. This specific contralateral activity supports the concept of a bilateral network underlying spatial cognition tasks.

Interestingly, using fMRI in patients with right stroke, three activation patterns were observed for both biomarkers during extracorporeal and corporeal tasks, recruiting either bilateral areas, left areas (contralateral) or right areas (perilesional). Moreover, We found activations in the cerebellum posterior and temporal gyrus involved in the spatial cognition adaptation process. However, our preliminary data did not provide a behavioural profile or brain lesion (in their location or size). Finally, the results of the multicenter randomized clinical study AVCPOSTIM assessing the effect of sensory stimulation as a potential rehabilitation strategy in patients presenting balance perturbation related to spatial cognition disorders did not confirm our prior hypothesis. Indeed, neither the prismatic nor the NMV sessions improved the weight-bearing asymmetry, whether used separately or combined. However, using another criterion such as SSA and SLB without waiting for the ability to stand up could change these results.

This work has promising perspectives. An ancillary study including earlier patients on the criteria of deviation of the axes has been initiated, using fMRI and diffusion. Investigating networks underlying brain activations during corporeal and extracorporeal, at rest and under vibration would be a step forward. Also, looking into VLSM analysis will bring insights into the impact of lesions on such spatial cognition abilities.

APPENDIX

Appendix 1 - Disturbances of spatial reference frame and postural asymmetry after a chronic stroke.

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Disturbances of spatial reference frame and postural asymmetry after a chronic stroke

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Abstract

Asymmetrical postural behaviors are frequently observed after a stroke. They are due in part to the sensorimotor deficit, but they could also be related to a disorder of the representation of the body in space. The objective was to determine whether the asymmetrical postural behaviors of chronic stroke patients are related with a disruption of the perception of spatial frame. 30 chronic stroke patients (mean age 60.3 year \pm 10, mean delay post-stroke 4.78 year \pm 3), 15 patients with right brain damage (RBD) and 15 patients with left brain damage (LBD), and 20 healthy subjects participated in the study. Postural asymmetry was detected by the evaluation of body weight repartition on a force platform (weight body asymmetry) and was related to the longitudinal body axis (LBA) and the subjective straight ahead (SSA) (egocentric space representation) and to the subjective visual vertical (SVV) (allocentric space representation) by a multivariate analysis of variance adjusted with motor function and sensitivity as covariables. Both patients with RBD (35% \pm 8) and LBD (39% \pm 4) had body weight asymmetry and there was still space misperception at this stage of recovery, especially in the RBD group. WBA was related to LBA when considering both patients with RBD and LBD ($p = 0.03$). However, this relation was dependent on the side of the lesion ($p = 0.0006$) with a stronger relation in the RBD group (0.01). No relation with WBA was found neither with SSA ($p = 0.58$) nor with SVV ($p = 0.47$). This study pointed out a strong relationship between disturbance in the perception of the longitudinal body axis and postural asymmetry in chronic strokes, and especially within the RBD group. Conversely, no other spatial perturbations seemed to be involved in this particular postural behavior.

Keywords Stroke · Postural asymmetry · Egocentric reference frame · Allocentric

Introduction

One of the causes of disability in the patient following a stroke is postural disturbances (Pérennou et al. 2005b), which cause a greater risk of falls and contribute to loss of

autonomy (Kim and Kim 2014). Postural control requires integration of vestibular, visual, and somatosensory information which is realized in different spatial reference systems such as allocentric and egocentric reference frames. This allows the patient to develop a perception of his body in

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space, thus maintaining its position and allowing the body to move (Barra et al. 2010; Bonan et al. 2013; Galati et al. 2010; Saj et al. 2014).

Postural imbalance is characterized in upright stance by an increased postural sway and more weight-bearing asymmetry (WBA) on the non-paretic leg (Mansfield et al. 2013; Pérennou 2005). This postural asymmetry is increased in the case of a right side lesion, which could be partly due to a disorder of the body orientation in space (Pérennou et al. 2014). Many researchers agree that the location for the determination of mental representation of the body in space is in the right cerebral hemisphere; the hemisphere which is specialized in spatial cognition (Barra et al. 2010; Bonan et al. 2013; Halligan et al. 2003; Rousseaux et al. 2014). This could explain why patients who have suffered from a right brain damage (RBD) have a lower prognosis in terms of balance and why they take a longer time to acquire a correct balance compared to patients in whom the lesion is located in the left hemisphere (LBD) (Bonan et al. 2007; Pérennou 2005; Rode et al. 1997).

Disorders of representation of body in space can be captured by measuring the perception of allocentric space representation such as vertical misperception and egocentric space representation such as the body midsagittal misperception. The allocentric reference frame involves the perception of space relative to information from the environment and also relative to one to another (Colombo 2017; Galati et al. 2010; Saj et al. 2014) and can be explored by assessing the subjective vertical (SV) (Bonan et al. 2006a, b; Pérennou et al. 2014; Piscicelli and Pérennou 2017; Rousseaux et al. 2013). While, the egocentric reference frame is body centered (Colombo 2017; Galati et al. 2010; Saj et al. 2014) and can be divided into two parts; first, the personal space, which corresponds to the body space and second, the extra-personal space, which refers to the out of body (Chokron et al. 2004; Chokron and Bartolomeo 1998; Committeriet al. 2007; Guariglia and Antonucci 1992; Rousseaux et al. 2014; Ventre-Domine 1984). Consequently, the egocentric space representation can be explored according to the part of space involved either in the extra-personal space representation with the subjective straight ahead (SSA) (Chokron 2003; Hugues et al. 2015; Jeannerod and Biguer 1989; Moulinet et al. 2016; Rousseaux et al. 2014) or the personal space representation with the longitudinal body axis (LBA) (Barra et al. 2009; Hugues et al. 2015; Moulinet et al. 2016). The disturbance in the perception of vertical subjective after a stroke is the subject of numerous studies and its relationship with postural disorders have been exposed in several studies (Bonan et al. 2006a; Pérennou et al. 2008). This is,

however, not the case for the egocentric spatial representation, where the relation with postural disorders was explored in only one study (Barra et al. 2009). Although, Barra et al. highlighted a relation between LBA and postural asymmetry

in acute stroke, these authors did not examine its relation with the SSA. Even though SSA is an accepted manner to assess the egocentric extra-personal space representation, (Chokron 2003; Hugues et al. 2015) which is often disturbed after a stroke, to our knowledge no authors have investigated its relation with weight-bearing asymmetry.

Therefore, the first objective of this research was to examine both egocentric and allocentric space representation and weight-bearing asymmetry in chronic stroke patients. The second objective was to study their relations. Hence, the assumption that the bias of both egocentric and allocentric space representation could be explained, at least in part, by the postural asymmetry of patients with right brain damage. Determining a link between disturbance of egocentric or allocentric space representation and the postural asymmetry would, therefore, allow for a better understanding of balanced disorders and provide for new approaches for the treatment of such disorders in stroke patients.

Methods

Participants

Stroke patients were recruited from a list of patients who were treated in the Department of the Physical Medicine and Rehabilitation (PMR) "Centre Hospitalier Universitaire (CHU)" of Rennes. The patients were contacted by phone after having confirmed the inclusion criteria and the foremost patients who responded were included in the study. The inclusion criteria incorporated the following two main considerations right or left brain unique supratentorial damage with a time post-stroke of more than 1 year without any neglect and, hemianopia or pusher syndrome as these disorders are known to modulate both spatial and postural biases (Honoré et al. 2009; Karnath et al. 2000; Pérennou et al. 2014; Richard et al. 2005; Saj et al. 2005, 2006, 2010). Four tests for visuo-spatial neglect were conducted: the bell cancellation test (Rousseaux et al. 2001), 20 cm line bisection (Rousseaux et al. 2001), the Fluff test (Cocchini et al. 2001), and the OTA test (Ota et al. 2001). The patient was considered as neglect if he/she had at least three positive tests out of the four. The presence or the absence of a homonymous hemianopia was clinically

tested with a confrontation visual field test on each quadrant with a ball. Concerning the laterality of patients, this was determined by the hand preference for writing. Patients had to be aged less than 80-year old presenting a weight-bearing asymmetry with less weight on the hemiplegic leg evaluated on the forceplate form. Those patients who were symmetrical on their weight bearing were excluded given that the objective was to better understand mechanism of disturbance of postural balance. The exclusion criteria also ruled out patients with ischemic or hemorrhagic brainstem stroke, with an orthopedic and or a rheumatologic history affecting the distribution of weight bearing when standing or a visual history which does not allow the realization of visual assessments as well as those patients with major disorders of understanding. Concurrently, healthy subjects, from the care team at the PMR, those without any history of neurological, orthopedic and vestibular disturbances, which could probably alter the balance and the feasibility tests, were included in the study so as to obtain a normal range of the spatial frame of reference. This study was approved by the local Ethics Committee of Rennes University Hospital number 16.23.

Procedures

The inclusion procedures took place over a period between February 2016 and July 2017 in the Department of the Physical Medicine and Rehabilitation. The patients all went through a doctor-patient medical consultation to validate the inclusion criteria and besides to test out for possible new functional deficits. They then signed up once their approvals were obtained after having explained the protocol. After the evaluation of the severity of stroke, patients followed an assessment in this order: assessment of postural asymmetry, evaluation of space representation (SSA, SVV, LBA), and finally the balance test rating (TUG and BBS).

Assessment of postural asymmetry

Weight-bearing asymmetry (WBA)

Postural assessment of the patient was performed on a double force platform (FP) (PostureWin V143 Techno Concept ©). The patient placed bare feet (without socks or stockings) separately at a distance of 14 cm apart, with the objective being to stand as straight as possible with arms alongside the body, looking straight ahead (position open eyes OE) or wearing a headband (eyes

closed position EC). The percentage of the WBA on the hemiparetic lower limb (WBA) was calculated as the mean of the four trials, each of a 30 s duration was chosen—two opened eyes (OP) and two closed eyes (CE) (Pérennou 2005; Pérennou et al. 2005a, b).

Evaluation of the egocentric space representation

Subjective straight ahead (SSA) (Chokron et al. 2004)

The evaluation was carried out on a measuring table on which the patient was required to move his hand in a blind-folded state. The table is graduated and 1° angle corresponds to 1 cm linear. The midsagittal almost coincides with the middle of the table with the head and trunk of the patient being placed in alignment. From a starting position where the hand of the patient was placed by the examiner and with no imposed time limit, the patient was pointing his right arm, for those patients with RBD and the left arm for patients with LBD; with fingers extended sliding on the support table, with the instruction to point “straight ahead” so as to divide the space into two parts. Ten tests were conducted with different starting positions in a randomized sequence (–10°, 5°, –15°, 10°, 30°, –5°, –20°, 15°, –30°, 20). The positive sign corresponded to the ipsilesional side, i.e., the scores on the right were positive annotated, whereas the scores on the left were negative for patients with RBD and vice versa for patients with LBD. The value (in degrees up to 0.5°) used was both the mean (M_SSA), the mean absolute value (AbM_SSA), and the standard deviation (SD_SSA) for ten measurements.

The longitudinal body axis (LBA) (Barra et al. 2009)

The evaluation of the LBA was performed using a light strip in front of the patient in supine position, in complete darkness, with the head, the trunk, and the lower limbs aligned and maintained by cushions. The rotation center of the visual line was aligned with the patient's navel and with the plumb line. The light wand was moved around its axis of rotation by the examiner from a starting position inclined at a prescribed angle [ten tests were performed with starting positions in a randomized sequence (–10°, 5°, –15°, 10°, 30°, –5°, –20°, 15°, –30°, 20)]. The patient was given the task to indicate when the strip was parallel to the axis of his body. The test took place in the dark with the patient's eyes open throughout the test. No visual reference other than the wand was available, and there was no time limit. The positive sign corresponded to the ipsilesional side, i.e., the scores on the right were positively annotated,

whereas the scores on the left were negative for patients with RBD and vice versa for patients with LBD. The value (in degrees up to 0.5°) used was both the mean (M_LBA), the mean absolute value (AbM_LBA) and the standard deviation (SD_LBA) for 10 measurements.

Evaluation of the allocentric reference: subjective visual vertical (SVV) (Bonan et al. 2006a, b)

The evaluation of the SVV was performed in a sitting position with the head fixed, using virtual reality helmet (Oculus®). From an imposed starting position without a time limit, the patient was presented with a blue background with an oblique red line with ten different starting positions in a random sequence (-10°, 5°, -15°, 10°, 30°, -5°, -20°, 15°, -30°, 20). The patient was given the task to indicate when the line is aligned to the vertical. The positive sign corresponded to the ipsilesional side, i.e., the scores on the right were positive annotated whereas the scores on the left were negative for patients with RBD and vice versa for patients with LBD. The value (in degrees up to 0.5°) used was both the mean (M_SVV), the mean absolute value (AbM_SVV), and the standard deviation (SD_SVV) for ten measurements.

Balance rating

Other balance tests to assess the functional impact of balance disorders have been carried out: Time Up And Go (TUG) (Podsiadlo and Richardson 1991) evaluating the time during which the patient gets up from a chair, walks 3 m, turns around and comes back to his seat, and Berg Balance Scale (BBS) (Berg et al. 2009) which includes 14 items assessing equilibrium in different positions such as picking up an object off the ground. The maximum score was 56.

Evaluation of the severity of stroke

Clinical tests were conducted as a motricity test (Motricity index which evaluates the hip flexion, the knee extension, and the ankle dorsiflexion with a score of 100 Collin and Wade 1990) and the spasticity test (Ashworth modified MAS) (Bohannon and Smith 1987) which targets the following muscle groups: sural triceps, quadriceps, and adductors, and finally the sensitivity (by a clinical examination of superficial tact on the foot and the lower limb and the arthrokinetic

sensitivity of the knee, ankle, and toe).

Statistical analysis

Statistical analysis was performed using SAS 9.3 Software. The clinical data between the patients with RBD and LBD were compared using a Student's test or Mann and Whitney test when the distribution was not normal at a significance level of $p = 0.05$. The relations between the spatial reference frame (SSA, LBA, and SVV) and the postural asymmetry (WBA) were first tested on the two groups of patients (RBD and LBD) by way of a multivariate analysis of variance (MANOVA) adjusted by the variable motricity and sensibility when the distribution was normal or by an ANOVA on ranks. After that, second, a partial correlation test with motor function and sensitivity as covariables was performed. The partial correlation was carried out for all the patients (RBD and LBD) and only thereafter taking the RBD group and the LBD into consideration. The space representation (SSA, LBA, and SVV) of patient with RBD and LBD was compared using a Student's test or Mann and Whitney test when the distribution was not normal. The comparison was based on the mean (M), standard deviation (SD), and absolute mean (AbM). The AbM was a unsigned mean not to take into account the plus or minus of the deviation and to better estimate what is moving away from zero for both group of patients. The relation between the assessment of space representation (SSA, LBA, and SVV) was tested by a Pearson correlation (or a Spearman correlation) taking into consideration M, AbM, and SD. The results of the evaluation of the spatial cognition for the healthy group were used so as to obtain a normal range of the spatial cognition.

Results

Population (Table 1)

From the list of stroke patients, 41 patients were contacted based on the inclusion criteria during the set period. With the exception of two patients who refused to participate, and one who died, all patients provided their approval. After having informed the patients and obtained their consent, 38 patients were integrated into the study. Of these, however, five patients with RBD patients and two patients with LBD patient were eventually excluded as they did not show signs of weight-bearing asymmetry on the force platform. Finally, one patient with RBD was also excluded because of neglect. Therefore, in this study, a total of 30 patients, 24 men and 6 women with an average age of 60.3 ± 10 years having had a delay after stroke (4.78 ± 3 years), with 15

patients with RBD and 15 patients with LBD cases were included (Fig. 1). Excepted two patients in each group, all the others were right handed. None of the patients presented a hemianopia. Out of the patients with LBD, two patients were with apha-sia, but it did not induce any difficulty when performing the assessment in understanding the aim of the protocol. When considering the severity of stroke with the Student's test, the two groups, patients with RBD and LBD, were similar in age ($p=0.4$) as, in motricity ($p=0.9$) and with the Mann and Whitney test in delay post-stroke ($p=0.4$) and sensibility ($p = 0.2$). The weight-bearing repartition was similar for both groups according to the Student's test and as for the balance rating with the Mann and Whitney test (Table 2). Half of the patients of each group needed a cane while walking. Further, 20 healthy volunteers (7 men and 13 women) with a mean age of 23.9 ± 3.09 years, including 15 right handers and 5 left handers participated in the study.

Spatial frame of reference

The healthy volunteers obtained a mean for LBA

$[0.24^\circ \pm 1.34^\circ]$, for SVV $[-0.97^\circ \pm 1.48^\circ]$, and for SSA $[-0.15^\circ \pm 2.37^\circ]$ when the test was performed with the right hand and $[-1.50^\circ \pm 4.28^\circ]$ when the test was performed with the left hand. We arbitrarily selected the threshold of normality as—average healthy subjects ± 2 standard deviations, i.e., for the LBA $[-2.44^\circ; 2.92^\circ]$, for the SSA $[-4.89^\circ; 4.59^\circ]$, and for SVV $[-3.93^\circ; 1.99^\circ]$. Despite the fact that our healthy subjects are not matched in age with

(156)

Table 1 Clinical characteristics of the patients

Partici- -pants	Lesion side/dela- ystoke	Sex/age	Cane	Lateral -ity	Etiol- ogy	VSN (/4)	Hemia- nopia	Motric- ity (/100)	Sensi- tivity (%)	SCP (/6)	WBA (%)	LBA (°)	SD (°)	SSA (°)	SD (°)	SW (°)	SD (°)	BBS	TUG (s)
P1	RBD/4.2	M/69	0	RH	I	2/4	-	73	6	0	30.6	2.35	3.5	-6.5	2	1.55	1.8	47	19.9
P2	RBD/2.7	M/62	1	RH	H	1/4	-	70	1	0	38.7	-2.3	2.04	4.5	2.3	-2	2.99	47	48.41
P3	RBD/2.1	M/41	0	RH	H	0/4	-	76	3	0	43.15	-1.9	2.4	1.9	4.45	4.7	3.52	47	13.13
P4	RBD/14.4	F/60	0	RH	H	0/4	-	54	6	0	45.225	1.35	1.49	-2.55	2.47	2.7	2.2	48	19.18
P5	RBD/3.1	M/78	1	RH	I	0/4	-	84	5	0	44.9	1.75	2.51	9	1.05	1.1	1.52	52	11.53
P6	RBD/3.6	M/48	0	RH	I	0/4	-	78	6	0	38.175	0.4	1.19	-4.4	2.24	4.6	3.2	51	11.19
P7	RBD/7	F/69	1	RH	H	2/4	-	59	2.5	0.5	25.075	-4.9	3.2	-7.7	3.8	1.5	3.86	26	62.5
P8	RBD/4.5	M/45	1	LH	I	1/4	-	60	2	0	43.2	-2.5	2.6	1.6	2.37	1	3.2	48	20.87
P9	RBD/4.9	M/49	1	RH	I	2/4	-	59	6	1	19	-4	2.7	3.1	3.9	-2.2	2.2	25	50.47
P10	RBD/12.3	M/72	0	RH	H	1/4	-	78	2.5	0	33	-1.9	1.9	-2.2	2.8	-0.38	4	46	20.37
P11	RBD/1	M/75	0	RH	I	0/4	-	92	5.5	0	46.3	0.05	2.51	-4.8	2.14	-1.6	3.9	49	11.32
P12	RBD/1.7	M/58	1	RH	I	2/4	-	45	4	0	32	-1.3	2.16	2.4	2.8	-0.76	3.27	41	26.65
P13	RBD/2.3	M/62	0	RH	H	0/4	-	91	6	0	28.8	0.55	1.09	-0.3	1.88	-0.41	3.1	46	19.91
P14	RBD/6.7	M/71	1	RH	I	0/4	-	91	4.5	0	26.72	-1.4	2.62	-4.45	2.38	-0.21	3.68	49	18.72
P15	RBD/12.4	M/62	0	RH	H	0/4	-	60	5.5	0	34.42	-1.1	3.45	-0.75	3.04	2.01	4.14	45	13.28
P1	LBD/3.1	M/51	1	RH	I	1/4	-	53	6	0	29.5	-0.4	1.07	5.5	1.7	2.1	3.54	40	25.69
P2	LBD/4.1	M/60	0	RH	H	0/4	-	81	4.5	0	41	-0.6	0.9	1.8	2.3	1.66	2.09	48	21.22
P3	LBD/4.9	M/72	1	RH	I	2/4	-	64	5.5	0	37.8	-1.4	2.03	4.8	3.85	-0.02	2.48	25	27.93
P4	LBD/7.2	F/69	0	RH	I	0/4	-	91	6	0	40.6	-0.95	1.58	2.35	2.05	0.62	1.97	52	12.03
P5	LBD/4.7	F/76	1	RH	I	2/4	-	53	6	0.5	31.7	1.15	1.95	7.4	1.89	0.7	2.87	25	60.02
P6	LBD/1.1	F/50	0	RH	I	0/4	-	92	6	0	38	1.15	0.85	2.95	0.76	1.87	1.91	52	9.87
P7	LBD/7.3	M/67	1	RH	I	0/4	-	92	3.5	0	40.77	-0.35	1.74	-0.75	0.75	0.82	1.1	45	18.34
P8	LBD/1.5	F/72	1	RH	I	0/4	-	59	5.5	0	37.1	0.65	2.77	2.6	1.57	-1.63	2.98	45	21.81
P9	LBD/3.1	M/51	0	RH	I	0/4	-	86	6	0	37.77	-0.9	0.93	-3.9	3.2	-1.89	1.93	51	15.12
P10	LBD/2.4	M/44	0	LH	I	0/4	-	86	6	0	43.87	-4.5	2.74	-0.55	1.7	0.93	1.13	54	10.56
P11	LBD/1.1	M/62	0	RH	I	1/4	-	76	6	0	45.02	-0.15	1.59	-0.6	2.5	0.46	1.19	51	13.69
P12	LBD/4.6	M/53	0	RH	H	0/4	-	45	1.5	0	45.5	-3.7	1.08	-2	2.62	0.11	1.81	46	19.75
P13	LBD/12.8	M/65	1	RH	H	1/4	-	76	3.5	0	38	2.25	2.13	-2.25	2.22	3.88	2.24	25	52.19
P14	LBD/1.1	M/51	1	RH	I	2/4	-	45	4.5	0	37.95	1.65	3.45	0.45	2.71	-1.81	1.81	49	14.25
P15	LBD/1.5	M/47	0	RH	I	0/4	-	67	6	0	41.27	0.75	0.79	-3.25	-1.18	-0.49	0.89	54	8.82

BBS Berg Balance Scale, H hemorrhagic, I ischemia, LBA longitudinal body axis, LH left handed, RH right handed, SCP Scale for Contraversive Pushing, SD standard deviation, SSA subjective straight ahead, SVV subjective visual vertical, TUG time up and go, VSN visuo-spatial neglect, WBA weight-bearing asymmetry

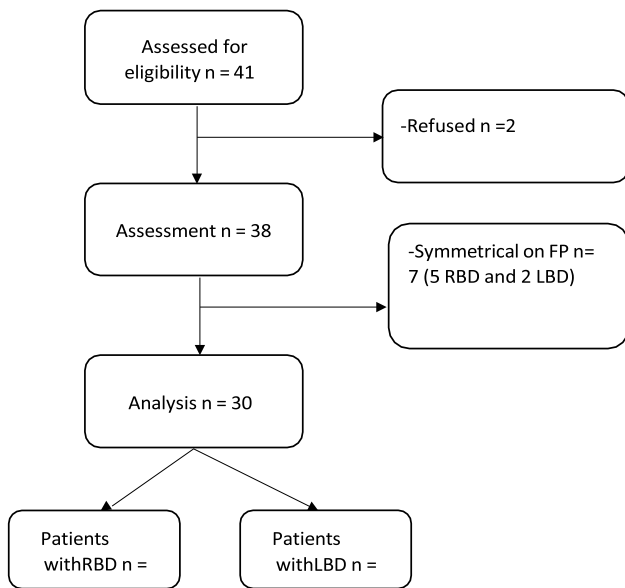


Fig. 1 Flowchart of participants (RBD right brain damage, LBD left brain damage, FP force platform)

Table 2 Clinical data, patients with right brain damage (RBD) and patients with left brain damage (LBD)

	RBD (15)	LBD (15)	<i>p</i>
Characteristics			
Male/female	13/2	11/4	-
Ischemic/hemorrhagic	8/7	12/3	-
Age (year)	61 +/- 11	59 +/- 10	0.45
Delay post-stroke (year)	5.5 +/- 4	4.25 +/- 3.1	0.41
Severity of stroke			
Motricity (/100)	71 +/- 14	71 +/- 17	0.96
Sensivity (/6)	4.3 +/- 1.7	5.1 +/- 1.3	0.2
Visuo-spatial neglect/hemianopia	0/0	0/0	-
Assessment of postural asymmetry			
Weight-bearing asymmetry(%)	35 +/- 8	39 +/- 4	0.13
Assessment spatial cognition			
Longitudinal body axis (°)	-1.3 +/- 1.9	-0.35 +/- 1.8	0.1
Subjective straight ahead (°) +/- 3	0.2	0.7 +/- 4.6	0.9
Subjective visual vertical (°) +/- 1.5	0.6	0.8 +/- 2.2	0.4

our patients, these results are consistent with those of the literature (Barra et al. 2007; Chokron et al. 2004; Pérennou et al. 2008).

Using the Student's test, no difference was found between the patients with RBD and LBD on the evaluations of the space representation when taking the mean (LBA $p = 0.1$; SSA $p = 0.2$; SVV $p = 0.6$), the AbM (LBA $p = 0.1$; SSA $p = 0.2$; SVV $p = 0.3$), and the SD (SSA $p = 0.07$) excepted for SD (LBA $p = 0.02$ and SVV $p = 0.0006$). However, when examining the individual results, even though most patients were within the normal range, some patients, and particularly those with RBD showed an abnormal shift (for LBA 3 out of 15 patients with RBD versus 2 out of 15 patients with LBD, and for SVV 3 out of 15 patients with RBD versus 1 out of 15 patients with LBD). Therefore, when individually observing the spatial cognition, 66% of RBD patients deviated on at least one of the tests of spatial cognition compared to 40% of the LBD patients.

No relation was found between either LBA, SSA, or SVV (M_LBA/M_SSA: $r = 0.23$; $p = 0.2$; M_LBA/M_SVV: $r = 0.14$; $p = 0.4$; M_SSA/M_SVV: $r = -0.09$; $p = 0.6$); (AbM_LBA/AbM_SSA: $r = 0.07$; $p = 0.6$; AbM_LBA/AbM_SVV: $r = 0.01$; $p = 0.9$; AbM_SSA/AbM_SVV: $r = 0.07$; $p = 0.6$); (SD_LBA/SD_SSA: $r = 0.35$; $p = 0.1$; SD_LBA/SD_SVV: $r = 0.27$; $p = 0.1$) expected for SD_SSA/SD_SVV: $r = 0.41$; $p = 0.02$.

By use of the MANOVA, no relation was found between WBA/SSA ($p = 0.58$); and WBA/SVV ($p = 0.47$) when considering both patients with RBD and LBD. Weight-bearing asymmetry was found to be related to LBA when considering the whole group of patients ($p = 0.03$). However, this relation was dependent on the group of patients ($p = 0.0006$). The partial correlation confirmed the strong relation between WBA/LBA in the patients with RBD ($r = 0.77$; $p = 0.02$) (Fig. 2), but not in the LBD ($r = -0.46$; $p = 0.1$). Moreover, by use of the multivariate analysis of variance (MANOVA) in percentage, when taking the whole group of patients into account, LBA represented 16% of WBA ($R^2 = 16.24$; $p = 0.03$) and 58.26% when considering only the patients with RBD ($R^2 = 58.26$; $p = 0.01$) which was not significant in the group of patients with LBD ($p = 0.12$).

Discussion

Balance rating

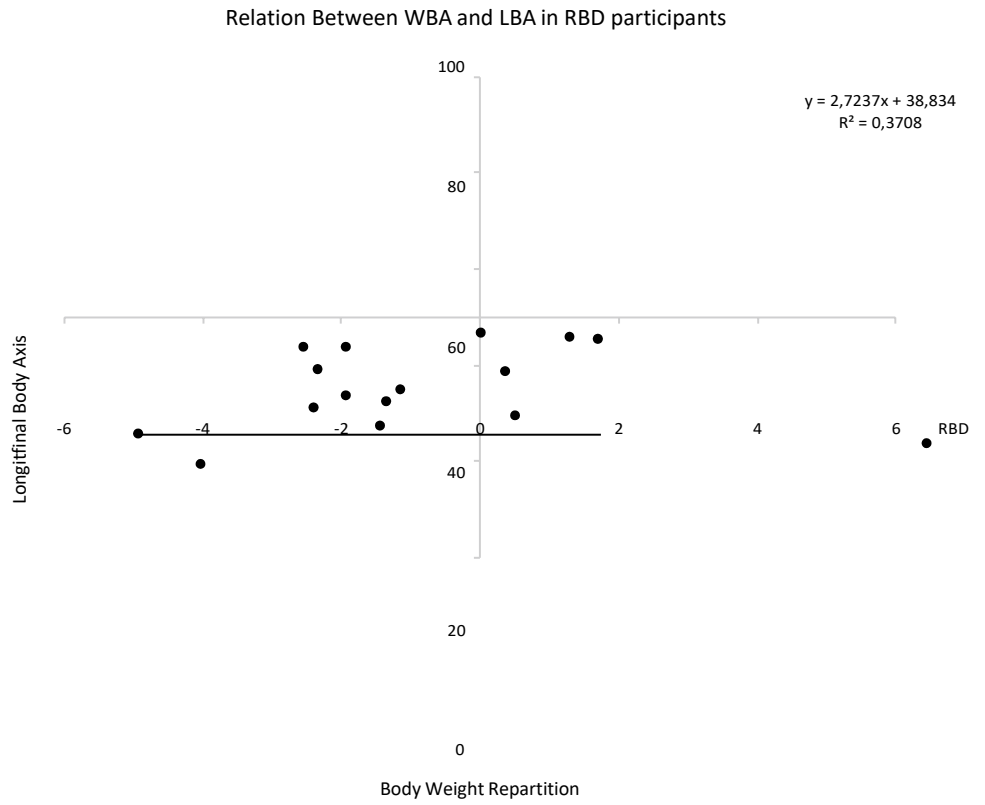
Time up and go (s)	24 +/- 16	22 +/- 15	0.71
Berg Balance Scale (/56)	44 +/- 8	44 +/- 10	0.66

Data are presented with mean (\pm standard deviation)

The main objective of this study was to determine whether the asymmetric posture of patient with RBD and LBD was related to a poor perception of body representation in space. The assumption was that the disturbance of the body perception in space explains at least in part, the postural asymmetry of brain damage patients and that this relation was more pronounced in the patients with RBD.

In this study, different aspects of the body representation in space were taken into consideration, both those with egocentric and allocentric space representation. Overall, 11 several months or years from stroke, there was still space misperception at the stage of recovery, especially in the RBD group (approximately 2 out of 3 patients) but also

Fig. 2 Relation between weight-bearing asymmetry (WBA) and longitudinal body axis (LBA) in patients with right brain damage(RBD)



for the LBD group (approximately 40% of patients). These results are in line with other studies which assume that the location of the representation of the body in space is in the right cerebral hemisphere (Halligan et al. 2003; Rousseaux et al. 2014; Saj et al. 2014). Regarding the SVV, it is known that this disturbance may last longer in time after a stroke (Bonan et al. 2007). This result is a novelty in the egocentric space representation (LBA and SSA) and which was extensively studied in early stroke (Barra et al. 2009) rather than at a chronic stage (Hugues et al. 2015; Rossit et al. 2017). Patients with RBD had less weight on their paretic limb ($35\% \pm 8$) compared to patients with LBD ($39\% \pm 4$). However, compared to the literature (Bonan et al. 2007; Pérennou 2005; Rode et al. 1997), this difference was not significant due to a possible insufficient number of patients for statistical power to have a significant effect. Likewise, even if 66% of RBD patients deviated on at least one of the tests of spatial cognition compared to 40% of the LBD patients, no difference was revealed in the statistics concerning the spatial cognition between the two groups.

To meet our main objective related to the relationship between the postural asymmetry and the perception of the space representation in chronic stroke, a relation was found only between WBA and LBA in our group of patients with RBD. Jointly with the results of Barra et al. (2009) who also found the same relation but in early stroke, it seems that the relation between WBA and LBA is persistent whatever the delay after a stroke. This relation is in favor that at least a part of the body weight asymmetry comes from a body misperception in space. Using a multivariate analysis of variance, we did find that LBA represent 16% of WBA. Unlike Barra et al., we analyzed the influence of the side of stroke and found that the relation between postural asymmetry and LBA depended on the side of stroke with a more pronounced relation in the RBD group. Therefore, in patients with RBD, LBA represent 58.26% of WBA. Our result reinforces this hypothesis of spatial body misperception for the reason that the right hemisphere is thought to be the place of spatial elaboration (Barra et al. 2010; Bonan et al. 2013; Halligan et al. 2003; Rousseaux et al. 2014). No relation was found between either WBA or the SSA or the SVV. This quite certainly

reinforces the fact that postural asymmetry, could partly be due, more to a disorder of the egocentric personal representation in space (LBA), than to an egocentric extra-personal representation of space (SSA) or to an allocentric representation of space (SVV), at least for chronic patients with a RBD.

Despite the fact that the LBA and the SSA are both two evaluations of the egocentric space representation, to our knowledge, their relationship has not yet been studied. Thus, no relationship was found here between these two evaluations. Our results are not surprising, as one corresponds to the egocentric representation in personal space (LBA), while the other relates to the egocentric representation in extra-personal space (SSA) (Moulinet et al. 2016; Hugues et al. 2015). Moreover, this result is not so original as in lesioned study, dissociated personal and extra-personal neglect were repeatedly found suggesting a different central processing (Committeri et al. 2007; Guariglia and Antonucci 1992). In addition, these two tests are not performed in the same postural position (sitting versus supine). Hence this supports our main result, in that, knowing the relation between WBA and LBA is significant, as they are both in the same personal space. As regards the SVV, no relation was found between the allocentric (SVV) and the egocentric (LBA, SSA) space representation. Some authors (Barra et al. 2009; Rousseaux et al. 2013) did, however, find a relationship and their results are indeed not astonishing as all disturbances of the space representation could coexist without being linked. Because other asymmetrical postural behaviors seem to be related to the verticality misperceptions like body lateropulsion, it would appear that different asymmetric postural behavior exist. Body lateropulsion could be related to the SVV misperception (Pérennou et al. 2008) and asymmetry of body weight repartition would be more linked to the egocentric personal space misrepresentation. Indeed body lateropulsion is tilted toward the hemiparetic side while body weight asymmetry is tilted toward contralateral side.

In our study, we should, however, point out a few limitations, namely, the large range of delay post-stroke, despite the fact that all the patients are chronic. In the same vein, due to the large range and even though the patients were examined by way of a medical consultation to

single out the possibility of any new functional deficits, patients could have gone through new cerebrovascular accidents. Therefore, CT-scan or MRI examinations should have been performed at the inclusion to firmly verify that all included patients had a unique and unilateral brain damage. Despite the fact that our results were consistent with those of the literature (Barra et al. 2007; Chokron et al. 2004; Pérennou et al. 2008), another limitation within our study was that our healthy subjects were not matched in age with our patients. Then, if all our patients were without neglect, confirmed through our battery of visuo-spatial neglect tests (3 positive tests out of 4), some of our patients (7 out of 30) had 2 out of 4 positive tests. This result reflects an element of doubt and may be questionable, not allowing us to totally consider them absolutely without neglect. For further future studies and to ensure that patients have no neglect, the entire group should not have any positive tests of the four carried out. Finally, the entire assessment was carried out in the same order which could have also been handled in a randomly manner so as to avoid exhaustion in the repetition.

To conclude, disturbances in the perception of the longitudinal body axis and its relationship with the balance disorders have already been pointed out. Our study goes a step further and confirms this relationship also at the chronic stage. We also disclose that the relation is dependent on the location of the stroke. In all our findings are in favor that the weight-bearing asymmetry of patients after a stroke is almost in part due to a disorder of the egocentric spatial representation, whereby the causal relationship still remains to be established. Moreover, our results show the absence of relation found between WBA and SSA and between WBA and SVV and when considering the results of other studies (Pérennou et al. 2008) who established a relation between body lateropulsion and disturbance in verticality perception, it would clearly appear that different mechanisms of asymmetrical postural behavior exist; body lateropulsion and asymmetry of body weight repartition. Further studies are therefore necessary so as to investigate in depth these different asymmetrical postural behaviors and their mechanism.

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Appendix 2 - Postural asymmetry and hemiplegia post-stroke: a systematic review and meta-analysis.

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Gait and Posture , proof reviewing in sept 2021

Evolution and factors related to body weight distribution and increased body sway in post-stroke hemiplegia: a systematic review and meta-analysis

Background : Weight-Bearing Asymmetry (WBA) and Increased Body Sway (IBS) are frequently observed among post-stroke patients in static standing position on a force platform. **Research Questions** : This systematic review and meta-analysis is aimed first at describing them according to the time-lapse post-stroke and second at studying their relation with the characteristics of the hemiplegia, balance and gait functions. **Methods**: Following the PRISMA guidelines, a systematic review was performed using the databases MEDLINE, EMBASE, Cochrane library, Web of Science and PEDRO for articles published before January 2020. **Results**: 200 articles in the standing position with poor methodology quality were included for the description of WBA and IBS. Both were found at all stages and significantly more marked at the acute stage rather than at the sub-acute stage (respectively for WBA 32.0% and 41.5% of body weight on the paretic leg). No statistical difference was found between the right-hemisphere stroke and the left-hemisphere stroke on their weight on the paretic limb, even though WBA was slightly more important in the right-hemisphere stroke (40.8% versus 43.2%). Identical results were found for IBS. The second meta-analysis (34 articles) showed that WBA was moderately related to spatial cognition ($r=0.34;p=0.03$) and motor weakness ($r=-0.51;p<0.001$) rather than hypoesthesia ($p=0.19$). IBS was neither found to be related to any characteristics of hemiplegia nor to WBA. **Significance** : WBA and IBS are present at any stages after stroke but they are not related to the same characteristics of stroke and thus suggesting that they probably stem from two separate mechanisms. However, the small number of articles and the high heterogeneity of the results reached by this meta-analysis suggest that these results should be taken into consideration with caution. Good quality studies with larger samples should be conducted so as to confirm these results.

Key words

Weight-Bearing Asymmetry, Body Sway, Stroke, Hemiplegia, Review

Highlights

- WBA and IBS were found at the early stages and still present at the chronic stage
- WBA was more important in right hemisphere stroke but not significant
- WBA was moderately related to motor weakness and spatial cognition
- IBS was neither found to be related to any characteristics of hemiplegia nor to WBA
- WBA and IBS probably stem from two separate mechanisms

1. Introduction

After a stroke, postural imbalance is an important issue, as it is associated with a greater risk of falls and a factor of loss of autonomy [1]. Postural imbalance in standing position is first characterized by an insufficient weight on the paretic leg (weight-bearing asymmetry WBA) and a shift of the position of the center of pressure in the medio-lateral plane (CoP ML) towards the non-paretic side of the body [2-4]. Genthon *et al.* [3] found these two measures, WBA and the position of CoP ML, to be strongly related ($r=0.97$; $p<0.001$), and these authors calculated that a shift of the position of CoP of 10 mm in the medio-lateral plane corresponded to a 5% increase in body weight towards that side. Postural imbalance after a stroke can also be characterized by an increased body sway (IBS) resulting in an increase in area or velocity sways [5,6]. To date, there have been some follow-up studies in the literature that take into account either WBA or IBS among stroke patients [7-11]. However, due to their differences in length of follow-up and the fact that they were instated at different post-stroke stages, it is interesting to pool the data from the literature in order to describe both WBA and IBS according to the different stages in stroke recovery.

Besides few reviews on the subject [12-15], the determinants of WBA and IBS after a stroke still remain unanswered. In order to better understand the mechanism underlying both WBA and IBS, the different factors related to them need to be investigated. Therefore, the question of the relationship between WBA and IBS and the characteristics of hemiplegia, balance and gait functions are of major interest. The objectives of this systematic review and meta-analysis were 1) to describe WBA and IBS according to the time-lapse post-stroke and 2) to map out the different factors related to WBA and IBS. The hypothesis is that these two parameters remains perturbed at distance from stroke but that they relate to separate factors.

2. Method

2.1 Eligibility criteria

This review followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [16] and was registered on the international prospective register of systematic reviews PROSPERO ([CRD42018083338](https://www.crd42018083338)). Inclusion criteria regarding the population included studies with only subjects over 18 years of age with a stroke diagnosis. Patients with an orthopaedic, rheumatologic, or visual history, and/or a neurological disorder associated with a stroke diagnosis were excluded. The studies were eligible if they include either an assessment of WBA or IBS in static seated and/or standing positions at rest. In case of studies which evaluated the effect of an intervention on the variables of interest, and in order to avoid the effect of the intervention, then only the assessment of WBA or IBS prior to the intervention were extracted. Studies focusing on the assessment of WBA or IBS during walking or transfer were excluded. Consequently, WBA expressed in percentage of body weight on the paretic side irrespective of the time-lapse since the stroke as well as the other posturography parameters were considered. A shift of the position of CoP in the medio-lateral plane (CoP ML) expressed in mm was included while an expression of the CoP ML in length, maximum or minimum amplitude or by way of calculation of the root mean square (RMS) were not considered. IBS expressed by area sway (mm^2) and velocity sway in the medio-lateral plane (mm/s) were included. A first meta-

analysis was performed to describe the evolution of these parameters according to the different stages of stroke (acute, sub-acute and chronic) [17]. Thereafter a second meta-analysis was carried out to calculate the correlation across these posturography parameters, characteristics of the hemiplegia, balance and gait functions. The studied characteristics of hemiplegia were: age, time post-stroke, side of stroke, hemi-spatial neglect, spasticity, hypoesthesia, motor weakness, spatial cognition (subjective visual vertical (SVV), subjective straight ahead (SSA), longitudinal body axis (LBA) and balance abilities or gait functions).

2.2 Search strategy and data extraction

This systematic search, which was first validated by a librarian, was performed with the keywords presented in Table 1 by using the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), PEDRO and Web of Science. A manual search was also carried out for unpublished studies on Google Scholar, ClinicalTrials.gov and EUCTR. After having eliminated all duplications, an independent examination of the remaining studies was performed by two researchers (KJ and TL) based first on the titles and then on the abstracts for eligible studies that measured WBA in percentage (and CoP in ML) or IBS among stroke patients. Thereafter the full-texts were screened. In the event of a divergence between them over the eligibility of any particular study, the disparity was subsequently resolved by way of a discussion between two other researchers (SL and IB). All study designs were considered, with the exception of reviews and meta-analyses. Lastly, only studies published in either French or English up to January 2020 were integrated in this review of literature. Authors were contacted when the articles or data were not available. For each eligible study, valid information was extracted on the basis of the following criteria: a) the characteristics of the study: authors, year and type of design; b) the characteristics of the trial participants: age, number of subjects included in the analysis and data analyzed (time since stroke, side of the lesion); c) the outcome measures, as mentioned above (section 2.1); e) the correlation between WBA/IBS and characteristics of the hemiplegia, balance and gait functions.

2.3 Risk of bias (quality) assessment

The studies included were actually used as observational studies to assess WBA and IBS across time. The methodological quality of the studies was measured using the modified version of the Downs and Black Checklist [18] which is an appropriate tool for all observational studies whether they are randomized or non-randomized studies. The studies were classified according to scores ranging from 0 to 28 with a score of 20-26 considered as excellent, 20-25 as good, 15-19 fair and <14 as poor [18]. The methodological quality of the studies was assessed independently by two researchers (KJ and SL) and consensus was reached through discussions with two other researchers (TL and IB) in case of disagreement.

2.4 Strategy for data synthesis

The approach used for the data synthesis was to describe WBA and IBS after a stroke in the literature and then to map out the different factors related to these parameters. To this end, a random effects pooling model was used on the different parameters of posturography. In the first place, a subgroup meta-analysis relative to the time post-stroke (acute, sub-acute, and chronic) and relative to the lesion side (right and left) were performed. Herein for the second subgroup, only the articles comparing WBA and IBS relating to the lesion side were included. In case of a variable with a single study, no statistical comparison was made. Thereafter, we extracted correlations between WBA or IBS over the following factors: time post-stroke, age, side of stroke, neglect, spasticity, motor weakness, hypoesthesia, spatial cognition (SVV, SSA, LBA), balance and gait. As WBA and CoP ML were found to be strongly related [3], this data was pooled together. WBA or IBS quantified by the area and velocity sways, depending on the stage of the stroke, the side of the lesion and correlation coefficient values, are displayed with 95% confidence intervals. Heterogeneity was assessed using the I^2 statistic. The correlation coefficient (r) was defined as <0.25 weak relationship, $0.25<0.50$ fair, $0.50<0.75$ moderate to strong, and >0.75 strong [20]. Statistical analysis was performed using RStudio v. 1.3.959 statistical software and the “meta” package. [21].

3. Results

3.1 Studies included

This systematic search identified 22 448 articles of which 39 references were added thereafter by way of a manual search process. Subsequently, only 1536 articles met the eligibility criteria and were requested for full-text evaluation. Only 211 articles were ultimately included in this review (Fig. 1). These articles were published between 1983 and 2020 (Appendix A). As regards to the assessment methodology for WBA or IBS, 200 of the studies were carried out in the standing position, while 10 were conducted in the sitting position and one in a supine position. Due to the paucity of studies in sitting position, these were excluded from the analyses. The results thus include only articles with measures in the standing position. Regarding the methodological quality of the studies included in this review, the average score was 14.5/28 corresponding to a poor quality, with the lowest score of 4/28 and the highest of 25/28 (Appendix B).

3.2 Patients

Concerning the participants, a total of 5975 [min=1; max=359] were included (Table 2) of which a total of 2508 with a right brain damage (RBD) and 2649 with a left-brain damage (LBD). Concerning the age and the time post-stroke, studies had an average age of 59.6 (SD of average ages 6.6) years and an average of time post-stroke of 112 (SD of average ages 127) weeks. Only 99 stroke survivors were in the acute phase (before the 14th day after stroke), 2057 in the sub-acute phase (between day 14 and 6 months post-stroke) and 3438 in the chronic stage (after 6 months post-stroke) [17,22].10 articles (n=201) did not provide information on the stage post-stroke (Table 2).

3.3 WBA and IBS according to the time-lapse post-stroke and lesion side

By pooling in the first meta-analysis, the studies that were performed in the acute stage illustrated a WBA of 32.0% (95%CI [30.2; 33.8] $I^2= 99.9\%$ [99.9%; 99.9%] (3 articles, fair methodological quality 18/28)), the sub-acute stage of 41.5% (95%CI [39.6; 43.3] $I^2= 96.5\%$ [95.8%; 97.1%] (25 articles poor methodological quality 14.5/28) and the chronic stage of 41.0% (95%CI [39.8; 42.2] $I^2= 95.7\%$ [95%; 96.3%] (39 articles poor methodological quality 14.9/28). Statistical difference was observed only between the acute and sub-acute stage for WBA ($p<0.0001$)(Table 3). Additional data on IBS are set out in Table 3.

Regarding the lesion side (Table 4), 12 articles provided differences between patients with RBD and LBD with fair methodological quality (16.3/28). Patients with RBD were found to have 40.8% of their body weight on their paretic leg (95%CI [32.9; 48.6] $I^2 = 94.0\%$ [89.6%; 96.6%]) compared to 43.2% (95%CI [39.8; 46.5] $I^2 = 87.2\%$ [74.5%; 93.6%]) for patients with LBD without any statistical difference ($p=0.58$). Additional data on IBS are set out in Table 4.

3.4 Factors related to WBA and IBS

Out of the 200 articles reviewed, 34 articles calculated correlations and therefore were included in the second meta-analysis (Appendix C) with a score of methodological quality of 14.4/28 corresponding to poor quality. Among these 34 articles, a total of 89 correlations were extracted, 50 (56%) of the correlations were found with only one reference and therefore no random effects model could be used. All results are presented in Appendix C. For those without random effects model, the review revealed significant correlations between WBA and time post-stroke ($r=-0.39$ $p=0.01$; 1 article), spasticity ($r=-0.42$ $p=0.009$; 1 article), and balance (Postural Assessment Scale for Stroke (PASS) ($r=0.56$ $p=0.01$, 1 article) and the Berg Balance Scale (BBS) ($r=0.74$ $p=0.04$; 1 article)). For the correlations pooled in the meta-analysis, significant correlations were found between WBA and motor weakness ($r=-0.51$ 95%CI[-0.67; -0.31] $p<0.001$ $I^2= 23\%$ [0.0%; 81.8%] 5 articles), hemi-spatial neglect ($r=-0.37$ 95%CI[-0.53; -0.20] $p<0.001$; $I^2=20\%$ [0.0%; 85.4%], 3 articles), spatial cognition (SVV ($r=0.34$ 95%CI[0.03; 0.68] $p=0.03$; $I^2=33\%$ [0.0%; 93.0%], 3 articles), LBA ($r=0.45$ 95%CI [0.16; 0.63] $p=0.002$; $I^2=0.0\%$, 2 articles)) (Fig.2), but not between WBA and hypoesthesia ($p=0.19$; 3 articles).

Concerning the correlations with IBS, none was found with the characteristics of hemiplegia excepted with the time post-stroke ($r=-0.37$ 95%CI[-0.63; -0.11] $p=0.001$; $I^2= 0.0\%$ 2 articles) (Appendix C). Significant correlations were found between sway velocity and BBS ($r= -0.35$ 95%CI [-0.55; -0.11] $p=0.005$; $I^2= 56\%$ [2.6%; 80.0%], 8 articles). WBA was not found to be related to IBS (WBA/sway velocity ($r=-0.41$ [-0.84; 0.42] 95%CI $I^2= 78.4\%$ [6.3%; 95.0%] $p=0.33$ 2 articles), WBA/sway area ($r=0.28$; $p=0.12$ 1 article)).

4. Discussion

The first objective of this systematic review and meta-analysis was to describe body weight distribution (WBA) and increased body sway (IBS) evaluated on a force platform at different stages of stroke recovery. The first meta-analysis was rather large and included 200 articles in the standing position. It

highlighted patients with both WBA and IBS in the early stages and still persistent in the chronic stage. While this meta-analysis was based on a small number of articles in the acute stage (WBA 3 articles and IBS 1 article), our results are supported by a large number of articles concerning the sub-acute stage (WBA 25 articles and IBS 54 articles), and the chronic stage (WBA 39 articles and IBS 163 articles). WBA and IBS were found significantly more marked at the acute stage rather than the sub-acute stage. Despite this finding, there was great heterogeneity and only a few articles handled the acute stage (2% of the articles extracted). This inconsistency can be viewed as problematic and therefore these results should be considered with caution. That said although, these observations are in accordance with several longitudinal studies [7-11], these studies did report that in the acute stage, patients were found with less weight on their paretic leg and increased body sway and that in the first few months a rapid regression of both was observed [7-11]. However in the sub-acute and chronic stages, WBA and IBS were nonetheless still present [8,11,23]. However, this alteration in weight distribution or increased body sway cannot be generalized to the entire stroke population. In fact, and it is important to note, these studies only included patients undergoing rehabilitation. Further, those stroke patients who recovered rapidly and who were not followed up in rehabilitation units were not evaluated [12,24].

Concerning the side of the lesion, both right (RBD) and left-brain damage (LBD) patients exhibited a tendency to put less weight on the paretic leg and an increased shift of the center of pressure towards the non-paretic leg with a tendency which was more pronounced for patients with a RBD (WBA RBD: 40.8%95%CI [32.9; 48.6] versus LBD: 43.2%95%CI [39.8; 46.5]; CoP ML RBD: 25.9 mm 95%CI [15.7; 36.1] versus LBD: 17.3 mm 95%CI [12; 22.6]). Yet, no statistical difference was found between the two groups. For IBS, as for WBA no statistical difference was found although patients with RBD had a greater sway area and the difference between RBD and LBD on velocity sway was less pronounced. Although there was no significant difference revealed by this meta-analysis, the slight evidence of the lesion side affecting the variables are indeed in agreement with the literature confirming a higher postural imbalance for the patients with RBD [25-27] which may explain the longer length of stay for these patients in the rehabilitation departments [28,29]. A possible explanation for this absence of significant difference can be related to the small number of studies and their quality when comparing these two groups i.e. only 6% of the articles extracted from the review with fair methodological quality. Further, due to the small numbers of articles included when pooling, no difference was taken into consideration regarding the time lapse post-stroke, which could also explain the marked heterogeneity observed in this meta-analysis. Patients included were either at a sub-acute or chronic stage. It must be pointed out once again, for the purpose of consistency and reliable results, it would be interesting for future studies to compare the time lapse post-stroke and in particular to investigate this with those patients in the acute phase, a comparison which has to date not been undertaken.

The second meta-analysis included 34 articles where more than half of the correlations were reported in only one reference. Considering this information along with the poor methodological quality, the obtained results are to be taken with caution and need to be confirmed through further studies. This meta-analysis found moderate but significant relationships between WBA and the characteristics of hemiplegia, such as motor weakness ($r=-0.51$ $p<0.001$) and spatial cognition (neglect $r=-0.37$ $p<0.001$, SVV: $r=0.34$ $p=0.03$; LBA: $r=0.45$ $p=0.002$). Indeed, patients with more marked leg motor impairment bear less weight on their paretic leg. That said the review did however reveal a correlation between WBA and spasticity, but this relation was not pooled in the meta-analysis as it was supported by only one article. This result should be confirmed but yet is not so surprising as spasticity affects the ability to modulate motor activity in the paretic limb in standing balance and is a factor of inter-limb weight

symmetry disturbances [30-32]. Hypoesthesia was not related to WBA ($p=0.2$) (3 articles). The absence of the relationship can partially be explained by the variability and the poor quality of the assessment implemented and the heterogeneity of the studies. But sensory disorders, in particular proprioceptive disorder, are rarely very severe and consequently their effect on balance could be moderate [33]. WBA was found to be related to spatial cognition. Although few articles studied these relationships (3 articles), the results are remarkably homogeneous. This relationship suggests that the patients with disturbed spatial cognition (neglect, altered SVV and/or LBA) bear less weight on their paretic leg. The relationship between spatial cognition disorders and WBA was previously shown to be more marked among patients with RBD than among patients with LBD [34-36]. This result suggests that WBA could be almost partly due to spatial cognition disorders, especially in patients with RBD [34,35,37,38]. Concerning the relationship between IBS and the characteristics of hemiplegia, these correlations have been less studied but neither sway velocity nor sway area were found to be correlated with motor weakness. But, the small number of articles exploring these relationships and the heterogeneity of the results reached by this meta-analysis suggest that these results should be considered with caution and do not enable conclusions to be drawn.

This review and its two meta-analysis identified a large number of articles focusing on WBA and IBS and their relationships with the characteristics of hemiplegia. But despite the considerable number of articles, several correlations were found with only one reference and for those based on a number of articles, the meta-analysis found weak relationships and large heterogeneity in the results on several points. The first explanation could be the poor quality of the studies. Indeed, the average score was 14.4/28 corresponding to poor quality. Alternatively, the weakness of the relationships and the heterogeneity of the results that were found here despite the relatively large number of subjects included in the meta-analysis could lead to suppose that the relative contribution of the factors are not the same for all the patients and that their contributions could not be stable throughout the recovery. Raising the question of the level of contribution of different factors on WBA, Genthon *et al.* [39], who studied 41 stroke patients in a subacute stage, reported that, in this population, spatial cognition was the best predictor of WBA among motor weakness, spasticity, and hypoesthesia in their model. Unfortunately, due to the marked heterogeneity of the results and the small number of articles identified with correlations, it was not possible to explore the relative contributions of each characteristic to WBA or IBS in this meta-analysis.

No relationship was found between WBA and IBS. WBA was neither found to be related to sway velocity ($p=0.33$) nor to sway area ($p=0.12$). This result tends to support the hypothesis that the underlying mechanism of weight distribution could be separated from that of body sway. These two parameters could operate independently for postural control [40]. This result of our meta-analysis is new, and not in accordance with the earlier systematic review by Kamphuis *et al.* [14] based on fewer studies. This absence of relationship between WBA and IBS is neither in favor of the hypothesis that bearing less weight on the paretic limb could be a compensation mechanism for IBS, nor that the primary cause of IBS is WBA as claimed by some authors [12,14,39]. Furthermore, this is supported by the fact that unlike WBA, neither sway velocity nor sway area were found to be correlated with motor weakness. But it is important to remain cautious about this result, as only a few studies were found and therefore this result should be confirmed in further studies.

Finally, both WBA and IBS were interestingly related to balance abilities. The relationship with the Berg Balance Scale was high for WBA ($r=0.74$, $p=0.04$) whereas weaker for IBS ($r=-0.37$, $p=0.005$). This relationship was based on many studies for IBS with little heterogeneity ($n=8$ articles) but only one for WBA and therefore these relationships remain to be confirmed. Yet, these relationships suggest that neither WBA nor IBS have an nonexclusive role in postural imbalance [12,14,39]. However, the question of the causal relationship remains to be elucidated. Therefore, even though symmetrizing weight and decreasing body sway are often major goals in rehabilitation [14,39] given these relationships, our study suggests to clinicians the advantages of working on primary deficiencies such as either motor weakness or spatial cognition instead of WBA nor IBS.

The high heterogeneity of our results is an important limitation in our meta-analysis. This high heterogeneity can be explained by several reasons such as the small number of studies which introduce a bias in the heterogeneity calculation as well as their poor quality. Indeed, only the shift of the position of the CoP ML was extracted and consequently when it was expressed in length, maximum or minimum amplitude or by way of calculation of the root mean square (RMS) it was not considered, which has subsequently reduced the number of studies included. Another possible reason is the different clinical profiles of our patients within the studies themselves (side of the lesion, time lapse post-stroke) which can partially explain the high heterogeneity. As an example, Mansfield *et al.* [23], on a large population in the chronic phase highlighted three different clinical profiles (symmetrical, asymmetrical on their healthy side and asymmetrical on their injured side). Their observation already underlines the heterogeneity within a study and can therefore explain our results. Further this review also highlighted the question of the evaluation methods of WBA and IBS which can also explain the high heterogeneity of our results. To enhance knowledge in future studies, the methodology of WBA and IBS evaluation should be clearly described on the basis of recommendations in the literature. It should be harmonized i.e. avoiding certain pitfalls. Some authors, such as Genthon *et al.* [39], suggested performing the evaluation using recordings from two separate force plates in order to measure weight under the two feet. Then several studies have advised a foot spacing of between 15 and 20 cm as an ideal parameter, with an angle of 14° between the long axes of the feet [41,42] and a duration of around 60 seconds [43]. In the case of a shorter duration, the authors suggested averaging several force platform recordings. Yet measurements of more than 60 seconds are still recommended for greater reliability [44,45]. Therefore, we strongly advise authors for their future publications to take these points into consideration and make this information and the description of their methods available. In addition to the heterogeneity reported, the small number of studies for certain variables is without doubt an important limitation of this review, particularly in the interpretation of the various results. When evaluating variables in accordance to the stroke stage, a large number of studies focused on the chronic stage compared with the acute stage and by doing this, further caution is necessary as these variables at that stage are minimal and only reported in one study. When concerning correlations, some results should also be taken with caution as they are based on a few number of studies. These limitations therefore suggest for more studies to be concluded so as to confirm these results and especially for those in the acute stage.

5. Conclusion

To sum up, this review evidenced long-lasting alterations in WBA and IBS in the post stroke phase even in the chronic stage. Indeed, with the pooling in the first meta-analysis, WBA was observed in the early

stages and was still present in the chronic stage. No statistical difference was found between patients with RBD and LBD on their weight on the paretic limb, however for those patients with RBD less weight on the paretic leg was observed, and this possibly due to the small numbers of studies and the marked heterogeneity. Identical results were found for IBS. The second meta-analysis showed that WBA was found to be moderately related to motor weakness and spatial cognition rather than hypoesthesia. Further both WBA and IBS were found to be related to balance abilities but IBS was neither found to be related to any hemiplegia characteristics nor to WBA. These results suggest that WBA and IBS probably stem from two separate mechanisms. However, the results of this systematic review are based on few articles and the results remain highly heterogeneous and consequently should be taken with caution. Therefore, these results should only be considered as exploratory and as such higher quality studies with larger sample should be conducted to confirm our finding.

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Declaration of conflict of interest

The authors declare that they have no competing interests.

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Table 1: Search strategy in PubMed

#1 posture OR equilibrium OR balance OR weight asymmetry OR lateropulsion Or pusher Or pushing OR weight-bearing asymmetry OR WBA OR body weight distribution OR weight repartition OR weight shift OR postural asymmetry OR postural imbalance OR body weight shifting OR center of pressure OR COP OR body repartition OR postural balance OR (weight AND (distribut* OR transfer*)) OR postural sway OR postural tilt OR postural shift OR postural perturbation OR postural disorders OR postural deficit OR postural trouble OR postural stability OR body sway OR upright stance OR sitting balance OR balance disorders OR balance deviation Or balance tilt

#2 stroke OR poststroke OR post-stroke OR hemipleg* OR hemipar* OR paretic OR paresis OR CVA OR cerebrovascular accidents

#3 (right OR left) AND brain AND (lesion OR damage)

#4 #2 OR #3

#5 #1 AND #4

#6 meta-analysis OR review* OR animal* OR child*

#7 #5 NOT #6

Table 2 = Description of the stroke population in the 200 articles included. Left Brain Damage (LBD), Numbers (n), Not Available (NA), Right Brain Damage (RBD).

Population characteristics	Studies (n)*	Population (n)
Total Population	200	5795
Side of lesion		
-RBD	167	2508
-LBD	161	2649
-NA	28	556
-Right and Left brain damaged	3	82
Gender		
-Male	181	3316
-Female	171	2034
-NA	19	445
Stage of stroke		
-Acute (0-14days)	3	99
-Sub-acute (14 days-6months)	55	2057
-Chronic (after 6 months)	134	3438
-NA	10	201

*The values in this column describe the quantity of studies which reported on each category. These values can not be summed up as different stages of stroke have been reported within the same article. The same applies for the other two categories.

Table 3 = Posturography parameters (Mean) depending on the time-lapse post-stroke (acute, sub-acute, chronic). Center of Pressure (CoP), Eyes closed (EC), Eyes open (EO), Medio-lateral (ML), Total (T), Velocity (Vel), Weight-bearing asymmetry (WBA).

Posturography parameters	Number_Studies	Number_Population	Mean [95%CI]	I2 (%)	Comparison (pValue)
	200				
Acute Stage (0-14days)					
*WBA EO (%)	3	99	32 [30.2; 33.8]	99.9% [99.9%; 99.9%]	
*Sway Vel EO (mm/s)	1	26	6.8 [5.2; 8.4]		
*Sway Vel EC (mm/s)	1	26	9.5 [7; 12]		
Quality methodology (I28)	18				
Sub-Acute stage (14 days-6months)					<i>Between Acute and Sub-Acute</i>
*WBA EO (%)	25	966	41.5 [39.6; 43.3]	96.5% [95.8%; 97.1%]	p < 0.0001
*WBA EC (%)	1	50	47.2 [44.7; 49.7]	0.00%	
*CoP ML EO (mm)	10	315	14.4 [11.8; 17]	99.4% [99.3%; 99.5%]	
*CoP ML EC (mm)	3	69	24.4 [10.7; 38.2]	96.2% [92.9%; 97.9%]	
*Sway Vel EO (mm/s)	14	376	19 [15.7; 22.3]	98.4% [98.1%; 98.7%]	*
*Sway Vel EC (mm/s)	8	234	18.3 [14.4; 22.2]	95.8% [94.0%; 97.1%]	*
*Sway area EO (mm2)	12	294	358.4 [296.1; 420.6]	94.9% [93.4%; 96.1%]	
*Sway area EC (mm2)	7	163	700.8 [540.3; 861.4]	96.9% [95.7%; 97.7%]	
Quality methodology (I28)	14.5				<i>Between Sub-Acute and chronic</i>
Chronic Stage (after 6 months)					
*WBA EO (%)	39	1168	41 [39.8; 42.2]	95.7% [95.0%; 96.3%]	p = 0.68
*WBA EC (%)	6	125	37.7 [35.5; 40]	55.9% [10.6%; 78.3%]	*
*CoP ML EO (mm)	14	274	15.7 [12.6; 18.9]	90.6% [86.9%; 93.2%]	p = 0.53
*CoP ML EC (mm)	9	185	16 [6.7; 25.2]	93.9% [91.2%; 95.7%]	p = 0.31
*Sway Vel EO (mm/s)	54	1409	14.6 [13.9; 15.4]	99.6% [99.5%; 99.6%]	p = 0.01
*Sway Vel EC (mm/s)	30	767	17.4 [16.1; 18.6]	99.5% [99.4%; 99.5%]	p = 0.61
*Sway area EO (mm2)	34	898	321.5 [270.8; 372.2]	99.9% [99.9%; 99.9%]	p = 0.36
*Sway area EC (mm2)	22	561	522.3 [412.4; 632.2]	99.9% [99.9%; 99.9%]	p = 0.07
Quality methodology (I28)	14.9				

*Statistical analysis was not made due to insufficient number of studies (n=1)

Table 4 = Posturography parameters (Mean) depending on the side of the lesion (right or left brain damage patients). Center of Pressure (CoP), Eyes closed (EC), Eyes Open (OE), Heterogeneity (I2), Left brain damage (LBD), Medio-lateral (ML), Right brain damage (RBD), Total (T), Velocity (Vel), Weight-bearing asymmetry (WBA).

Posturography parameters	Number_Studies	Number_Population	LBD Mean [95%CI]	I2 (%)	Number_Population	RBD mean RBD [95%CI]	I2 (%)	p Value
	12							
*WBA OE (%)	6	124	43.2 [39.8; 46.5]	87.2% [74.5%; 93.6%]	102	40.8 [32.9; 48.6]	94.0% [89.6%; 96.6%]	0.58
*WBA EC (%)	4	66	42.9 [38.7; 47.1]	83.5% [58.0%; 93.5%]	60	42 [33; 51]	94.9% [90.0%; 97.4%]	0.85
*WBA T (%)	2	31	39.5 [37.9; 41.1]	0.00%	31	34.4 [31.2; 37.7]	0.00%	0.01
*CoP ML EO (mm)	4	68	17.3 [12; 22.6]	56.3% [0.0%; 85.5%]	60	25.9 [15.7; 36.1]	72.1% [20.9%; 90.2%]	0.14
*CoP ML EC (mm)	3	50	18 [14.3; 21.8]	36.2% [0.0%; 79.6%]	43	24.2 [11.1; 37.4]	77.8% [28.3%; 93.1%]	0.37
*Sway Vel EO (mm/s)	4	46	11.8 [5.6; 17.9]	87.8% [71.1%; 94.9%]	48	12.4 [6.4; 18.4]	88.8% [74.0%; 95.2%]	0.88
*Sway Vel EC (mm/s)	1	16	28.6 [20.5; 36.7]		16	27.6 [21.8; 33.3]		*
*Sway area EO (mm2)	3	46	473.7 [80.8; 866.6]	80.6% [39.2%; 93.8%]	42	403.3 [153.1; 653.4]	77.2% [25.9%; 93.0%]	0.76
*Sway area EC (mm2)	2	32	842 [-157.2; 1841.3]	91.4% [69.8%; 97.6%]	31	785.3 [-43.8; 1614.4]	91.2% [68.7%; 97.5%]	0.93
Quality methodology (I28)	16.3							

*Statistical analysis was not made due to insufficient number of studies (n=1)

Figure 1: Selection of studies.

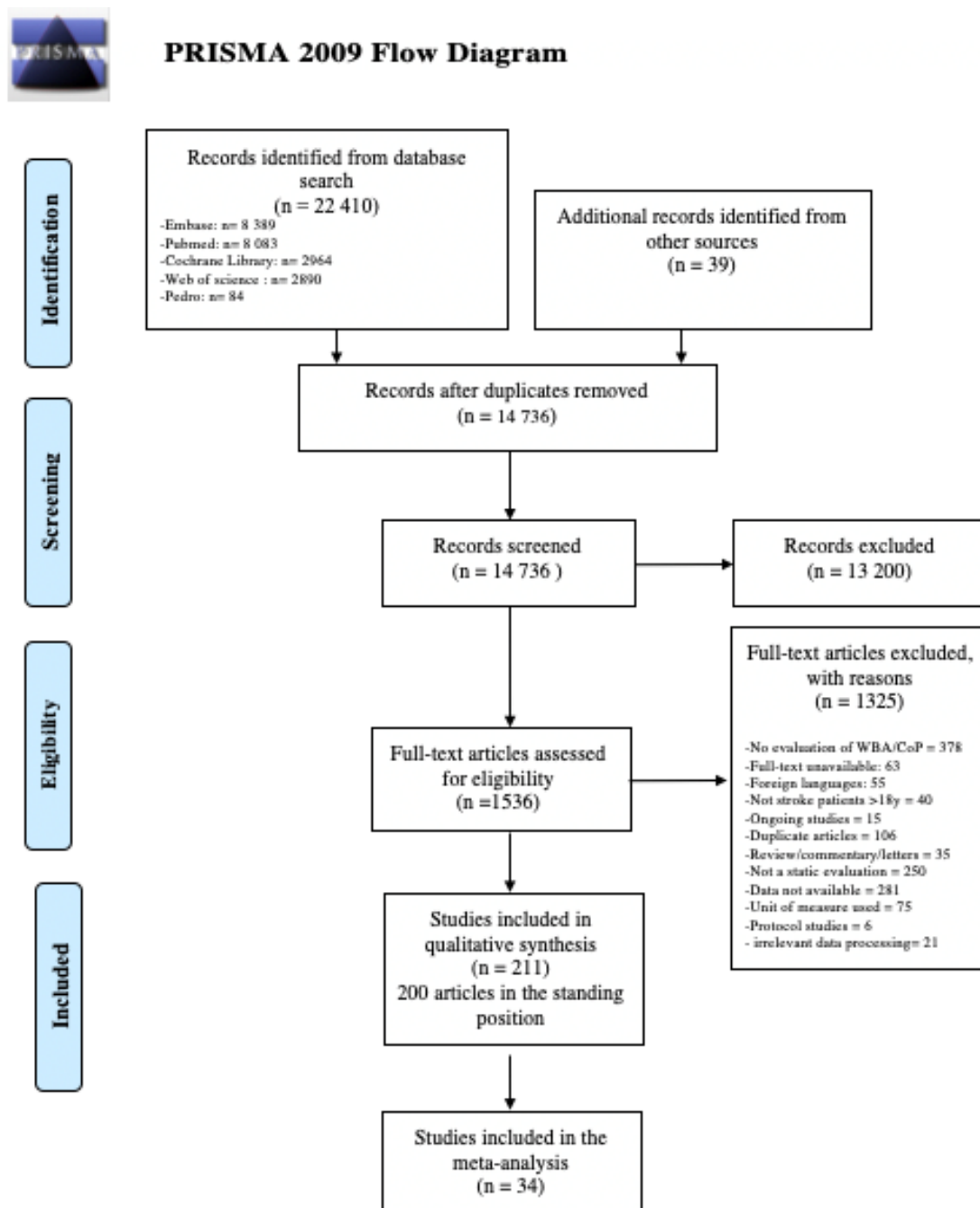
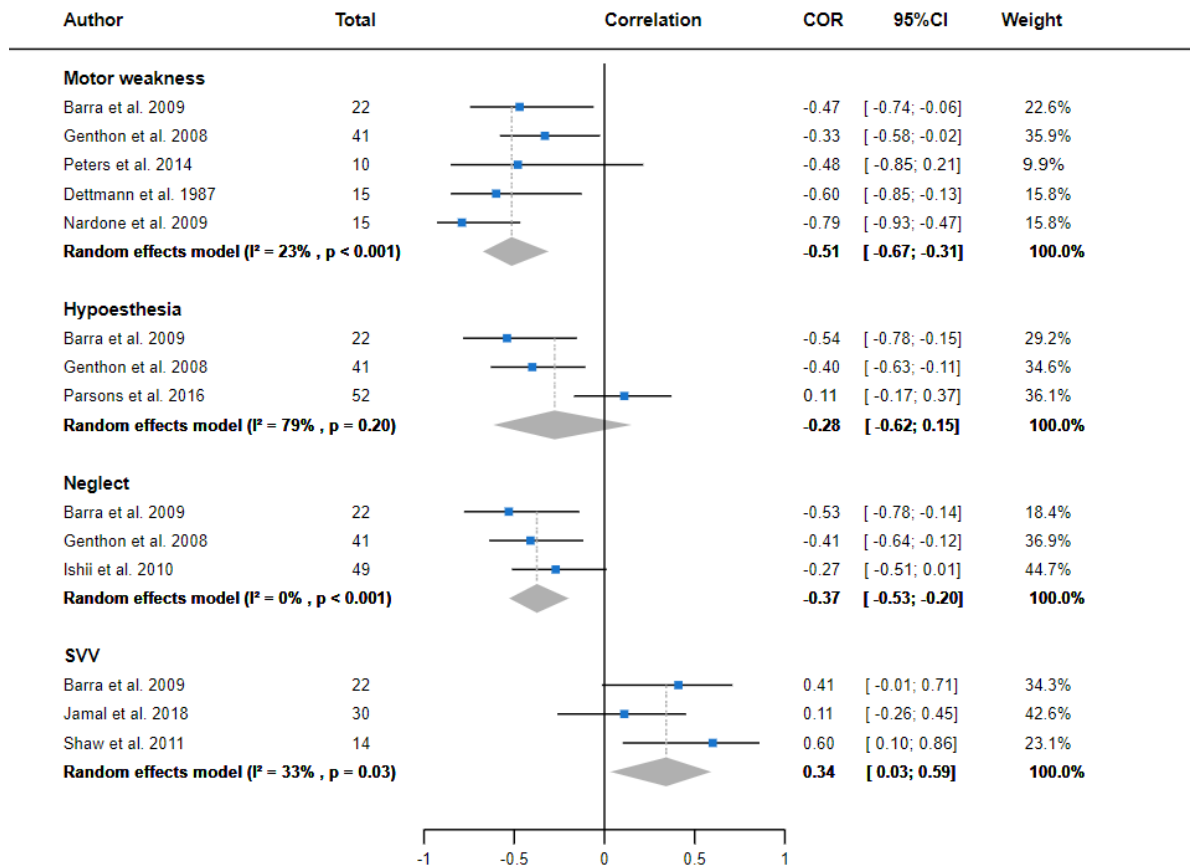


Figure 2 : Meta-analysis of correlations between Weight-bearing asymmetry (WBA) and characteristics of the hemiplegia. Longitudinal Body Axis (LBA), Subjective Visual Vertical (SVV).



Appendix 3 - Effect of sensorial stimulations on postural disturbances related to spatial cognition disorders after stroke.

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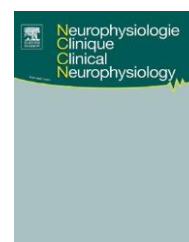
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REVIEW/MISE AU POINT

Effect of sensorial stimulations on postural disturbances related to spatial cognition disorders after stroke



Effet des simulations sensorielles sur les troubles de l'équilibre liés à des troubles de la cognition spatiale après accident vasculaire cérébral

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Summary Balance disorders related to disturbances in perception of spatial reference systems are common especially after right hemispheric stroke. Mental misrepresentation of bodily orientation in space is then often superimposed upon other factors affecting imbalance such as motor and sensory impairments. Traditional rehabilitation for balance recovery has not been specifically designed to improve balance disorders related to spatial cognition. The traditional approach, consisting of stimulating the conscious perception of body orientation in space, is demanding and laborious. The approach based on sensorial stimulation is completely different. The relevance of this method lies in the fact that, firstly it is specifically active in the cognitive component of balance disorders; and secondly, it can passively be applied with minimal patient participation, which is of particular importance for this patient group characterized by disorders of attention and concentration. These techniques, such as proprioceptive, visual or vestibular stimulation, have been found to correct spatial neglect but also postural bias. Clinical and data from functional neuro-imaging suggest a direct central action on cortical structures involved in

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the elaboration of spatial representation. These are promising techniques for the rehabilitation of postural disturbances related to spatial cognition disorders but are as yet at the stage of preliminary results.

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Résumé Les troubles de l'équilibre liés à des troubles de la perception des systèmes de références spatiales sont communs en particulier après un AVC de l'hémisphère droit. La mauvaise représentation mentale de l'orientation du corps dans l'espace est alors souvent superposée à d'autres facteurs tels que le déséquilibre moteur et des déficiences sensorielles. Les techniques de rééducation actuelles pour la récupération de l'équilibre n'ont pas été spécifiquement conçues pour améliorer les troubles de l'équilibre liés à la cognition spatiale. L'approche traditionnelle, consistant à stimuler la perception consciente de l'orientation du corps dans l'espace, est exigeante et laborieuse. Les stimulations sensorielles sont une approche complètement différente. Leur intérêt réside dans le fait que, d'abord elles sont spécifiquement actives dans la composante cognitive des troubles de l'équilibre et, d'autre part, elles peuvent passivement être appliquées avec une participation minimale du patient, ce qui est d'un intérêt particulier pour ce type de patients porteurs de troubles de l'attention et de la concentration. Ces techniques, telles que la stimulation proprioceptive, visuelle ou vestibulaire qui ont été d'abord utilisées pour corriger le biais spatial dans la négligence spatiale, paraissent actives sur le biais postural. Les données cliniques et de l'imagerie fonctionnelle suggèrent une action directe sur le centre de structures corticales impliquées dans l'élaboration de la représentation spatiale. Elles sont prometteuses pour la rééducation des perturbations posturales liées à des troubles de la cognition spatiale, mais sont encore au stade des résultats préliminaires.

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Introduction

Balance recovery is a prognostic factor for autonomy, transferring and walking recovery [7,23]. Postural disorders can be explained by motor or sensory deficits [26,58], but spatial cognition deficit causing a distortion of the mental representation of space and body in space could also contribute to balance disturbance [54]. Disorders of spatial cognition observed after brain injury are more frequent after right brain injury and would explain the predominance of balance disorders after injury affecting the right hemisphere [12,46,54]. Data from the literature show that left hemiplegia caused by right brain injury is associated with poor prognosis in terms of balance and autonomy [46]. With comparable motor and sensory loss, balance disorders predominate in right brain versus left brain damage [46,54]. The hypothesis to explain the prognostic differences between left and right lesions is the presence of more severe disorders of spatial cognition when the brain injury is situated in the right hemisphere, which is devoted to spatial cognition [29].

Despite this overriding issue of the management of balance disorders related to spatial disorders, only a few authors have studied techniques for specifically treating this cognitive component of imbalance. Sensorial stimulations have been shown to be effective in correcting spatial bias found in cases of neglect [41]. It would seem to be of interest to test these techniques (comprising vestibular, visual or proprioceptive stimulations) for imbalance due to cognitive disorders after stroke, because of the closed cerebral mechanisms leading to biases in neglect and in postural impairment.

Representation of space and spatial references

Representation of space comes from the convergence of vestibular, visual and proprioceptive inputs and intrinsic knowledge about the spatial geometry of the body. This knowledge is partly innate, and partly acquired from sensorimotor experiences. Multiple mental representations of space are elaborated, interposed between sensory input and motor output, by using signals from the modulation process of sensorial information encoded in different frames of reference [1,3]. The environment in which we operate is thus perceived through several spatial referentials, including the allocentric frame and egocentric frame of reference. The allocentric referentials, such as the gravity reference frame, are extracted from the environment. The egocentric referentials are centered on the body and move with it [70]. Many brain regions are involved in the elaboration of representations of space. The parietal cortex plays a key role, since it facilitates the transformation of spatial coordinates extracted from sensorial information collected from the periphery, and the coordinates of the movement of the body, within a coherent framework [31]. For example, a visual input signal encoded in an allocentric retinotopic coordinate system (centered in the retina) can be gradually transformed into self-centered reference frame centered on the head and on the body due to the inclusion of proprioceptive information from neck and extraocular muscles. Misperception of the body in space and spatial reference system disorders can be measured by evaluating subjective estimation of the direction of the vertical (gravity reference frame) and the subjective estimation of the direction of the axis of the body

(egocentric reference frame) [51,57]. A more approximate approach can also be achieved by evaluating postural trunk tilt observed in sitting or standing position through clinical scales for trunk tilt, or by the mean position of the center of pressure on a force platform. Excessive shift of the Center of pressure toward the lesion side after right brain damage could be secondary to disorders of spatial cognition [46,48,54] since a relationship was found between perturbations of the longitudinal body axis and postural tilt observed in stroke patients while standing on a force platform [4].

Spatial references system disorders after stroke

A cerebral lesion may lead to spatial reference system disorders and consequently postural misorientation [45,55]. The perception of the direction of the vertical is often disrupted after cerebrovascular accident (CVA) in 40 to 60% of the visual modality in patients (subjective visual vertical) [10,16,52,71] and in more than 40% of patients with postural mode (subjective postural vertical) [47]. These changes are clearly greater and more persistent in patients with right hemispheric lesion [13]. The relationship between the postural disturbances observed in stroke patients and the disturbed perception of verticality has been previously discussed [51]. There is an association between balance disorders and disorders of the perception of the vertical in the visual modality [10,11] and postural modality [50]. The most severe postural disorders include “pusher syndrome” in which the subject is not only passively tilted toward the hemiplegic side but resists to any attempt to straighten the maneuver. This would be observed when the representation of verticality is altered for the three modes, that is, when the disturbance is multimodal [50]. The alteration of the egocentric reference frame, evaluated by the direction of the longitudinal axis or the subjective perception of straight ahead also seems common after stroke and is associated with balance disturbances [57]. These biases in spatial orientation, which are greater in patients with right hemispheric lesion (RHL), are thought to be a distortion of the internal representation of the body in space due to spatial cognitive impairment [55].

Effect of sensorial stimulations on balance disturbances after stroke

Sensorial stimulations represent a new approach for the rehabilitation of postural disturbances related to the misrepresentation of body in space. No awareness by the patient of their disorder is required, in contrast to the traditional approach (top-down techniques), the aim of which is to consciously improve the patient’s perception of their body in space. Among the top-down techniques, some authors have tested corrective exercises of the trunk tilt relative to the vertical in the sitting position with biofeedback [21] or corrective exercises of the trunk

rotation in the horizontal plane [18,19]. Similarly, corrective exercises of the tilt of the body in sitting or standing position using a force platform, which gives online information about the position of the center of pressure, have also been developed

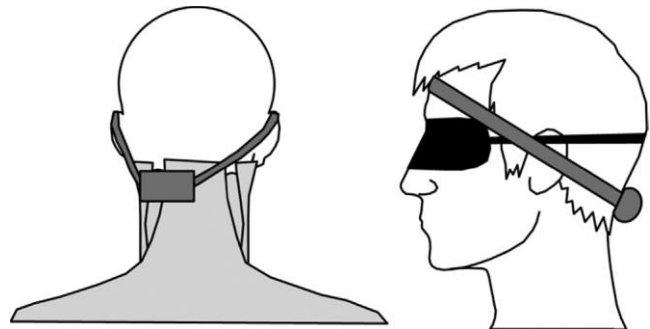


Figure 1 Left neck muscle vibration.

From Challois-Leplaideur S et al. In: Hamaoui A, Lacour M, eds. Du controle postural à l’exécution du mouvement. Paris: Deboeck and Solal; 2011. p. 17–29 [17].

[2,69]. Finally, several authors have proposed specific trunk control programs with interesting results [63]. However, these programs are demanding and laborious. The bottom-up approach, in contrast to the above techniques, does not require any participation from the patient. These techniques are thought to act directly on the central level cortical structures involved in the development of the mental representation of the body in space and are essentially represented by sensorial stimulations. Sensorial stimulations, whatever their modality (vestibular, proprioceptive or visual) could correct spatial bias. Sensorial stimulations were initially used to improve visuospatial neglect. They were thought to decrease the distortion of the internal representations of the body in space by restoring the symmetry of sensorial inputs. Different stimulations showed immediate effectiveness in improving postural imbalance after stroke, especially in right brain-damaged patients, even in the absence of negligence. Perennou has shown that the balance tested while sitting on a rocking platform was improved by proprioceptive transcutaneous nerve stimulation of the cervical region, both with eyes open and with eyes closed, in 8 subjects who had postural vertical outside the norms [48]. We have obtained encouraging results with vibratory proprioceptive stimulation of the neck muscles (Fig. 1) [16]. Another way to manipulate the somatosensory input is the degree of body tilt [51]. Some minutes of whole body tilt induce a transitory normalization of verticality perception in stroke patients [3]. Rode et al. found a corrective effect of caloric vestibular stimulation on the asymmetry of the center of pressure (CP) in right and left brain-damaged patients and controls with a higher effect in right brain damaged subjects [55]. An improvement of balance in standing position on a force platform and also more recently in sitting position was observed after prism adaptation [44,66]. Finally, optokinetic and galvanic

stimulations have been recently tested in stroke patients [12]. Both optokinetic and galvanic vestibular stimulations could modulate the position of the hemiparetic subject's Center of pressure (CP).

Despite being less effective than for RHL, postural asymmetry is reduced by sensorial stimulation in LHL patients. However, the responses to sensorial stimulation of LHL patients do not differ from those of the control group, and do not differ between left and right directions [12]. Therefore, it would appear that the presence of a left cerebral lesion does not seem to influence the effect of sensorial stimulation, since the effect is the same as for normal subjects. Yet, LHL sufferers do often have a spontaneous bias at rest, albeit smaller than that found in RHL patients. It could therefore be assumed that the ipsilateral bias observed in LHL is not related to high level postural disturbances, but could be mostly due to the biomechanical consequences of impaired motor function or sensory function, or due to compensatory processes established to address imbalance [25,26]. The potential benefits for the correction of this bias in LHL should then be discussed as this may actually represent a useful adaptation for hemiparetic patients, thereby allowing them to cope with imbalance [25,56].

Mechanism of action of sensorial stimulations

Thus, a number of different sensorial stimulations have shown efficacy for immediate correction of postural imbalance after stroke: caloric and galvanic vestibular stimulation; proprioceptive modification by transcutaneous nerve stimulation or neck muscle vibration; optokinetic stimulation; and visual prism adaptation. The mechanism underlying such postural effects is not yet fully understood but is likely to be explained by a high level effect on body and spatial representation, rather than by a sensorimotor effect. This assumption comes from a variety of theories. Firstly, the effect of sensorial stimulations predominates in patients with right hemispheric lesion (RHL), as compared to patients with left hemispheric lesion (LHL) [12,45,55]. For galvanic vestibular and optokinetic stimulations, the postural effect was nearly double for RHL patients compared to that for LHL, and compared to the responses of LHL and control subjects [12,66]. Therefore, localization of the lesion in the right hemisphere seems to be responsible for the specific effect of sensorial stimulation on postural disturbances. This is likely to be related to the spatial role of the right hemisphere. Secondly, sensorial stimulation is effective in reducing postural bias, whatever their modalities, which suggests an action on supramodal cerebral structures. Moreover, the magnitude of the displacement induced by the optokinetic and galvanic stimulations are linearly correlated [12]. This linear effect reinforces the assumption that the postural effect of the sensorial stimulation is a supramodal effect. Finally, sensorial

stimulation reduces not only postural imbalance, but also numerous symptoms related to spatial cognition, such as visuospatial impairment in all its manifestations (sensory impairment as well as representational impairment or motor impairment).

Sensorial stimulations could then activate supramodal structures, which synthesize information from disparate sensorial modalities and create the representation of the body in space [27]. This is consistent with previous neuro-imaging findings in normal subjects. The effect of optokinetic stimulation is not due to a simple phenomenon confined to the visual modality, but extends to other areas such as proprioception and vestibular systems, since optokinetic stimulation activates not only visual areas, but also other cerebral areas, notably multisensory areas [15,20]. Similarly, the effect of galvanic vestibular stimulation is not confined to the vestibular tracts, but also involves multisensory areas [5,28,67,72]. Neck muscle vibration was also shown to activate regions involved in the representation of the body in space [14]. The process creating representations of the body's position in space uses a process of modulation of the multiple sensorial inputs coded from different frames of reference [1]. A right focal brain lesion could produce a disconnection in the circuits supporting one or more of these spatial encoding systems and generate a general imbalance of the spatial reference frame. This could lead to a spatial bias manifested in a variety of spatial tasks, including posture [34,53,68]. Activation of one or the other of these impaired systems by sensorial stimulation might be sufficient to partially compensate for the spatial bias. All together, these results are in favor of a central action of the sensorial stimulations on the coordinate transformation process [14,35,36]. They are thought to offset the distortion of body representations in space by restoring sensorial input symmetry. Sensorial stimulations could activate preserved cerebral structures involved in the body's representation in space, i.e. the right posterior parietal cortex and the temporoparietal junction. The results of several fMRI studies in stroke patients support this assumption. Optokinetic stimulation was shown to activate the posterior part of the parietal cortex [8,65,73]. Vestibular stimulation activates the so-called vestibular cortex, especially the right temporoparietal junction, which has a fundamental role in the mental representation of body position and movement in space [22]. The study by Bottini et al. using PET scan during neck muscle vibration shows altered activity in the insula, parietal operculum and superior temporal gyrus [14]. This is also in accordance with findings showing that lesions of the right temporoparietal junction are related to imbalance after stroke [9,49]. The involvement of this region seems particularly unfavorable for the balance of patients suffering a stroke [9,43,50]. Moreover, distortions of spatial references (the subjective vertical or longitudinal axis), which are linked to postural bias, are elaborated in such multisensory areas and are related to postural imbalance [4,11,13,52].

Characteristics of sensorial stimulations

Interestingly, sensorial stimulations do not need to be simultaneously activated [53]. Activation of one or the other of the impaired systems by sensorial stimulation might be sufficient to partially compensate for the spatial bias. The central network stimulated by the different sensorial stimulations is likely to slightly differ, even if it is situated in the same areas [12]. The efficacy of the specific stimulation modality may depend on the characteristics of the lesion. Therefore, it would be useful to identify those patients likely to respond to each type of stimulation before commencing treatment. An interesting study showed that, unlike optokinetic manipulation, neck vibration does not seem to be effective on judgments of object size, suggesting that neck muscle vibration may not act on the allocentric references [59]. Neck vibrations seem thus particularly effective on the modulation of the egocentric frame of reference [35]. The vibrations of the neck muscles induce a lateral illusion of translation of the visual environment in healthy subjects. Along with the illusion of movement of the visual environment, concomitant deviation of the subjective straight ahead position occurs. This is consistent with the role of proprioceptive information provided by neck muscle proprioceptors. Neck proprioceptive receptors provide head movement information and together with the eye direction information, they are involved in the representation of the body in relation to egocentric referential [6,35]. Two mechanisms of action are proposed to explain the effectiveness of prism adaptation on visuospatial bias. The first mechanism is an involuntary correction mechanism of visuomotor behavior, which can account for the gradual adaptation of visual-manual tasks such as drawing or bisecting a line. However, the improvement of other tasks that do not require motor action, such as visual scanning, reading or mental imagery, suggests that the process of prism adaptation activates cognitive processes located at a higher level in structures involving mental representation of space. This assumption is supported by functional imaging studies [42]. Interestingly, Pisella et al. showed that after prism adaptation, the evolution of straight-ahead and line bisection tasks are dissociated. This suggests that the benefit of prism adaptation is not mediated by the modification of the egocentric reference [52].

Utilization of sensorial stimulation in postural rehabilitation after stroke

Sensory stimulations, whether vestibular, proprioceptive or visual, could correct spatial bias. Their relevance lies in the fact that, firstly they are specifically active in the cognitive component of balance disorders; and secondly, they can passively be applied with minimal patient participation, being particularly suitable for this type of very distractible patient with

disorders of attention and concentration. Finally, they are very easy to use and inexpensive.

The long-term effectiveness of sensorial stimulation has not yet been tested in the specific indication of balance disorder due to misrepresentation of the body in space, except for prismatic adaptation. However, these stimuli appear to be effective in the long-term on neglect symptoms if they are repeated, and it could be hoped to see a similar effect to long-term rehabilitation of balance disorders secondary to disorders of spatial cognition [37]. Prismatic adaptation has first shown long lasting improvement for neglect symptoms [24]. Recently, a preliminary study has shown that repetitive prismatic adaptation involves a persistent reduction in postural asymmetry in 6 right-brain damaged patients without neglect [30]. Neck muscle vibrations were also shown to be effective on neglect symptoms if repeated [32,60]. Repetitive optokinetic stimulation has been also investigated [39,40], as well as repetitive galvanic stimulation [38,64,65]. These investigators found stable treatment effects that outlasted the stimulation period. Likewise, another recent study using repetitive galvanic stimulation as treatment for RHL with left arm proprioceptive disorder could be temporarily normalized during and after a session of 20 min of galvanic stimulation [61]. Finally, 3 sessions of galvanic stimulation were shown to reduce left-sided somatosensory extinction by some 50%, the effects lasting for at least 3 months [62]. Further studies are needed to investigate the therapeutic potential of repetitive sensorial stimulation to achieve longer lasting improvements in postural disturbances. The combined effect of sensorial stimulation should also be tested, since the effects appear to be cumulative. Karnath [36] found increased benefits when using visual and proprioceptive stimulation together. The reduction of bias that occurred when the 2 types of sensorial stimulation were combined correlated with the sum of the respective bias correction when either type of stimulation was applied alone. It was also shown that sensorial stimulation combined with standard rehabilitative exercises is more effective than sensorial stimulation alone [33,60].

Conclusion

Sensorial stimulations could specifically improve postural disorders related to disorders of spatial cognition. Several clinical and imaging data are in favor of a central action on cerebral structures involved in spatial cognition. The postural effect of such stimulations probably results from activation of the supramodal areas involved in the neural representation of the body in space that are situated in high-level CNS centers. These various stimulations are very simple to implement in rehabilitation center and are inexpensive. They do not require any active participation by the patient. Preliminary studies have shown their short-term effectiveness. This bottom-up approach requires future scientific studies to test its effectiveness over the

medium- and long-term as well as the effect of repetition. Top- down approaches aimed at controlling body orientation, by improving the perception of spatial reference systems such as body egocentric axis and vertical axis, have also been proposed but their results remain to be confirmed.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix 4 - Tables of the article : The effects of neck muscle vibration on postural orientation and spatial perception: A systematic review.

**Jamal K, Leplaideur S, Leblanche F, Moulinet Raillon A, Honoré T, Bonan I.
Neurophysiol Clin. 2020 Sep;50(4):227-267. doi: 10.1016/j.neucli.2019.10.003.**

Table 1 Quality of methodology of randomized control trials and crossover trials with Pedro scale.

Title	Author	1	2	3	4	5	6	7	8	9	10	11	Total/10
Adaptation of a bimodal integration stage: Visual input needed during neck muscle vibration to elicit a motion aftereffect (experiment 2)	Seizova-Cajic et al.	X	0	0	0	0	0	0	1	1	1	0	3
Eye movements cannot explain vibration-induced visual motion and motion after-effect.	Seizova-Cajic et al.	X	0	0	0	0	0	0	1	1	1	0	3
Time course of gaze influences on postural responses to neck proprioceptive and galvanic vestibular stimulation in humans	Grasso et al.	X	0	0	1	0	0	0	1	1	0	0	3
Effects of neck muscle vibration on subjective visual vertical: Comparative analysis with effects on nystagmus	Kawase et al.	X	0	0	1	0	0	0	1	1	1	0	4
Adaptation of a bimodal integration stage: Visual input needed during neck muscle vibration to elicit a motion after-effect (experiment 1)	Seizova-Cajic et al.	X	0	0	1	0	0	0	1	1	1	0	4
Neck muscle vibration modifies the representation of visual motion and direction in man (Experience 2)	Biguer et al.	X	0	0	1	0	0	0	1	1	1	0	4
Changes in apparent body orientation and sensory localization induced by vibration of postural muscles: vibratory myesthetic illusions (Experience 3)	Lackner et al.	X	0	0	1	0	0	0	1	1	1	0	4
Asymmetric vestibular function in the elderly might be a significant contributor to hip fractures	Kristinsdottir et al.	X	0	0	1	0	0	0	1	1	1	0	4
Vibration-induced postural post-effects	Wierzbicka et al.	X	0	0	1	0	0	0	1	1	1	0	4
The Subjective Visual Vertical and the Subjective Haptic Vertical Access Different Gravity Estimates	Frase et al.	X	0	0	1	0	0	0	1	1	1	1	5
Prism adaptation and neck muscle vibration in healthy individuals: Are two methods better than one?	Guinet et al.	X	0	0	1	0	0	0	1	1	1	1	5
Neck muscle vibration in full cues affects pointing.	McIntyre et al.	X	0	0	1	0	0	0	1	1	1	1	5
Effects of neck muscles vibration on the perception of the head and trunk midline position (experience 1)	Ceyte et al.	X	0	0	1	0	0	0	1	1	1	1	5
Convergent and divergent effects of neck proprioceptive and visual motion stimulation on visual space processing in neglect	Schindler et al.	X	0	0	1	0	0	0	1	1	1	1	5
The perception of body orientation after neck-proprioceptive stimulation: Effects of time and of visual cueing (Experience0)	Karnath et al.	X	0	0	1	0	0	0	1	1	1	1	5
Vibration-induced shift of the subjective visual horizontal: A sign of unilateral vestibular deficit	Karlberg et al.	X	0	0	1	0	0	0	1	1	1	1	5
Neck muscle vibration alters visually-perceived roll after unilateral vestibular loss	Betts et al.	X	0	0	1	0	0	0	1	1	1	1	5
Visual and oculomotor responses induced by neck vibration in normal subjects and labyrinthine-defective patients	Popov et al.	X	0	0	1	0	0	0	1	1	1	1	5
Changes of visual localization induced by eye and neck muscle vibration in normal and strabismic subjects	Han et al.	X	0	0	1	0	0	0	1	1	1	1	5
Ocular exploration of space as a function of neck proprioceptive and vestibular input - Observations in normal subjects and patients with spatial neglect after parietal lesions	Karnath et al.	X	0	0	1	0	0	0	1	1	1	1	5

Table 1 (Continued)

Title	Author	1	2	3	4	5	6	7	8	9	10	11	Total/10
Properties of eye movements induced by activation of neck muscle proprioceptors	Lennerstrand et al.	X	0	0	1	0	0	0	1	1	1	1	5
The interactive contribution of neck muscle proprioception and vestibular stimulation to subjective "straight ahead" orientation in man	Karnath et al.	X	0	0	1	0	0	0	1	1	1	1	5
Subjective body orientation in neglect and the interactive contribution of neck muscle proprioception and vestibular stimulation	Karnath et al.	X	0	0	1	0	0	0	1	1	1	1	5
Clinical interest of postural and vestibulo-ocular reflex changes induced by cervical muscles and skull vibration in compensated unilateral vestibular lesion patients	Dumas et al.	X	0	0	1	0	0	0	1	1	1	1	5
Vibration-induced post-effects: A means to improve postural asymmetry in lower leg amputees?	Duclos et al.	X	0	0	1	0	0	0	1	1	1	1	5
Neck proprioception and spatial orientation in cervical dystonia	Bove et al.	X	0	0	1	0	0	0	1	1	1	1	5
Neck vibration causes short latency electromyographic activation of lower leg muscles in postural reactions of the standing human	Andersson et al.	X	1	0	1	0	0	0	1	1	1	0	5
Neck muscle vibration disrupts steering of locomotion	Bove et al.	X	0	0	1	0	0	0	1	1	1	1	5
Methods for evaluation of postural control adaptation	Fransson et al.	X	0	0	1	0	0	0	1	1	1	1	5
Neck muscle vibration makes walking humans accelerate in the direction of gaze	Ivanenko et al.	X	0	0	1	0	0	0	1	1	1	1	5
Influence of vibration to the neck, trunk and lower extremity muscles on equilibrium in normal subjects and patients with unilateral labyrinthine dysfunction.	Yagi et al.	X	0	0	1	0	0	0	1	1	1	1	5
From balance regulation to body orientation: Two goals for muscle proprioceptive information processing?	Kavounoudias et al.	X	0	0	1	0	0	0	1	1	1	1	5
Postural responses to vibration of neck muscles in patients with uni- and bilateral vestibular loss	Lekhe et al.	X	0	0	1	0	0	0	1	1	1	1	5
Analysis of adaptation in anteroposterior dynamics of human postural control	Fransson et al.	X	0	0	1	0	0	0	1	1	1	1	5
Postural responses to vibration of neck muscles in patients with idiopathic torticollis	Lekhe et al.	X	0	0	1	0	0	0	1	1	1	1	5
Effects of neck muscles vibration on the perception of the head and trunk midline position (experience 2)	Ceyte et al.	X	1	0	1	0	0	0	1	1	1	1	6
Neck Muscle Vibration Alters Visually Perceived Roll in Normals	McKenna et al.	X	1	0	1	0	0	0	1	1	1	1	6
Neck muscle vibration induces lasting recovery in spatial neglect	Schindler et al.	X	1	0	1	0	0	0	1	1	1	1	6
The perception of body orientation after neck-proprioceptive stimulation: Effects of time and of visual cueing (Experience1)	Karnath et al.	X	1	0	1	0	0	0	1	1	1	1	6
Differences in the use of vision and proprioception for postural control in autism spectrum disorder	Morris et al.	X	1	0	1	0	0	0	1	1	1	1	6

Table 1 (Continued)

Title	Author	1	2	3	4	5	6	7	8	9	10	11	Total/10
Effect of neck muscles and gluteus medius vibrations on standing balance in healthy subjects	Challos et al.	X	1	0	1	0	0	0	1	1	1	1	6
Neck muscle vibration can improve sensorimotor function in patients with neck pain	Beinert et al.	X	1	0	1	0	0	0	1	1	1	1	6
Role of proprioceptive information to control balance during gait in healthy and hemiparetic individuals	Mullie et al.	X	1	0	1	0	0	0	1	1	1	1	6
Effects of manipulations with visual feedback on postural responses in humans maintaining an upright stance	Smetanin et al.	X	1	0	1	0	0	0	1	1	1	1	6
Local and global effects of neck muscle vibration during stabilization of upright standing	Verrel et al.	X	1	0	1	0	0	0	1	1	1	1	6
Interaction between vision and neck proprioception in the control of stance (Experience 1)	Bove et al.	X	1	0	1	0	0	0	1	1	1	1	6
Interaction between vision and neck proprioception in the control of stance (Experience 2)	Bove et al.	X	1	0	1	0	0	0	1	1	1	1	6
Effects of ageing on adaptation during vibratory stimulation of the calf and neck muscles	Patel et al.	X	1	0	1	0	0	0	1	1	1	1	6
Stance- and locomotion-dependent processing of vibration-induced proprioceptive inflow from multiple muscles in humans	Courtine et al.	X	1	0	1	0	0	0	1	1	1	1	6
The postural disorientation induced by neck muscle vibration subsides on lightly touching a stationary surface or aiming at it (experience 1)	Bove et al.	X	1	0	1	0	0	0	1	1	1	1	6
The postural disorientation induced by neck muscle vibration subsides on lightly touching a stationary surface or aiming at it (experience 2)	Bove et al.	X	1	0	1	0	0	0	1	1	1	1	6
Cervical muscle afferents play a dominant role over vestibular afferents during bilateral vibration of neck muscles	Magnusson et al.	X	1	0	1	0	0	0	1	1	1	1	6
Head stabilization on a continuously oscillating platform: The effect of a proprioceptive disturbance on the balancing strategy	De Nunzio et al.	X	1	0	1	0	0	0	1	1	1	1	6
Effect of gaze on postural responses to neck proprioceptive and vestibular stimulation in humans	Ivanenko et al.	X	1	0	1	0	0	0	1	1	1	1	6
Postural and symptomatic improvement after physiotherapy in patients with dizziness of suspected cervical origin	Karlberg et al.	X	1	0	1	0	0	0	1	1	1	1	6
Effects of vibrations on gait asymmetry: a prospective randomized controlled study in patients with chronic stroke	Leblong et al.	X	1	0	1	0	0	0	1	1	1	1	6

1/the eligibility criteria were specified, 2/subjects were randomly allocated to groups, 3/allocation was concealed, 4/the groups were similar at baseline regarding the most important prognostic indicators, 5/there was blinding of all subjects, 6/there was blinding of all therapists who administered the therapy, 7/there was blinding of all assessors who measured at least one key outcome, 8/measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups, 9/all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat", 10/the results of between-group statistical comparisons are reported for at least one key outcome, 11/the study provides both point measures and measures of variability for at least one key outcome.

Table 2 Quality methodology of experimental studies with the Quality Assessment Tool for Before–After (Pre-Post) Studies with No Control Group.

Titles	Authors	1	2	3	4	5	6	7	8	9	10	11	12	Rating quality
Short-term effect of neck muscle vibration on postural disturbances in stroke patients	Leplaideur et al.	Y	Y	Y	Y	NR	Y	Y	N	Y	Y	Y	NA	Fair
Neck muscle vibration and stroke patients	Challos et al.	Y	Y	Y	Y	NR	Y	Y	N	Y	Y	Y	NA	Fair
Short term effects of neck muscle vibration on balance control of stroke patients: A preliminary study	Challos-Leplaideur et al.	Y	Y	Y	Y	NR	Y	Y	N	Y	Y	Y	NA	Fair
Discrepancy between the directions of body sway and gaze during simultaneous optokinetic and posterior neck muscle vibration stimulation	Tsutsumi et al.	Y	N	N	NR	NR	Y	Y	N	Y	Y	N	NA	Fair
Postural responses to continuous unilateral neck muscle vibration in standing patients with cervical dystonia	Bove et al.	Y	N	Y	NR	NR	Y	Y	N	Y	Y	Y	NA	Fair
Postural reactions to neck vibration in Parkinson's disease	Valkovic et al.	Y	N	Y	NR	NR	Y	Y	N	Y	Y	N	NA	Fair
Role of dorsal neck proprioceptive inputs to vestibular compensation in humans.	Yagi et al.	Y	N	Y	NR	NR	Y	Y	N	Y	Y	N	NA	Fair
Postural responses to vibration of neck muscles in patients with unilateral vestibular lesions	Popov et al.	Y	N	Y	NR	NR	Y	Y	N	Y	Y	N	NA	Fair
Lasting amelioration of spatial neglect by treatment with neck muscle vibration even without concurrent training	Johannsen et al.	Y	Y	Y	NR	NR	Y	Y	N	Y	Y	Y	NA	Fair
The perception of body orientation after neck-proprioceptive stimulation: Effects of time and of visual cueing (Experience2)	Karnath et al.	Y	N	N	NR	NR	Y	Y	N	Y	Y	Y	NA	Fair
Subjective straight-ahead during neck muscle vibration: Effects of ageing	Strupp et al.	Y	N	N	NR	NR	Y	Y	N	Y	Y	Y	NA	Fair
Perceptual and oculomotor effects of neck muscle vibration in vestibular neuritis. Ipsilateral somatosensory substitution of vestibular function	Strupp et al.	Y	Y	N	NR	NR	Y	Y	N	Y	Y	Y	NA	Fair
Pattern of postural changes after symmetric neck muscle vibration	Valkovic et al.	Y	N	N	NR	NR	Y	Y	N	Y	NR	N	NA	Poor
Is muscle spindle proprioceptive function spared in muscular dystrophies? A muscle tendon vibration study	Ribot-Ciscar et al.	Y	N	Y	NR	NR	Y	Y	N	Y	NR	N	NA	Poor
The influence of head rotation on human upright posture during balanced bilateral vibration	Gurfinkel et al.	Y	N	N	NR	NR	Y	Y	N	Y	N	N	NA	Poor
Decrease of contralateral neglect by neck muscle vibration and spatial orientation of trunk midline	Karnath et al.	Y	N	N	NR	NR	Y	Y	N	Y	Y	N	NA	Poor
Illusions of head and visual target displacement induced by vibration of neck muscles.	Taylor et al.	Y	N	N	NR	NR	Y	Y	N	Y	Y	N	NA	Poor
Neck muscle vibration modifies the representation of visual motion and direction in man (Experience 1)	Biguer et al.	Y	N	N	NR	NR	Y	Y	N	Y	N	N	NA	Poor

1/objective clearly stated, 2/eligibility criteria described, 3/representative patient population, 4/all eligible participants enrolled in the study, 5/sufficient sample size, 6/intervention described, 7/outcome measure specified, 8/outcome assessors blinded, 9/loss to follow-up, 10/statistical analysis of outcome measure before and after intervention, 11/interrupted time-series design, 12/individual data used for group level effects. Yes (Y), No (N), Not Reported (NR), Not Available (NA). Quality Good, Fair, Poor.

Table 3 Characteristics of the population.

Population characteristics	Numbers	%
Total population	1522	
Healthy subjects	958	62.6
Vestibular lesion	235	15.4
Unilateral lesions	184	
Bilateral lesions	51	
Strokes	154	10.1
RBD	87	
RBD with Neglect	15	
LBD	58	
Unknown	9	
Neck pain	30	1.9
Cervical dystonia	28	1.8
PD	26	1.7
Hip fractures Subjects	19	1.2
Spasmodic torticoli	19	1.2
Strabismic patients	16	1
Lower limb amputation	14	0.9
Autism spectrum disorders	12	0.7
Muscular dystrophia	11	0.7

RBD: right brain damage; LBD: left brain damage, PD: Parkinson Disease

Table 4 Characteristics of the intervention.

Characteristics	Studies	%
Muscles		
Dorsal neck muscles	23	31
Trapezius	9	12.3
Neck muscles	8	10
Splenius	8	10
SCOM	6	8
Splenius and Trapezius	5	6.7
Splenius and Trapezius and SCOM	5	6.7
Splenius and Semispinalis and	3	4
Trapezius		
Splenius and Semispinalis	2	2.7
Splenius and SCOM	2	2.7
Trapezius and Dorsal neck muscles	1	1.3
Trapezius and Semispinalis and	1	1.3
SCOM		
Splenius or SCOM or Trapezius	1	1.3
Side vibrated		
Bilateral	21	28
Right and left side	20	27.3
Left side	14	19.1
Contralesionnel side	5	6.7
Right side	3	4
Symmetrical to the supine	3	4
Bilateral and right side and left	3	4
side		
Bilateral and left side	1	1.3
Bilateral and right side	1	1.3
Painful side	1	1.3

Table 4 (Continued)

Characteristics	Studies	%
Amputation side	1	1.3
Not available	1	1.3
Eyes		
Eyes Open (EO)	31	41
Eyes Closed (EC)	22	30.1
EO and EC	20	27.3
Not available	1	1.3
Vibrator		
Duration – mean 20 s (min = 1 s; max = 28 min)	53	70
Amplitude – mean 0.8 mm (min = 0.13 mm; max = 1.4 mm)	50	66
Frequency – mean 90 Hz (min: 20 Hz; max: 140 Hz)	72	96
Postural orientation	43	
Muscle tracking		
Not available	20	46
Anatomical location	17	39.5
Illusion movement visual target	4	9
Illusion of movement of head	3	7
Position		
Standing position	31	75
Sitting position	5	11
Standing with different head position and eyes position	3	7
Standing with hand contact	2	4.6
Standing with different head position	1	2.3
Not available	1	2.3
Spatial perception	32	
Muscle tracking		
Illusion movement visual target	19	59
Anatomical location	7	21
Muscle palpation	3	9
Not available	3	9
Position		
Sitting position	25	78
Sitting position with different head position	2	6
head position		
Standing position	2	6
Sitting and supine position	1	3
Standing with body tilt	1	3
Standing and lying side position	1	3
Room light		
Dark	23	25
Dark/Light	8	3
Light	1	

Table 5 Effect of neck muscle vibration (NMV) on postural orientation of healthy subjects.

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Morris et al., 2015	CO (6/10)	Healthy 20/ 23.4 ± 5.1		Dorsal neck muscles	Anatomical location/ Bilateral	NA/NA	5	EO/EC – standing	–	–	Pre-test(15 s)/ test under vibration(5 s)	Antero- postero plane = no effect EO. Effect EC with shift forward		
Challois et al., 2015	CO (6/10)	Healthy 13/23		Splenius and semispinalis	VTI/ left	70/NA	300	EC – standing	GMV Right side	–	Pre-test(52 s)/ test under vibration (5 min)/ post-test (5 min)	Medio- lateral plane = effect not significant (EC). Shift toward the left side in 5/13 subjects. Effect maintained in time		Comparator = effect significant with shift toward the left side in 9/13. Effect not maintained in time
Beinert et al., 2015	CO (6/10)	Healthy 10/21.8		Neck muscles	Anatomical location painful side/ right/ left	100/1	30	NA-NA	–	–	Pre-test(60 s)/ vibration (30 s)/ post test (immediate)		No effect	
Mullie et al., 2014	CO (6/10)	Healthy 12		Dorsal neck muscles	NA/ Bilateral	80/0.5	NA	EC – sitting	TSV paretic/ non dominant side	–	Pre-test(10 s)/ test under vibration(20 s)	Antero- postero plane = effect (EC) with a shift forward		Comparator = effect (EC) with a shift backward
Dumas et al., 2013	CO (5/10)	Healthy 9/43 ± 15		Trapezius	Anatomical location/ right/ left	85/NA	10	EO/EC – standing	Mastoid vibration. TSV Left/Right	–	Test under vibration (25.6 s)	No effect		Comparator = TSV effect with a shift backward in healthy and medio- lateral in unilateral vestibular lesion
Valkovic et al., 2012	CS (POOR)	Healthy 12/ 20–35		Splenius and trapezius	Anatomical location/ Bilateral	70/ 1.4	2	EC – standing	–	–	Test under vibration	Antero- postero plane = effect (EC) with a shift backward shift (106 ms) then forward (359 ms)		

Table 5 (Continued)

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Smetanin et al., 2011	CO (6/10)	Healthy 11/ men 46.6 ± 9.6 and women 54.0 ± 6.2		Trapezius	Anatomical location/ Bilateral	70–100/1	4	EO/EC – standing	TAV bilateral	–	Pre-test (9–10 s)/ vibration (4 s)/ post test (5 s)	Antero- postero plane = effect (EC > EO2 = EO3D) with a shift forward		Comparator = NMV greater than TAV
Verret et al., 2011	CO (6/10)	Healthy 8/ 21.4 ± 2.4		Dorsal neck muscles	NA/ Bilateral	100/0.8	10	EO/EC – standing	–	–	Pre-test(10 s)/ test under vibration(10 s)	Antero- postero plane = effect (EC > EO) with a shift forward		
Bove et al., 2009	CO (6/10)	Healthy 6/ 26.7 ± 2.5		Splenius and semispinalis and trapezius	Anatomical location/ Bilateral	100/0.8	5 × 10	EO/EC – standing	–	–	Pre-test (15 s)/ vibration (5 s)/ post test (15 s)	Antero- postero plane = effect (ECEC > EOEC/ ECEO > EOEO) shift forward during vibration then return to initial. Effect Increasing with successive vibration pulses		
Bove et al., 2009	CO (6/10)	Healthy 6/26.2 ± 2.6		Splenius and semispinalis and trapezius	Anatomical location/ Bilateral	100/ 0.8	5 × 10	EO/EC – standing	–	–	Pre-test(15 s + 3 s/ 6 s/ 9 s)/ vibration (5 s)/ post test (15 s)	Antero- postero plane = increasing duration EO reduce effect/ increasing duration EC increase effect. Effect with shift forward during vibration then return to initial		

Table 5 (Continued)

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Patel et al., 2009	CO (6/10)	Healthy (young) 18/29.1 ± 7.8	Healthy (old) 16/71.5 ± 3.9	Dorsal neck muscles	NA/ Bilateral	85/1	50/(PRBS)	EO/EC – standing	TSV bilateral	–	Pre-test(30 s)/ test under vibra- tion(PRBS)	Antero- postero plane and mediolat- eral = Decrease effect EO/Increase effect EC. When repetition = Adaptation on antero- postero plane and lateral	Antero- postero plane and lateral = Decrease effect EO/Increase effect EC. When repetition = Adaptation on antero- postero plane not on lateral	Comparator = TSV lager effect on antero- postero plane and lateral
Duclos et al., 2007	CO (5/10)	Healthy 18/37 ± 10		Trapezius	Illusion head move- ment/ left side/ amputa- tion side	80/0.5–0.8	30	EC-sitting	GMV left side/ amputa- tion	–	Pre- test(2 × 60 s)/ vibration (30 s)/ post test (immediate until 13 min)	Medio- lateral plane = effect with a shift to one side (half subject) and to the opposite side (half of subject). Effect maintained 13 min	No effect	Comparator = no difference CP shift amplitude. No difference in CP shift between two groups
Tsutsumi et al., 2007	CS (FAIR)	Healthy 8/21.4 ± 2.4		Dorsal neck muscles	NA/ Bilateral	50/0.2	NA	EO – standing	–	OKS	Pre-test/ test under vibration	No effect		Adjuvant = the direction of CoP translation was related to OKS velocity
Bove et al., 2007	CS (FAIR)	Healthy 12/51 ± 15.5		SCOM	NA/ right/ left	90/NA	NA	EC – standing	–	–	Test under vibration (51.2 s)	Medio- lateral plane = effect with a shift toward the right with left vibration and to the left with right vibration.		

Table 5 (Continued)

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Courtine et al., 2007	CO (6/10)	Healthy 8/26–58		Splenius or SCOM or trapezius	Anatomical location/ left	80/0.8	60	EC – standing	TH. LU. AB. GL. RF. BF. TI. TE. TA. SOL. AI. AE vibration	–	Pre-test (60 s)/ test under vibration (60 s)	Antero- postero plane and mediolat- eral = effect with a shift toward opposite of the vibrated side. Effect in the mediolat- eral plane = Splenius/ SCOM/ Trapezius and Antero- Post plane = Splenius		Comparator = Effect in the medio- lateral plane = Lu. TI. TE. AI. AE. Sol. Effect in the Antero- posterior plane = Th. Lu. AB. GL. RF. BF. TA. Sol
Bove et al., 2006	CO (6/10)	Healthy 7/ 28.4 ± 6.7		SCOM	NA/ Bilateral/ right/ left	100/NA	60	EC – standing and hand contact	–	–	Pre-test/ test under vibration/ post test	Antero- postero plane and lateral = Light Finger Touch (LFT) during vibration or post- vibration reduce effect. LFT has more effect in plane of the deviation		
Bove et al., 2006	CO (6/10)	Healthy 5/27 ± 6.4		SCOM	NA/ Bilateral/ left	100/NA	5	EC – standing and hand contact	–	–	Pre-test/ test under vibration/ post test (2/5 s)	Antero- postero plane and mediolat- eral = LFT before vibration suppress effect. Intended reduce effect		

Table 5 (Continued)

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Magnusson et al., 2006	CO (6/10)	Healthy 10/ 16–27		splenius	NA/ Bilateral	55/85/ 0.4/1	1X10	EC – standing	Mastoid vibration	–	Pre-test (30 s)/ test under vibration (110 s)	Antero- postero plane = effect with vibration on = backward then forward and when vibration switched off opposite effect. Effect larger with higher intensity		Comparator = lower and less effect
Valkovic et al., 2006	CS (FAIR)	Healthy 13/63.9 ± 11.3		Splenius and trapezius	Anatomical location/ Bilateral	80/1	3X10	EO/EC	–	–	Test under vibration (60 s)	Antero- postero plane = Effect wit a shift backward (119 ms to 123 ms) than forward (250 ms to 400 ms). Effect EC > EO. With repetitive vibration no effect EO and decrease effect EC		
De Nunzio et al., 2005	CO (6/10)	Healthy 14/33 ± 11.3		Splenius	Anatomical location/ Bilateral	90/0.9	30	EO/EC – standing	QV, TAV, BFV, TSV bilateral	–	Test under vibration (30 s)	Antero- postero plane = Effect with a shift forward. EC > EO		Comparator = Effect forward = Q/TA and backward for TS/BF

Table 5 (Continued)

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Bove et al., 2004	CO (5/10)	Healthy 12/51.6 ± 15.5		SCOM	Anatomical location/ right/ left	90/NA	51.2	EC – standing	–	–	Pre-test (51.2 s)/ test under vibration (51.2 s)	Medio- lateral plane = Effect with a shift to the left with right vibration and to the right with left vibration		
Ribot-Ciscar et al., 2004	CS (POOR)	Healthy 10/ 35.1 ± 10.2		Splenius	Anatomical location/ left	80/0.5	2	EC – standing	TAV bilateral/ TSV bilateral	–	Pre-test(0.5 s)/ test under vibration (20 s)/ post test (immediate)	Antero- postero plane = Effect with a shift forward		Comparator = Effect with a shift forward for TAV and backward for TSV
Andersson et al., 2002	CO (5/10)	Healthy 10/37		Splenius	NA/ Bilateral	85/1	0.25	EC – standing	–	–	Test under vibration (1 s/4 s)	Antero- postero plane = Effect with a shift forward (250 ms) then backward (350 ms). Same effect for 1s or 4 s		
Bove et al., 2001	CO (5/10)	Healthy 9/32.5		Neck muscles	Anatomical location/ right	70/NA	NA	EO/EC – standing	–	–	Pre-test (51.2 s)/ test under vibration (51.2 s)/ post test (60 s)	Medio- lateral plane = Effect both during and before vibration. More effect during than before and EC > EO		
Kristinsdottir et al., 2000	CO (4/10)	Healthy 28/72		Dorsal neck muscles	NA/ Bilateral	60/1	PRBS	EO/ EC- standing	TSV bilateral	–	Pre-test(30s)/ test under vibration (PRBS)	No effect		Comparator = TSV EC S1(8/19) S2(1/28)

Table 5 (Continued)

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Fransson et al., 2000	CO (5/10)	Healthy 10/37.5		Dorsal neck muscles	NA/ Bilateral	60/1	PRBS	EO/EC – standing	TSV bilateral	–	Pre-test (30 s)/ test under vibration (PRBS)	Antero- postero plane = EC > EO		Comparator = more sway
Ivanenko et al., 2000	CO (5/10)	Healthy 7/22–39		Splenius and trapezius	Anatomical location/ Symmetri- cal to supine	80/0.8	0.75	EO/EC – standing with different head position and eye position	–	–	Pre-test(5 s)/ test under vibration (6/8 s)	Antero- postero plane = effect to the side of head position but more influenced by to eye position. EO effect toward the visual target and EC toward the imaginary target		
Yagi et al., 2000	CO (5/10)	Healthy 59/25.6		Trapezius and dorsal neck muscles	NA/ Bilateral	100/1	20	EC – standing	–	–	Pre-test(20 s)/ test under vibration (20 s)	Antero- postero plane = Effect maximum with the upper dorsal neck with a shift in the sagittal plane		–

Table 5 (Continued)

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Grasso et al., 1999	CO (3/10)	Healthy 4/33 ± 7		Splenius and trapezius	Anatomical location/ Symmetri- cal to supine	50/0.8	NA	EO/EC – standing with different head position and eye position	Galvanic vestibular stimulation	–	Pre-test (5 s)/ test under vibration (2 min)	Medio- lateral plane = Effect with a shift toward the eyes position when EO and toward to the Imaginary eye position when EC. Effect with latency 2 s and stable at 5 s. When repetitive neck vibration effect with a shift opposite eye deviation		Comparator = same effect
Ivanenko et al., 1999	CO (6/10)	Healthy 13/20 –39		Splenius and trapezius	Anatomical location/ Symmetri- cal to supine	50/0.8	15	EO/EC – standing with different head position and eye position	Galvanic vestibular stimulation	–	Pre-test (5 s)/ test under vibration (15s)	Antero- postero plane = Effect with a shift toward the eyes position when EO and toward to the Imaginary eye position when EC. Effect linked with eyes position > head position = head and trunk position		Comparator = Effect in the medio- lateral plane and biased toward eyes deviation

Table 5 (Continued)

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Kavounoudias et al., 1999	CO (5/10)	Healthy 11/22–55		Splenius and trapezius and SCOM	NA/ right/ left	80/0.2–0.4	2	EC – standing	TSV. TAV. PV	TSV. TAV. PV	Pre-test (1 s)/ test under vibration (2/3 s)/ post-test (4 s)	Medio- lateral plane = Effect with a shift con- tralateral to the muscle vibrated. When vibration of 2 antagonist muscles. No effect. When vibration of an antero- posterior muscle and lateral one. Effect with a shift in the oblique direction. SCOM = effect backward. Splenius = effect forward		Comparator = Effect with a shift Ipsilateral to muscle vibrated/ adjuvant = When vibration of 2 antagonist muscles. No effect. When vibration of an antero- posterior muscle and lateral one. Effect with a shift in the oblique direction
Yagi et al., 1998	CS (FAIR)	Healthy 30/29		Dorsal neck muscles	NA/ Bilateral	110/1	30	EC – standing	–	–	Pre-test (15 s)/ test under vibration (30 s)/ post-test (15 s)	Antero- postero plane = Effect with a shift forward		
Lekhe et al., 1998	CO (5/10)	Healthy 19/33.8 ± 10	Unilateral vestibular lesion 13/49 ± 15	Trapezius	NA/ right/ left	90/0.5	35/PRBS	EC – standing	–	–	Pre-test (4/5 s)/ test under vibration (35 s/PRBS)/ post-test (2/40 s)	Antero- postero plane = When vibration on = effect with a shift backward then forward. When the vibration is switched off = shift goes back to initial		

Table 5 (Continued)

Author	Design/ score	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Wierzbicka et al., 1998	CO (4/10)	Healthy 12/23–59		Splenius and trapezius and SCOM	NA/ Bilateral	80/0.2	30	EC – sitting	TAV bilateral/ TSV bilateral	–	Pre-test (60 s)/ vibration (30 s)/ post-test (19 min)	Antero- postero plane = Effect with a shift backward when vibration of the front NM and forward when vibration of the back of the neck. Post effect varied across subjects (3min-3H)		Comparator = Effect with shift forward for Soleus = forward and backward for TAV. Same effect for post- vibration
Fransson et al., 1998	CO (5/10)	Healthy 12/34.8		Dorsal neck muscles	NA/ Bilateral	60/1	PRBS	EO/EC – standing	TSV bilateral	–	Pre-test(30s)/ test under vibration (PRBS)	Antero- postero plane = Effect with a shift forward. EC > EO		Comparator = Effect with a shift backward

Table 5 (Continued)

Author	Design/ score	S1/number/ Age (Years)	S2/number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/ EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ adjuvant
Lekhe et al., 1997	CO (5/10)	Healthy 19/33.8 ± 10		Trapezius	NA/ right/ left	90/0.5	35/PRBS	EC – standing with different head position	–	–	Pre-test (4/5 s)/ test under vibration (35 s/PRBS)/ post-test (2/40 s)	Antero- postero plane = Effect with a shift forward		
Karlberg et al., 1996	CO (6/10)	Healthy 17/36 (25–55)		Dorsal neck muscles	Anatomical location/ Bilateral	20/ 40/60/ 80/100 – 0.4	10	EO/EC- standing	–	–	Pre-test (10 s)/ test under vibration (10 s)	Antero- postero plane = Effect with a shift on the antero- postero direction EO/EC and at different frequency		
Popov et al., 1996	CS (FAIR)	Healthy 19		Trapezius	NA/ right/ left	90/0.5	PRBS	EC – standing	–	–	Pre-test (30 s)/ test under vibration (PRBS)	Antero- postero plane = Effect with a shift forward and little right side with left vibration and forward and little left side with right vibration. No difference in amplitude of deviation between right/ left side vibration		
Gurfinkel et al., 1995	CS (POOR)	Healthy 12		Splenius	Illusion head move- ment/ NA	NA/NA	NA	EC – standing	–	–	NA	Medio- lateral plane = effect with a lateral body tilt		

AB: abdominal; AE: ankle external; AI: ankle internal; BF: biceps femoris; CS: case-study; CO: cross-over trail; EO, EC: eye open and closed; GL: gluteus; GMV: gluteus medius vibration; NA: not available; OKS: optokinetic stimulation; PRBS: pseudorandom binary sequence schedule; QV: quadriceps vibration; RF: rectus femoris; S: soleus; S1, S2: Subjects; TE: thigh external; TI: thigh internal; TAV: tibialis anterior vibration; TSV: triceps surae vibration; LU: trunk lumbar; TH: trunk thoracic; VTI: visual target illusion.

Table 6 Effect of neck muscle vibration on postural orientation of patients with disturbed balance.

Author	Design/ score	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Difference between groups	Comparator/ adjuvant
Leplaideur et al., 2016	CS (FAIR)	Stroke (RBD) 15/62.1 ± 8.5	Stroke (LBD) 16/60.9 ± 12	Splenius and semispinalis	VTI/ con- estionnel side	80/NA	600	EC – sitting	–	–	Pre-test (50 s)/ vibration (10 min)/ post test (immedi- ate)	Medio- lateral plane = Signifi- cant effect with a shift toward the hemi- plegic side	Medio- lateral plane = Signifi- cant effect with a shift toward the hemi- plegic side	No dif- ference	
Morris et al., 2015	CO (6/10)	Autism spectrum disorders 12/23.6 ± 7.9		Dorsal neck muscles	Anatomical location/ Bilateral	NA/NA	5	EO/EC – standing	–	–	Pre-test (15 s)/ test under vibra- tion(5 s)	Antero- postero plane = Effect both EO/EC with shift forward No effect			
Belnert et al., 2015	CO (6/10)	Neck pain 13/22.4		Neck muscles	Anatomical location painful side/ right/ left	100/1	30	NA-NA	–	–	Pre-test (60 s)/ vibration (30 s)/ post test (immedi- ate)				
Challots et al., 2014	CS (FAIR)	Stroke (RBD) 14/61.6	Stroke (LBD) 16/61.6	Neck muscles	VTI/ con- estionnel side	80/NA	600	EC – sitting	–	–	Pre-test (50 s)/ vibration (10 min)/ post-test (immedi- ate)	Medio- lateral plane = Effect (EO/EC) with a shift toward the hemi- plegic side	Medio- lateral plane = Effect (EO/EC) with a shift toward the hemi- plegic side	No dif- ference	
Mullie et al., 2014	CO (6/10)	Stroke 9/47.8 ± 11.8		Dorsal neck muscles	NA/ Bilateral	80/0.5	NA	EC – sitting	TSV paretic/ non dominant side	–	Pre-test (10 s)/ test under vibra- tion(20 s)	Antero- postero plane = Effect (EC) with a shift forward			Comparator = Effect (EC) with a shift backward

Table 6 (Continued)

Author	Design/ score	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Difference between groups	Comparator/ adjuvant
Dumas et al., 2013	CO (5/10)	Compensate Unilat- eral vestibu- lar lesions (left) 12/54± 8		Trapezius	Anatomical location/ right/ left	85/NA	10	EO/EC – standing	Mastoid vibra- tion. TSV Left/ Right	–	Test under vibration (25.6 s)	No effect		No dif- ference	Comparator = TSV effect with a shift back- ward in healthy and medio- lateral in unilat- eral vestibu- lar lesion
Challois- Lepplaideur et al., 2012	CS (FAIR)	Stroke (RBD) 7/60.3	Stroke (LBD) 7/60.3	Neck muscles	VTI/ contral- estonnel side	80/NA	600	EC – sitting	–	–	Pre-test (50 s)/ vibration (10 min)/ post-test (immedi- ate)	Medio- lateral plane = Effect (EC) with a shift toward the hemi- plegic side		Effect on RBD only	
Duclos et al., 2007	CO (5/10)	Lower limb amputa- tion 14/43 ± 10		Trapezius	Illusion head move- ment/ left side/ amputation side	80/0.5- 0.8	30	EC – sitting	GMV left side/ amputation	–	Pre-test (2 × 60 s)/ vibration (30 s)/ posttest (immedi- ate until 13 min)	Medio- lateral plane = Effect with a shift to one side (half subject) and to the opposite side (half of subject). Effect main- tained 13 min		Effect with a shift larger for Amputees	Comparator = No dif- ference CP shift ampli- tude. No differ- ence in CP shift between two groups

Table 6 (Continued)

Author	Design/ score	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Difference between groups	Comparator/ adjuvant
Bove et al., 2007	CS (FAIR)	Cervical dystonia 16/60.2 ± 14		SCOM	NA/ right/ left	90/NA	NA	EC – standing	–	–	Test under vibration (51.2 s)	Antero- postero plane = No effect or minor shift			
Valkovič et al., 2006	CS (FAIR)	PD (severe) 13/61.8 ± 9.2	PD (mod- erately affected) 13/ 64.2 ± 8.9	Splenius and trapezius	Anatomical location/ Bilateral	80/1	3X10	EO/EC	–	–	Test under vibration (60 s)	Antero- postero plane = Effect with a shift back- ward (119 ms to 123 ms) than forward (250 ms to 400 ms). Effect EC > EO. With repeti- tive vibration no effect (EO/EC)	Antero- postero plane = Effect with a shift back- ward (119 ms to 123 ms) than forward (250 ms to 400ms). Effect EC > EO. With repeti- tive vibration no effect EO and decrease effect EC	Larger effect in S1	
Bove et al., 2004	CO (5/10)	Cervical dystonia 12/59.6 ± 15		SCOM	Anatomical location/ right/ left	90/NA	51.2	EC – standing	–	–	Pre-test (51.2 s)/ test under vibration (51.2 s)	No effect		Weaker effect for S1	
Ribot- Ciscar et al., 2004	CS (POOR)	Muscular dys- trophia 11/35.4 ± 13		Splenius	Anatomical location/ left	80/0.5	2	EC – standing	TAV bilat- eral/ TSV bilateral	–	pre-test (0.5 s)/ test under vibration (20 s)/ post-test (immedi- ate)	Antero- postero plane = Effect with a shift forward		Same effect	Comparator = Effect with a shift forward for TAV and back- ward for TSV

Table 6 (Continued)

Author	Design/ score	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Difference between groups	Comparator/ adjuvant
Kristinsdottir et al., 2000	CO (4/10)	Hip fracture subjects 19/ 72.5		Dorsal neck muscles	NA/ Bilateral	60/1	PRBS	EO/EC – standing	TSV bilateral	–	Pre-test (30 s)/ test under vibration (PRBS)	Antero- postero plane = Effect in EC for 2/19			Comparator = TSV EC S1(8/19) S2(1/28)
Yagi et al., 2000	CO (5/10)	unilateral vestibu- lar lesions 12/55.5		Trapezius and dorsal neck muscles	NA/ Bilateral	100/1	20	EC – standing	–	–	Pre-test (20 s)/ test under vibration (20 s)	Medio- lateral plane = Effect with dorsal neck toward the ipse- sional side. No effect with the trapezius		Less effect for S1 with the upper dorsal neck	
Yagi et al., 1998	CS (FAIR)	Unilateral vestibu- lar lesions (compen- sated) 37/55.5 ± 11.8	Unilateral vestibu- lar lesions(acute) 37/51.9 ± 12.6	Dorsal neck muscles	NA/ Bilateral	110/1	30	EC – standing	–	–	Pre-test (15 s)/ test under vibration (30 s)/ post-test (15 s)	Antero- postero and medio- lateral plane = Effect with a shift forward and toward the lesion side	Antero- postero and medio- lateral plane = Effect with a shift forward and toward the lesion side	S1/S2 larger shift then S3	

Table 6 (Continued)

Author	Design/ score	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Difference between groups	Comparator/ adjuvant
Lekhe et al., 1998	CO (5/10)	Bilateral vestibular lesions 11/52 ± 14	Unilateral vestibular lesion 13/49 ± 15	Trapezius	NA/ right/ left	90/0.5	35/PRBS	EC – standing	–	–	Pre-test (4/5 s)/ test under vibration (35 s/PRBS)/ post-test (2/40 s)	No effect	Antero- postero and medio- lateral plane = ipsilat- eral vibration = effect with a shift toward the side of lesion and back- ward. Contra- lesional vibration = Effect with a shift forward		
Lekhe et al., 1997	CO (5/10)	Spasmodic torticollis 19/42.4 ± 7	Bilateral vestibular lesions 11/52 ± 13	Trapezius	NA/ right/ left	90/0.5	35/PRBS	EC – standing with different head position	–	–	Pre-test (4/5 s)/ test under vibration (35 s/PRBS)/ post-test (2/40 s)	Antero- postero plane = Little effect with a shift forward or no effect	Antero- postero plane = Little effect with a shift forward or no effect	S1 = S2	

Table 6 (Continued)

Author	Design/ score	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Zone or muscles vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Duration (s)/ repetition	Vibration EO/EC – position	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Difference between groups	Comparator/ adjuvant
Karlberg et al., 1996	CO (6/10)	Neck pain 17/37 (26-49)		Dorsal neck muscles	Anatomical location/ Bilateral	20/40/ 60/80/ 100 - 0.4	10	EO/EC – standing	–	–	Pre-test (10 s)/ test under vibration (10 s)	Antero- postero plane = Effect with a shift on the antero- postero direction EO/EC and at different fre- quency		Effect signifi- cantly greater in S1	
Popov et al., 1996	CS (FAIR)	Unilateral vestibular lesions 9		Trapezius	NA/ right/ left	90/0.5	PRBS	EC – standing	–	–	Pre-test (30 s)/ test under vibration (PRBS)	Medio- lateral plane = Effect vibration of the contral- esternal (forward) side higher than ipsile- sternal side (back- ward and rotation to the ipsile- sternal side)		Effect smaller during vibration of the affected side	
Leblong and al. Unpub- lished	CO (6/10)	Stroke (RBD) 11/63.3 ± 14	Stroke (LBD) 10/58.2 ± 11	Dorsal neck muscles	NA/contral- esternal side	70/NA	300	EO – standing	Ipsilateral GMV/ contral- esternal Biceps Brachial vibration	–	Pre-test (52 s)/ test under vibration (5 min)/ post-test (2/10min)	No effect	No effect	No dif- ference	Comparator = No effect

CS: case study; CO: crossover trial; EO, EC: eye open and closed; GMV: gluteus medius vibration; LBD: left brain damage; NA: not available; PD: Parkinson disease; QV: quadriceps vibration; RBD: right brain damage; S1, S2: subjects; TAV: tibialis anterior vibration; triceps surae vibration (TSV); visual target illusion (VTI).

Table 7 Effect of neck muscle vibration (NMV) on spatial perception of healthy subjects.

Author	Design	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC – Duration (s)	Vibration position – Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Frase et al., 2015	CO (5/10)	Healthy 16/21–60		SVV/SHV	Dorsal neck muscles	Anatomical location/ bilateral	30/NA	EO – NA	Standing with body tilt – light	–	–	Test under vibration	Effect with a shift opposite body tilt		
Gulnet et al., 2013	CO (5/10)	Healthy/ 54/ 25.11 ± 8.28		SSA. VTI	Splenius	VTI/ right	80/NA	EO – 150	Sitting – dark	Prism	Prism	Pre-test/ vibration/ post-test	SPA = Effect on subjects with illusion of LED in sagittal plane. SVA = No effect		Comparator = Effect/ adjuvant = Effect
McIntyre et al., 2007	CO (5/10)	Healthy/11		VTP	Splenius	Anatomical location/ muscle palpa- tion/ VTI/ right/ left	90/NA	EO – 8	Sitting – dark/ light	–	Prism	Test under vibration	Effect toward the opposite side of stimulus in dark (11/11) and light (3/11) but more pronounced in dark		
Seizova- Cajic et al., 2007	CO (4/10)	Healthy/21		VTP	Splenius and trapezius and SCOM	Anatomical location/ right/ left	140/NA	EO – 15	Sitting – dark/ light	–	–	Test under vibra- tion(15 s)/ post-test (15 s)	Effect with a shift toward opposite side of the vibration. Post-effect in all condition light with less post effect when the VT was not present during the period of vibration		
Seizova- Cajic et al., 2007	CO (3/10)	Healthy/9		VTP	Splenius and trapezius and SCOM	Anatomical location/ right/ left	140/NA	EO – NA	Sitting – dark/ light	–	–	Test under vibration (15 s)/ post-test (15 s)	Post-effect in all condition but smaller when the VT was absent under the period of vibration		

Table 7 (Continued)

Author	Design	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC – Duration (s)	Vibration position – Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Ceyte et al., 2006	CO (5/10)	Healthy/ 13/27		SSA	Trapezius	Muscle palpa- tion/ left	100/0.2	EO – NA	Standing – dark	–	–	Test under vibration	Effect with a shift toward the left side (vibrated side)		
Ceyte et al., 2006	CO (6/10)	Healthy/ 7/30		SSA	Trapezius	Muscle palpa- tion/ left	100/0.2	EO – NA	Standing or lying Right/ left side – dark	–	–	Test under vibration	Effect with a shift toward the left side. Effect larger when lying on the left side than standing. No effect when lying on the right side		
Seizova- Cajtc et al., 2006	CO (3/10)	Healthy/12		VTP	Trapezius and semispinals and SCOM	Anatomical location/ Bilateral/ right	125/NA	EO – 15	Sitting – dark	–	–	Pre-test (60/2 s)/ test under vibration (15 s)/ post-test (15 s)	Effect for SCOM upward during vibration, downward during post- vibration and for splenius = Left and/or upward during vibration and opposite during post- vibration. Effect in 7/10 subjects		
McKenna et al., 2004	CO (6/10)	Healthy/ 26/36		SVV	Dorsal neck muscles	Anatomical location/ right/ left	100/A	EO – NA	Sitting with different head position – dark	Left and right mastoid vibration	–	Pre-test/ test under vibration	Effect with a shift opposite direction head roll-tilt with more effect when vibration on the side of the head opposite to the head tilt		Comparator = Main effect for neck vibration

Table 7 (Continued)

Author	Design	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC – Duration (s)	Vibration position – Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Karnath et al., 2002	CO (5/10)	Healthy 18/27.3		SSA	Neck muscles	VTI/ left	80/0.4	EO – 180	Sitting – dark	Left hand vibration	–	Pre-test/ test under vibration (3 min)	Effect with a shift toward the left side (vibrated side)		Comparator = No effect
Karnath et al., 2002	CO (6/10)	Healthy 6/29.5		SSA	Neck muscles	VTI/ left	80/0.4	EO – 60/300/ 900/1800	Sitting – dark	–	–	Pre-test/ test under vibra- tion/ post-test (3 min)	No difference of the duration on the deviation but on the maintaining of the effect. The more the duration is increased the more the effect is maintained		
Karnath et al., 2002	CS (FAIR)	Healthy 6/27.5	Healthy/6/25	SSA	Neck muscles	VTI/ left	80/0.4	EO – 1680	Sitting – dark	–	Visual Informa- tion	Pre-test/ test under vibra- tion/ post-test (3 min)	Effect with a shift toward the left side (vibrated side)		Adjuvant = Reduce effect of NMV
Karlberg et al., 2002	CO (5/10)	Healthy 13/32		SVH	SCOM	Palpation muscle/ right/ left	92/0.6	EO – NA	Sitting – dark	Mastoid bone vibration	–	Pre-test/ test under vibration	Effect only in 1/13 subjects		Comparator = Less effect
Betts et al., 2000	CO (5/10)	Healthy 21/40		SVH	SCOM	Palpation muscle/ right/ left	100/0.4	EO – 100	Sitting with different head position or standing with whole body tilt – dark	–	–	Pre-test (100 s)/ test under vibration (100 s)	No effect		
Strupp et al., 1999	CS (FAIR)	Healthy 30/46.1 ± 12.9		SSA	Dorsal neck muscles	NA/ right/ left	100/1	EO – 20	Sitting – dark	–	–	Pre-test/ test under vibration	Effect with a shift toward the side of stimulation, which increases with the age		

Table 7 (Continued)

Author	Design	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC – Duration (s)	Vibration position – Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Popov et al., 1999	CO (5/10)	Healthy 5/25–51		VTI	Trapezius	VTI/ right	90/0.5	EO – 10	Sitting and supine position – dark/ light	–	–	Pre-test (5 s)/ test under vibration (10 s)	Effect with a shift toward the left. Same effect in sitting and supine position. In supine position also a shift in the vertical plane (up or down). No effect when light on		
Han et al., 1999	CO (5/10)	Healthy 8/32–49		VTP, VTI	Splenius and SCOM	VTI/ right/ left	70/1	EO – 8/10	Sitting – Dark	–	–	Pre-test (8/10 s)/ test under vibration (8/10 s)	Effect with a shift to the left when vibration of the left SCOM/right splenius and to the right with right SCOM/ left splenius. Vibration off VTI goes back or continue		
Strupp et al., 1998	CS (FAIR)	Healthy 25/49.1 ± 14.2		SSA	Dorsal neck muscles	VTI/ right/ left	100/1	EO/EC – 20	Sitting – dark	–	Prism	Pre-test/ test under vibra- tion/ post-test (1 year)	Effect with a shift toward the side of muscle vibrated. No difference between Right/ Left vibration		Adjuvant = Opposite effect
Karnath et al., 1996	CO (5/10)	Healthy/ 10/50		SSA	Dorsal neck muscles	VTI/ left	100/0.4	EO – NA	Sitting – dark	Vestibular stimula- tion	–	Pre-test/ test under vibration	Effect with a shift toward the left side		Comparator = Same effect

Table 7 (Continued)

Author	Design	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC – Duration (s)	Vibration position – Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Lennerstrand et al., 1996	CO (5/10)	Healthy 8/29–36		VTI	Splenius and SCOM	NA/ Bilateral/ right/ Left	70/1	EO – 10	Sitting – dark/ light	–	–	Pre-test (10 s)/ test vibration (10 s)/ post-test (10 s)	Effect with a shift toward the left when vibration of the left SCOM and right splenius. To the right with right SCOM and left splenius. Downward with both splenius. No effect in fully light		
Karnath et al., 1994	CO (5/10)	Healthy 17/31		SSA. VTI	Dorsal neck muscles	VTI/ right/ left	100/0.4	EO – NA	Sitting – dark	Vestibular stimula- tion	Vestibular stimula- tion	Pre-test/ test under vibration	Deviation of SSA only for patients with VTI (9/17). VTI = Effect with a shift toward the right with left NMV vs versa (±vertical). SSA = Effect with a shift toward the left with left NMV vice versa		Comparator =Effect with a shift on the right side for 17/17/ Adjuvant = When in the same side = Larger effect than alone. When in opposite side = Neutral- ize effect
Karnath et al., 1994	CO (5/10)	Healthy/ 10/50		SSA. VTI	Dorsal neck muscles	VTI/ right/ left	100/0.4	EO – NA	Sitting – dark/ light	Vestibular stimula- tion	Vestibular stimula- tion	Pre-test/ test under vibration	Effect with a shift toward the left and (±vertical) with left vibration vice versa and Effect on SSA only on patient with VT motion (10/10)		Comparator = Effect in 10/10/ Adjuvant = Same side = Larger effect than alone. Opposite side = Neutral- ize effect

Table 7 (Continued)

Author	Design	S1/ number/ Age (Years)	S2/ number/ Age (Years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC – Duration (s)	Vibration position – Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Karnath et al., 1993	CS (POOR)	Healthy/ 15/46		VTI	Dorsal neck muscles	VTI/ right/ left	100/NA	EO – NA	Sitting – dark	Left hand vibration		Pre-test/ test under vibration	Effect in 10/15 subjects with a shift to the right with Left NMV and to the left with right NMV		Comparator = No effect
Taylor et al., 1991	CS (POOR)	Healthy 13		VTI	Neck muscles	VTI/left	100/NA	EO – 15	Sitting – dark	–	–	Test under vibration	Effect in 9/13 subjects with a shift toward the left (3) and toward the right (6)		
Biguer et al., 1998	CS (POOR)	Healthy 10/25–55		VTP, VTI	Dorsal neck muscles	VTI/ left	100/0.3	EO – NA	Sitting – dark/ light	–	–	Pre-test/ test under vibration	Effect with a shift to the right side (±vertical). Relation between VTI and VTP. Effect 9/10 subjects in Dark and middle dark and 2/10 when in light. Vibration off VTI goes initial position		
Biguer et al., 1998	CO (4/10)	Healthy 9		SSA, VTP	Dorsal neck muscles	VTI/left	100/ 0.13/ 0.29/ 0.49	EO – NA	Sitting – dark	–	–	Pre-test/ test under vibration	When increasing the amplitude of vibration. It increases the amplitude of deviation of VTP		
Lackner et al., 1979	CO (4/10)	Healthy 10/25–55		VTI	Splenius and trapezius and SCOM	NA/ Bilateral/ right/ Left	120/NA	EO – NA	Standing – dark/ light	Muscles vibration		Test under vibration	VTI moving according to head change. No effect in fully light		Comparator = Moving accord- ing to head or body motion

CS: case study; CO: crossover trial; EO, EC: eye open and closed; NA: not available; SSA: subjective straight ahead; SVH: subjective visual haptic; SVV: subjective visual vertical; S1, S2: VTI: Subjects, visual target illusion; VTP: visual target pointing.

Table 8 Effect of neck muscle vibration (NMV) on spatial perception of patients with disturbed balance.

Author	Design	S1/ number/ Age (years)	S2/ number/ Age (years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC- Duration (s)	Vibration position- Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Leplaldeur et al., 2016	CS (FAIR)	Stroke (RBD) 15/62.1 ± 8.5	Stroke (LBD/ 16/ 12)	VTI	Splenius and semisp- inalis	VTI/ contral- esternal side	80/NA	EO-600	Sitting- dark	—	—	Test under vibration	Effect toward the opposite side of the stimulus in 11/15 subjects	Effect toward the opposite side of the stimulus in 9/16 subjects	
Kawase et al., 2011	CO (4/10)	unilateral vestibu- lar lesions/ 14/ 54.2		SVV	Dorsal neck muscles	Anatomical location/ right/ left	110/NA	EO-NA	Sitting- dark	—	—	Test under vibration	Effect with a shift toward the ipsile- sional side. Effect larger when vibration in the ipsile- sional side		
Schindler et al., 2004	CO (5/10)	Stroke (RBD)/5/ 44–70		SSA	Splenius	VTI/ left	100/NA	EO-NA	Sitting – dark	vibration left dorsal palm and visual motion stimula- tion (left and right)	—	Pre-test/ test under vibration	Effect with a shift toward the left side (vibrated side)		Comparator = vibration left dorsal palm = no effect. No dif- ference between VMS and NMV
Johannsen et al., 2003	CS (FAIR)	Stroke (RBD with neglect) /6/68 ± 9.5		VTI	Dorsal neck muscles	VTI/ left	80/0.4	EO-120	Sitting – dark	—	—	Test under vibration	Effect of deviation in 3/6 subjects toward the right		
Schindler et al., 2002	CO (6/10)	Stroke (RBD) 20/48.7 ± 14.3		SSA, VTI	Dorsal neck muscles	VTI/ contrale- sionnel side	80/0.4	EO-NA	Sitting – dark	—	Visual explor- ation training	Pre-test/ test under vibra- tion/ post-test (2 months)	Effect with a shift toward the left side and stable. VTI in all subjects		Adjuvant = More effect

Table 8 (Continued)

Author	Design	S1/ number/ Age (years)	S2/ number/ Age (years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC- Duration (s)	Vibration position- Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Karlberg et al., 2002	CO (5/10)	Unilateral vestibular lesions 23/53.6		SVH	SCOM	Palpation muscle/ right/ left	92/0.6	EO-NA	Sitting – dark	mastoid bone vibration	–	Pre-test/ test under vibration	Effect with a shift toward the ipsile- sional side. Effect larger when vibration in the ipsile- sional side. Effect in 21/23 subjects		Comparator = Less effect
Betts et al., 2000	CO (5/10)	Unilateral vestibular lesions 27/32		SVH	SCOM	Palpation muscle/ right/ left	100/0.4	EO-100	Sitting with different head position or standing with whole body tilt – dark	–	–	Pre-test (100 s)/ test under vibration (100 s)	More effect when vibration in the ipsile- sional side with the head roll-tilt in the contrale- sional side		
Popov et al., 1999	CO (5/10)	Bilateral vestibular lesions 4/43–76		VTI	Trapezius	VTI/ right	90/0.5	EO-10	Sitting and supine position – dark/ light	–	–	Pre-test (5 s)/ test under vibra- tion(10 s)	Effect with a shift down- ward. Same effect in sitting and supine position. In supine position also a shift in the vertical plane (up or down). No effect when light on		

Table 8 (Continued)

Author	Design	S1/ number/ Age (years)	S2/ number/ Age (years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC- Duration (s)	Vibration position- Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Han et al., 1999	CO (5/10)	Strabismic patients 16/26–54		VTP, VTI	Splenius and SCOM	VTI/ right/ left	70/1	EO-8/10	Sitting – dark	–	–	Pre-test (8/10 s)/ test under vibration (8/10 s)	Effect for good binocular with a shift to the left when vibration of the left SCOM/ right splenius and to the right with right SCOM/left splenius. Effect variable for poor binocular		
Strupp et al., 1998	CS (FAIR)	Unilateral vestibular lesions 25/50.2 ± 12.3		SSA	Dorsal neck muscles	VTI/ right/ left	100/1	EO/EC-20	Sitting – dark	–	Prism	Pre-test/ test under vibra- tion/ post-test (1 year)	Effect with a shift toward the side of the stimulus. Effect ipsile- sional side > contrale- sional side. Effect main- tained 60/80d then decreases. No effect with SSA finger EC		Adjuvant = Opposite effect
Karnath et al., 1996	CO (5/10)	Stroke (RDB with neglect) 3/61 ± 15		SSA	Dorsal neck muscles	VTI/ left	100/0.4	EO-NA	Sitting – dark	Vestibular stimula- tion	–	Pre-test/ test under vibration	Effect with a shift toward the left side		Comparator = Same effect

Table 8 (Continued)

Author	Design	S1/ number/ Age (years)	S2/ number/ Age (years)	Outcome measures	Muscle vibrated	Muscle tracking/ side	Frequency (Hz)/ Amplitude (mm)	Vibration EO/EC- Duration (s)	Vibration position- Room light	Comparator	Adjuvant	Protocol	Effect of vibration (S1)	Effect of vibration (S2)	Comparator/ Adjuvant
Karnath et al., 1994	CO (5/10)	Stroke (RDB with neglect) 3/61 ± 15	Stroke (LBD) 4/50.5	SSA, VTI	Dorsal neck muscles	VTI/ right/ left	100/0.4	EO-NA	Sitting – dark/ light	Vestibular stimula- tion	Vestibular stimula- tion	Pre-test/ test under vibration	Left NMV (con- trales- sional side) = Correc- tion effect. Right NMV (ipsile- sional side) = Worsen effect. Effect on SSA only on patient with VT motion (2/3)	Effect with a shift toward the left with left vibration vis versa. Effect on SSA only on patient with VT motion (2/4)	Comparator = Effect in 17/17/ Adjuvant = Same side = Larger effect than alone. Opposite side = Neutral- ize effect
Karnath et al., 1993	CS (POOR)	Stroke (RDB with neglect) 3/68 ± 15	Stroke (LBD)/5/58	VTI	Dorsal neck muscles	VTI/ right/ left	100/NA	EO-NA	Sitting – dark	Left hand vibration		Pre-test/ test under vibration	Effect In 1/3 subjects with a shift to the right with Left NMV and no effect with right NMV	Effect In 2/5 subjects with a shift to the right with Left NMV and to the left with right NMV	Comparator = No effect

CS: case study; CO: crossover trial; EO, EC: eye open and closed; LBD: left brain damage; NA: not available; PD: Parkinson disease; RBD: right brain damage; SSA: subjective straight ahead; SVH: subjective visual haptic; SVV: subjective visual vertical; S1, S2: Subjects; VTI: visual target illusion; VTP: visual target pointing.

Appendix 5 - Short term effects of neck muscle vibration on postural disturbances in stroke patients.

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Short-term effect of neck muscle vibration on postural disturbances in stroke patients

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Abstract Balance disorders after stroke have a particularly detrimental influence on recovery of autonomy and walking. The present study is aimed at assessing the effect of proprioceptive stimulation by neck muscle vibration (NMV) on the balance of patients with right hemispheric lesion (RHL) and left hemispheric lesion (LHL). Thirty-one (31) patients (15 RHL and 16 LHL), mean age 61.5 years (10.6), mean delay 3.1 (1.6) months after one hemispheric stroke were included in this prospective study. The mean position in mediolateral and anteroposterior plane of the CoP (center of pressure) and the surface were evaluated using a force platform at rest and immediately after 10 min of vibration on the contralesional dorsal neck muscle. NMV decreases the lateral deviation balance induced by the stroke. Twenty patients (64.5 %) experienced a visual illusion of light spot moving toward the side opposite stimulus. These patients showed more improvement by vibration than those without visual illusion. There was an interaction between sensitivity and side of stroke on the effect of NMV. Proprioceptive stimulation by NMV

reduces postural asymmetry after stroke. This short-term effect of the vibration is more effective in patients susceptible to visual illusion. This result was consistent with a central effect of NMV on the structures involved in the elaboration of perception of body in space.

Keywords Stroke · Neck muscle vibration · Balance control · Posturography

Introduction

A major part of a stroke patient's rehabilitation is focused on balance training, because balance recovery crucially contributes to the end result. Balance is a prognostic factor for autonomy, transferring and walking recovery (Bohanon and Leary 1995; Fong et al. 2001; Nardone et al. 2009). Postural disorders can be explained by motor or sensory deficit (Geurts et al. 2005; Sackley 1990; Winstein et al. 1989), and spatial cognition deficit may add to balance disturbance (Rode 1998).

Compared to patients with left hemispheric lesion (LHL), those with RHL take longer to recover balance and independence (Rode 1998; Perennou 1999). And in left hemiplegics, slow balance recovery is likely to be related to spatial cognition disorders (Goto et al. 2009; Katz et al. 1999; Perennou 1999). Despite this overriding issue of balance disorder management, no treatment techniques specifically addressing this cognitive component of imbalance are currently being used. First tested for the correction of spatial bias in cases of neglect, vestibular, visual or proprioceptive are likely to be of interest in managing the postural deficiencies associated with cognitive disorders after stroke (Rode 1998; Perennou 1999). Several stimulations have been tested to improve body position shifts related

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to spatial cognition disorders (Bonan et al. 2015). But to our knowledge, neck vibrative stimulation has not yet been tested as a means of improving postural asymmetry after stroke.

The neck muscle proprioception system plays a particularly crucial role in the perception of the body in space and in postural orientation because of its direct links with the vestibular and oculomotor systems (Biguer et al. 1988; Kavounoudias et al. 1999; Marsden et al. 2005). Messages from the proprioceptive receptors of the neck and vestibular receptors in conjunction with eye direction information help to localize objects relative to the body. Vibration is a potent proprioceptive stimulus for the primary endings of the muscle spindles (Gilhodes et al. 1992). In addition to segmental response, neck muscle vibration (NMV) has been shown to produce global effects probably through activation of the brain function related to multisensory integration that help to restore the body representation (Ivanenko et al. 1999; Karnath et al. 2002; Pettorossi and Schieppati 2014).

Our working hypothesis was that proprioceptive stimulation by neck muscle vibration could improve mental body representation in space and consequently reduce the postural disturbance associated with cognitive impairment after stroke.

The aim of our study was to assess the effects of proprioceptive stimulation by one NMV session on balance disturbances in stroke patients. We also evaluated the relative importance of side of lesion, susceptibility to visual illusion and sensitivity.

Materials and methods

This prospective study was conducted in the physical and rehabilitation medicine (PRM) department of the University Hospital of Rennes and in the neurological PRM unit of Kerpape Center. From April 2011 to April 2013, all patients with either right or left hemispheric stroke were included if they met the inclusion criteria.

Population

The group consisted of thirty-one patients: 25 men and 6 women with a mean age of 61.5 years (standard deviation (SD) 10.6), all of them right-handed and who were admitted to the study less than 6 months after their first hemispheric stroke. Patients were included provided they were able to stand up with closed eyes for 30 s and had a lateral ipsilesional deviation of the CoP. Patients were not included if they were over 80 years of age, had a neurological history before stroke or suffered from vertigo, vestibular dysfunction, amblyopia or reduced alertness. Aphasic patients were

not included if they failed to understand the procedure. A complete examination was performed: functional independence using the Barthel Index (Mahoney and Barthel 1965), motor impairment using the motricity index (Collin and Wade 1990) and the functional ambulation classification modified (FAC, Holden et al. 1984). Postural performances were considered by the Postural Assessment Scale for Stroke (PASS). Neglect was evaluated by the Bells test, line bisection and figure copy and considered to be present if at least two tests were positive.

After having reviewed the research project, the local Ethics Committee of Rennes University Hospital has issued a favorable opinion (Number 11.12). Before testing, we collected informed written patient consent.

Experimental protocol

Neck muscle vibration

Subjects were made to sit in a dark room. A red light spot was projected on the wall in front of patient. Patients were classified as susceptible to vibration if a visual illusion of light spot deviation occurred toward the side opposite the stimulation. In this case, the vibrator was positioned on the neck so as to ensure that the vibration would cause the maximal illusion of light spot deviation. When no illusion was induced, the position of the vibrator was in the position mostly used in responsive patients: the paroccipital area on the contralesional side. In this position,

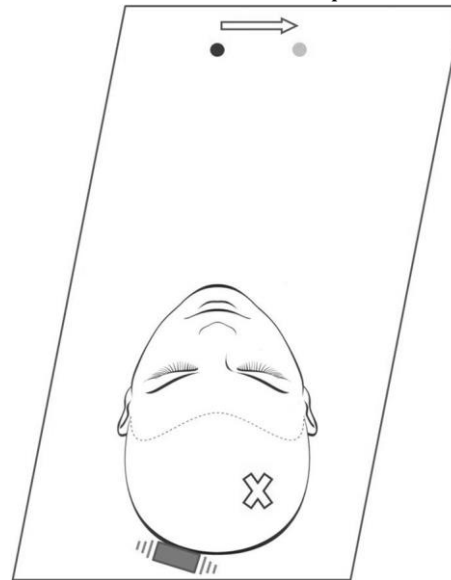


Fig. 1 Representation of patient with right hemisphere lesion (represented by a cross) receiving a contralesional side vibration (represented by a cube). This patient is susceptible to visual illusion: In the dark, the patient feels an illusion of light spot movement toward the side opposite the vibration area (illusion of spot deviation represented by an arrow)

vibration is presumably above the semispinalis and splenius (Fig. 1).

After vibration positioning, the subjects received neck muscle vibration for 10 min while blindfolded (Fig. 2). Following previous studies about neck muscle vibration (Gill- hodes et al. 1992; Biguer et al. 1988), we applied vibration on the side toward which we expect displacement. So the vibration is set up on the left side when the cerebral lesion is on the right.

The vibration was continuously delivered at 80 Hz by a plastic tube 7 cm long and 3 cm diameter (VB 115®, Techno Concept, France) held in place by a rubber band. Stimulation was given in the sitting position, which reduces the risk of falling that can be induced by a change of balance (Duclos et al. 2007; Wierzbicka et al. 1998).

Quantification of the postural responses to neck vibration

The first evaluation was carried out at rest. Patients stood on a force platform (SATEL®, France) for 25 s, and the displacement of the center of pressure (CoP) was recorded (Brun et al. 1993). The instruction given to the patient was to maintain a standing position, arms at the sides. The first evaluation consisted of 4 sessions: 2 sessions with open eyes (OE) and 2 sessions with closed eyes (CE). For the “closed eyes” situation, the patient was provided with a headband to reduce the risk of eyes opening. The second evaluation was carried out with the same protocol immediately after 10 min of dorsal neck vibrations in sitting position, beginning with the eyes-closed assessment (Fig. 3).

For each session, the mean position of the CoP in the mediolateral (ML) plane and in the anteroposterior (AP) plane (in mm) and the surface (mm²) were calculated. The average position during each of the two closed-eyes sessions and the average position during each of the two open-eyes sessions were then calculated for the first evaluation (at rest) and the second evaluation (after vibration). The difference in the mean position of the CoP (mm) between the first (at rest) and the second (after vibration) evaluation was calculated first with closed eyes and then with open eyes. Expressed in terms of pre-post difference, the difference was positive if the position of the CoP had improved once it had been completed and negative if it was worse.

Statistics

We used SAS software. Mean ML and AP position of the CoP and the surface during the eyes-open and the eyes-closed situations were compared at rest and after vibration with Wilcoxon test. The alpha level was set

at 5 %. We tested the effect of 3 factors on the variation using a mixed model with repeated measure subject adjusted to the rest position of the CoP: side of the lesion (RHL vs. LHL); susceptibility to visual illusion versus non-susceptibility to visual illusion; normal sensitivity versus low sensitivity. For multiple comparisons, we used a Bonferroni correction.

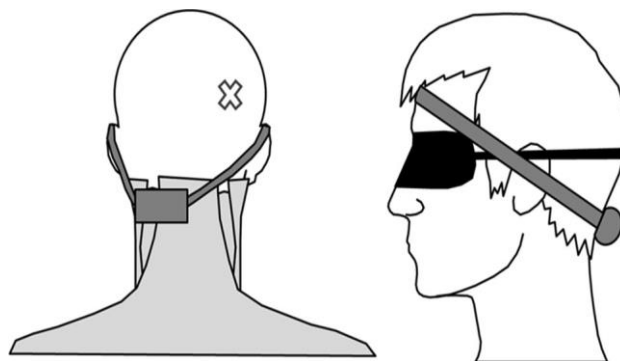


Fig. 2 Position of the neck muscle vibration (represented with a cube) on a blindfolded patient with right hemisphere lesion (represented with a cross)

Results

Clinical data (Table 1)

The evaluation was conducted on average 3.1 months after stroke (SD 1.6). The cerebral lesion was right in 15 cases and left in 16 cases: 19 ischemic and 12 hemorrhagic.

Four patients had left spatial neglect. The motricity index was 49.4/100 (SD 24.6).

Epicritic sensitivity is tested twice compared to the healthy side by a foam point on thigh, leg and foot. The test is abnormal if the patient describes one zone of hypoesthesia or anesthesia on the contralesional side. Sensitivity was normal in 16 patients, abnormal in 15 patients (14 with hypoesthesia, one with anesthesia). The mean modified functional ambulation classification was 3.7/8 (SD 2.1). There was no difference between the RHL group and the LHL group (Table 1).

The posturography results in LHL and RHL groups are summarized in Table 2, and in absolute terms, no difference was noted between the two groups.

Effect of neck muscle vibration on all patients

The mean mediolateral CoP position of the patients was significantly displaced after vibration toward the hemiplegic side, i.e., to the left for the RHL and to the right for the LHL (the variation was positive) (ML deviation: 20.7 ± 11.5 mm before NMV to 18.5 ± 13.5 mm after NMV; mean variation 3.1; $p < 0.005$) (Tables 3, 4).

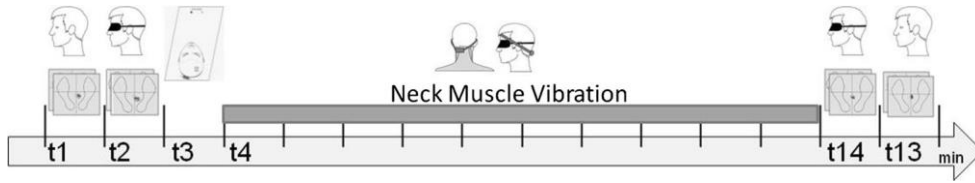


Fig. 3 Pattern of evaluation and stimulation procedure with time: t1—two posturographies (25 s each) with eyes open; t2—two posturographies (25 s) with eyes closed; t3—vibration positioning in

darkness; t4—10 min of neck muscle vibration (NMV); t14—two posturographies (25 s) with eyes closed after NMV; t15—two posturographies (25 s) with eyes open after NMV

Table 1 Clinical data, patients with right hemispheric lesion (RHL) and patients with left hemispheric lesion (LHL)

	RHL group <i>n</i> = 15	LHL group <i>n</i> = 16	<i>p</i>
Age (years)	62.1 (±8.5)	60.9 (±12)	0.76
Male/female	11/4		
Time after stroke (months)	2.6 (±1.6)	3.6 (±1.6) 14/2	0.10
Hypoesthesia	7	7	
Anesthesia	1	0	
Sensitivity			
Susceptibility to visual illusion	11	9	
Functional ambulation classification modified (/8)	3.8 (±2.3)	3.6 (±1.9)	0.77
Motricity index (/100)	49.4 (±26.9)	46.5 (±26.2)	0.7
Number of neglect patients	4	0	

Data are presented with mean (standard deviation) except for number of patients with sensitivity deficit, susceptibility to NMV visual illusion or neglect

Table 2 Posturography results in right hemisphere lesion and left hemisphere lesion patients

	RHL (15)	LHL (16)	<i>p</i>
ML deviation			
CE	21.6 (±14)	−18.5 (±6)	0.9
OE	21.9 (±13)	−21.1 (±10)	0.4
AP deviation			
CE	−37.9 (±10)	−34 (±12)	0.6
OE	−38.6 (±16)	−36.8 (±10)	0.5
Surface			
CE	1244 (±956)	1393 (±1169)	0.7
OE	642 (±475)	901 (±832)	0.6

Mediolateral (ML) deviation and anteroposterior (AP) deviation in mm, with closed eyes (CE) and open eyes (OE)

Table 3 For all patients mean anteroposterior (AP) position of the center of pressure, surface and (standard deviation), at rest and after neck muscle vibration (mm)

Twenty patients (64.5 %) (11 RHL and 9 LHL) were found to be susceptible to visual illusion as they described the illusion of light deviation toward side of the lesion. The effect of vibration was present in patients who felt visual illusion (mean displacement variation: 4.7 vs. 0.08 mm, $p < 0.05$) Table 5.

	Mean ML deviation	Mean AP deviation	Surface
Before NMV	20.7 (± 11.5)	-35.7 (± 12.3)	1866 (± 3882)
After NMV	18.5 (± 13.5)	-33.5 (± 12.8)	1035 (± 1055)
p	<0.005	0.36	0.11

Patients with a sensitivity deficit were more improved than those without it (4.3 vs. 1.7; $p < 0.05$). There is no dependence between motor capacities.

Overall, there was an interaction effect between side of stroke and sensitivity ($p < 0.05$). When comparing the two sides using multiple-comparison Bonferroni correction, we

noted a very wide variation in hyposensitive patients with LHL 8.51 versus with RHL 1.08 ($p = 0.19$) (Fig. 5). While

the effect of neglect was not statistically studied because the size of the group was insufficient (4 persons), these patients seemed to be more deviated at rest and to have more deviation in an eyes-open situation after NMV.

Table 4 Data for mean

mediolateral deviation of center of pressure before and after neck muscle vibration, with closed eyes (CE) and open eyes (OE), on patients with right hemisphere lesion (RHL) or left hemisphere lesion (LHL)

	All patients (31)		RHL patients (15)		LHL patients (16)	
	OE	CE	OE	CE	OE	CE
Before NMV	21.5	20	21.9	21.7	20.6	18.6
After NMV	19.4	17.6	19.4	20.1	17.2	13.7
Variation	2.9	3.2	2.5	1.4	3.4	4.8

Fig. 4 Example of an evaluation of a LHL patient by posturography before (a closed eyes, c open eyes) and after vibration (b closed eyes, d open eyes): The mediolateral deviation evolved from -19.1 to -8.5 mm with closed eyes after vibration and from -20.4 to -9.0 mm with open eyes

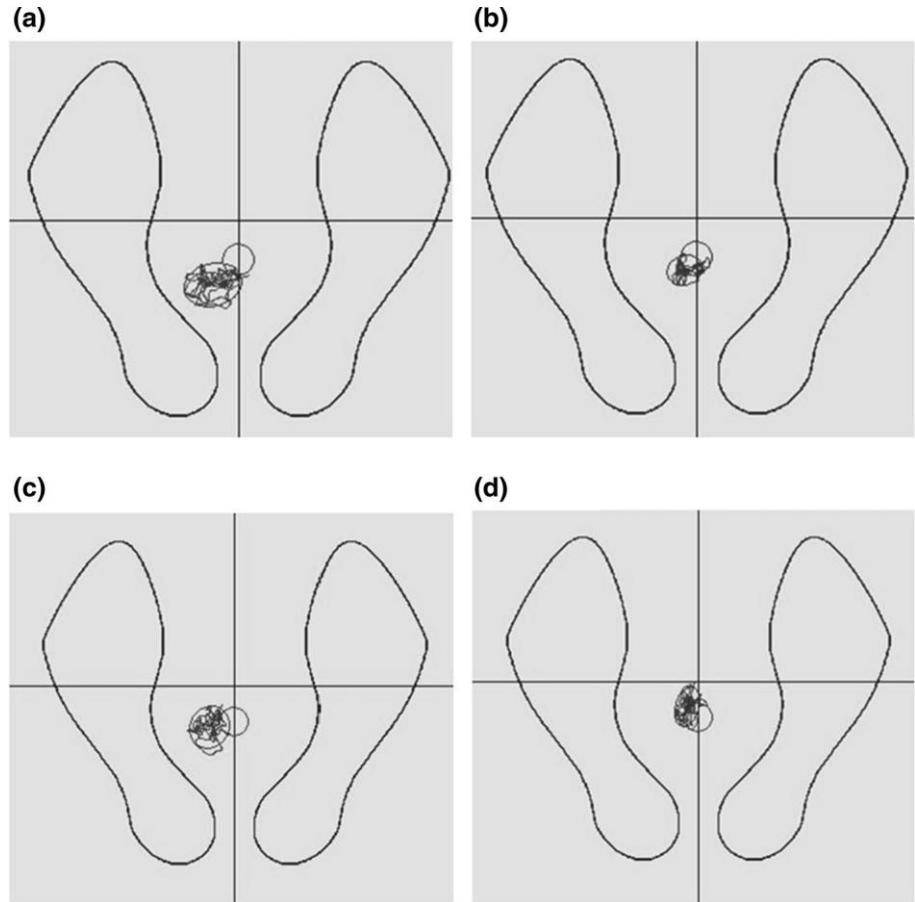


Table 5 Mean ML position of the center of pressure at rest and after neck muscle vibration (mm), with closed eyes (CE) and open eyes (OE), for patients susceptible to visual illusion/not susceptible to vis-

ual illusion, patients with abnormal sensitivity/normal sensitivity and neglect patients

	NMV visual susceptibility (20)			No NMV visual susceptibility (11)			Less sensitivity (15)			Normal sensitivity (16)			Neglect (4)		
	CE + OE	OE	CE	CE + OE	OE	CE	CE + OE	OE	CE	CE + OE	OE	CE	CE + OE	OE	CE
Before NMV	21	21	20.9	20.3	22.2	18.5	22.3	22.7	22.8	19.3	20.6	18	26	28.3	23.5
After NMV	16.7	17.9	15.4	21.8	21.9	21.6	18.9	19.3	19.2	18.1	18.1	18.1	24.4	25.9	23
Variation	4.7	3.3	6.1	-0.08	1.9	-2.1	4.3	2.0	6.7	1.7	3.5	-0.0	1.4	2.3	0.5

Discussion

Balance maintenance requires multiple afferent information (from vestibular, visual and proprioceptive receptors) and

efferent information (from motor effectors) in order to elaborate internal spatial representations of the body in space (Andersen et al. 1993; Merfeld et al. 1999). This information can be transformed into different and changing systems

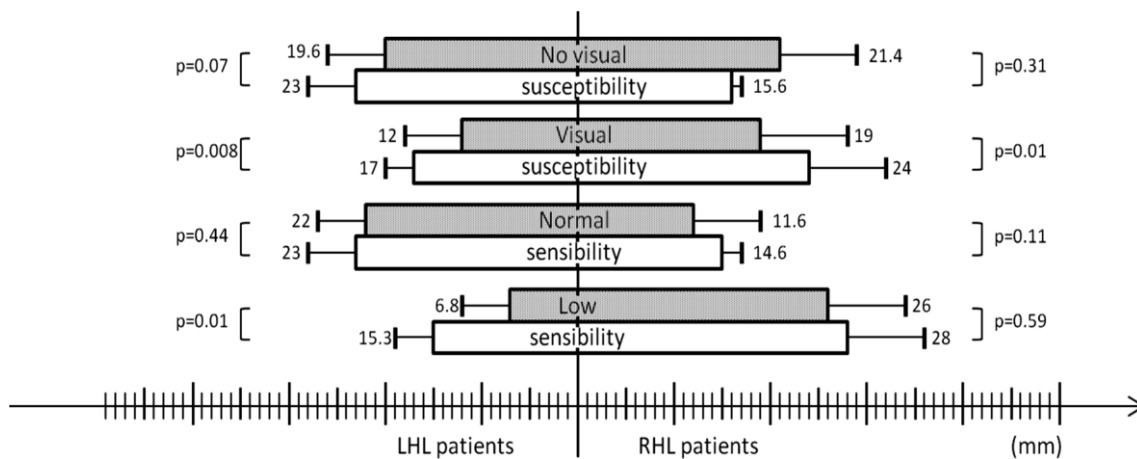


Fig. 5 Mean ML deviation of CoP (mm) before (*in white*) and after NMV (*in gray*) in groups with low sensitivity versus normal sensitivity, vis-ual susceptibility versus no visual susceptibility for patients with *left* hemispheric lesion (LHL) and patients with *right* hemispheric lesion (RHL)

of coordinates, using allocentric referential (environmental information) or egocentric referential (related to the subject's body), with regard to the position of the subject in space, and the task to be accomplished. This spatial cognitive processing can be altered by a stroke lesion, leading to a bias in body orientation (Perennou 1999; Rode 1998).

One session of NMV produces an immediate repositioning movement toward the stimulus. In addition, as previously described, in some patients it provokes the illusion of a lateral translation of the visual environment toward the contralateral side of the stimulus, which is typified by the illusory perception of movement to the right of a stationary light spot when the left neck muscle has received a vibration (Wierzbicka et al. 1998). As in other studies, we selected an area where the vibrations cause the greatest deviation of the light spot to the opposite side. Similarly to other authors, we found variable susceptibility to NMV visual illusion (Karnath et al. 2002; Schindler 2004). Nearly 2/3 of our patients were sensitive to visual illusion. Individual preference for proprioceptive input could explain this variability in behavior, a hypothesis supported by previous studies (Kluzic et al. 2007; Vibert et al. 2006). Interestingly, we found that the efficacy of NMV in correcting the postural bias was higher in patients who experience this visual illusion of an environmental displacement. This finding could be interpreted as no inhibition of descending signal in patients visually susceptible, and in this case, NMV might influence more the postural proprioceptive. NMV not only triggers a repositioning movement in the direction of the stimulation, but also provokes an illusory movement of the visual environment. This illusion was concomitant to a deviation of the subjective

perception of the body (Karnath et al. 2002; Magnusson and Fransson 2006). NMV consequently seems to influence the relative position of the body with respect to space.

This hypothesis is also reinforced by the study of Bottini (2001), which carried out position emission tomography scan during neck muscle vibration and showed cerebral activity in areas of multisensory integration, i.e., the insula, parietal operculum and superior temporal gyrus. Finally, some authors have studied cerebral activation during the illusion of movement produced by muscle vibrations, using functional magnetic resonance imaging (Naito et al. 2007; Romaguère et al. 2003). Romaguère et al. compared the cortical activities arising in subjects, with or without an illusion of movement. The illusion of movement specifically activated not only the contralateral sensorimotor and premotor, but also the parietal cortices in which the representation of body in space is elaborated. Moreover, Weiller et al. (1996) showed that while activation in the sensorimotor cortex was almost identical during voluntary and passive movements, the inferior parietal lobule was more active during passive movements, which suggests that a sensation of movement occurring in the absence of any voluntary command could lead to ascertaining by the central nervous system of the body representation in the parietal cortex. Altogether, these arguments are consistent with a central effect of NMV. NMV could ameliorate postural imbalance after stroke due to spatial cognitive impairment through central activation of the cortical areas involved in the mental representations of body (Roll 2003).

It should be added that neck vibrations seem particularly

effective as a means of modulating the egocentric frame of reference since they produce a bias in the subjective perception of the body median with “straight-ahead” perception deviated to the side of the vibration (Karnath et al. 1993, 2002). Moreover, neck vibrations have been shown to improve motor actions in a neglected space, i.e., tactile and visuospatial exploration and copying tasks in neglect patients (Johannsen et al. 2003; Schindler et al. 2002). Finally, another study has shown that unlike optokinetic manipulation, neck vibration does not seem to effectively contribute to judgments of object size, thereby suggesting that NMV may not act on the allocentric references (Schindler 2004).

A few studies have evaluated the effect of sensory stimulations on postural asymmetry in stroke patients. Prism adaptation using an artificial deviation of visual environment induced by 10° optical prisms was shown to effectively reduce postural asymmetry in right-lesioned patients (Tilikete et al. 2001). In 1998, Rode studied the effect of vestibular caloric stimulation which reduces the postural asymmetry. Finally, optokinetic and galvanic stimulations have been recently tested in stroke patients (Bonan et al. 2016). Both optokinetic and galvanic vestibular stimulations could modulate the position of the hemiparetic’s center of pressure (CoP), and the postural effect was nearly double for RHL patients compared to that for LHL. Our study is the first study testing the effectiveness of contralateral dorsal neck muscle vibration (NMV) as a means of reducing postural asymmetry in patients undergoing stroke rehabilitation. In our study, however, we found no significant difference between the RHL and the LHL groups in variation of the CoP after vibration. That said, our post-stroke delay was nearly 3 months, compared to 6 months in Rode’s study, and we assume that this difference explains the discrepancy. In our patients, postural asymmetry at rest in RHL and LHL was quite similar, which is probably due to the fact that over 3 months, spatial cognitive impairment is not limited to RHL. It would be useful to compare these findings to the symptoms of neglect that are known to be initially present in both RHL and LHL. At a later stage, the LHL patients recovered more rapidly from the visuospatial disturbances and differences in visuospatial behavior that arise only at a distance between the RHL and the LHL.

Perennou et al. tested 3 groups of stroke patients (RHL with neglect, RHL without neglect and LHL) by another proprioceptive stimulation: transcutaneous electrical stimulation on neck muscles during sitting position on a rocking platform (Perennou et al. 1996). The stimulation effectively reduced sitting balance

instability in neglect patients only. In our study, stability in the standing posture was not improved since the surface did not change. However, it is quite difficult to compare our study with the latter study because stimulation was given in a sitting position on a rocking platform and evaluation was performed under stimulation. It should also be recalled that our neglect patients were too few for statistical analysis. The statistical analysis was performed excluding neglect patients but do not influence results.

An interesting result of our study was that NMV was more effective in patients with abnormal sensitivity, especially in LHL. These patients with low sensitivity are probably more disturbed in their sensory integration and could be more receptive to sensory stimulation because of a higher spatial distortion. Those results were viewed with caution because of reduced statistical power due to the small sample. The particular effect in LHL could be explained by a more potent action of the stimulation due to the fact that the central structures of the right hemisphere receiving multiple sensory information involved in the elaboration of the representation of body in space have been spared.

In our study, contrary to what was expected an anterior-posterior deviation was not found. It could be explained by results in standard norms in our patients before stimulation, and probably because the stimulation is unilateral. Furthermore, our primary aim is to research the effect on the mediolateral deviation, so we positioned the vibrator to have a maximum of light spot deviation toward the opposite side of stimulation. If there was an illusion of vertical spot movement, we changed the vibrator position.

The order of post-stimulation tests (open eyes or closed eyes) has not been randomized. This would have been interesting, but we chose to conduct the assessment eyes closed just after stimulation so as not to cancel the effect of vibration by eyes opening. Visual feedback has a stabilizing influence on postural control, providing additional information on position and orientation. Maintenance of eye closure during evaluation increased the efficiency of neck vibration in many patients, thereby suggesting that sensory recalibration may be less effective when visual afference is present. In previous studies it was equally important to suppress visual cues in order to obtain a better result in terms of sensorial stimulation (Karnath et al. 2002; Gomez et al. 2009). Our findings are also consistent with the notion that the effect of sensory stimulation is induced by an illusion. The presence of visual cues definitely prevents the illusion of body translation relative to the visual environment elicited by vibration. This could be especially crucial for stroke patients who have been

shown to be visually dependent (Bonan et al. 2013; Yelnik 2005).

It is known that neck proprioception interacts with vestibular system. Vibration of the neck muscles modifies the perception of vestibular self-motion (Pettorossi et al. 2015). We cannot separate the interaction neck proprioception and the vestibular sense, but to our knowledge no study of the direct effect of neck vibration on vestibular system has been carried out. The stimulation is carried out some distance from the mastoid, and to limit the vestibular activation, we used a low vibration amplitude. Other study with vestibular evoked potential could answer this question.

We studied the immediate effect of neck muscle vibration after stimulation because fatigability of hemiplegic patients in a standing position did not allow for prolonged assessments. But in other studies on healthy subjects, correction of the bias, which was maintained throughout proprioceptive stimulation, did not stop once the vibration sensation had run its course, and even persisted after stimulation stopped (Karnath et al. 2002). This result suggests a long-lasting and significant change in the perception of the body in space. Pettorossi et al. (2015) found that high-frequency neck muscle vibration induces an effect during 4 h on self-motion perception. Filippi et al. (2009) found 90 days, a decrease in the area of sway of CoP after quadriceps vibration. However, the vibration of neck muscles appears to be effective in the long term on neglect symptoms if they are repeated (Johannsen et al. 2003). The long-term effectiveness of vibration in the specific indication of the balance disorder due to poor representation of body in space has to be confirmed in further study. That said, its long-lasting effect over several sessions remains to be verified, even though it has already been tested for symptoms of visuospatial neglect (Schindler 2004; Johannsen et al. 2003). Schindler showed that an effect on neglect symptoms could last at least 2 months. Johannsen demonstrated that ten 20-min NMV sessions may have an effect on neglect symptoms lasting for more than 1 year (Johannsen et al. 2003). Improvement for neglect symptoms was even more pronounced when the vibration was associated with visual scanning (Schindler 2004) or occupational therapy (Kamada et al. 2011). As regards postural control, it would be of major interest to have it performed in association. As for neglect, it could be carried out as a supplement to traditional rehabilitation (with the advantage that it requires no additional time for the therapist) either simultaneously with balance exercises in a seated or standing position,

or else during dynamic exercises. After our preliminary study, we have chosen to test in a new study the long-term effect of repetitive NMV sessions.

NMV is technically simple, easy to use in rehabilitation centers and very cheap. In our study, side effects were not described, as they had been in previous studies (Biguer et al. 1988). The technique will be easy to apply, especially in the immediate post-stroke period, when spatial disorders (body misorientation and neglect) are the most flagrant. It can conveniently be used before balance acquisition as the patient can remain in a seated position, and once the vibration is in place, his cooperation is not required.

Conclusion

One session of NMV could reduce postural asymmetry after stroke. The durability of its effects will require confirmation in future studies. Several findings underscore its therapeutic effects on the postural disturbances related to spatial cognition impairment, the effects being achieved through central action on the structures involved in the representation of the body in space. It could therefore be useful to include this technique in balance rehabilitation in order to specifically treat the cognitive component of postural disturbances.

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- Yelnik A (2005) Evolution of the concepts concerning rehabilitation treatment for hemiplegic patients. *Ann Read Med Phys* 48:270–277

Appendix 6 - Curriculum Vitae S Leplaideur

Stéphanie LEPLAIDEUR CHALLOIS

Rehabilitation Center of Kerpape

Neurological Physical Rehabilitation Medicine
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F-35000 Rennes. France

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[ORCID 0000-0003-3859-4644](https://orcid.org/0000-0003-3859-4644)

Born on 12th January 1981

Married, two children

Skills Profile

Physical and Rehabilitation Medicine formation and practice
Expertise in neurological rehabilitation, spasticity treatment (using ultrasound-guided botulinum toxin injection, anesthesia motor blocks) and exercise training
Ability to work as part of a multidisciplinary team
Scientific background with statistical and functional MRI interpretation capacity

Work experience

- 2011-present **Physical and Rehabilitation Medical Doctor** in the Neurology Physical Rehabilitation Medicine Department of the **CRRF Kerpape (Centre of rehabilitation)**
Attached doctor in the PRM department of the **University Hospital of Rennes**
- 2011- 2016 **Coordinating doctor** in a **Medico-social care centre** (FAM Rorh Mez)
- 2009-2011 **Head of clinic** of the University of Rennes 1
Assistant at the University Hospital of Rennes, PRM department - Pr Bonan
- 2005-2009 **Medical internship terms for PRM specialization**
(PRM, Rheumatology, Neurology, internal medicine departments)
University Hospital of Reims

Education

- 2017 -
forthcoming **PhD Student in Neuroscience – EMPENN Team**
University of Rennes, Inria, CNRS, Inserm, IRISA UMR 6074, EMPENN ERL U-1228, France
“The neural basis of egocentric spatial representation and neck muscle vibration effects on spatial cognition, in healthy subjects and patients who had a right stroke”
- 2019-2020 Visitor - **Neurology Research Team** – Pr Cathy Stinear
Faculty of Medical and health sciences – department of Medicine
University of **Auckland** – New Zealand
- April 2019 **Edinburgh SPM Course**
University of Edinburgh, Scotland
- 2015-2016 **Certification in interventional ultrasound in PRM**, SOFMER Lyon
- 2012-2013 **Two modules of the master biostatistics**
French Public Health School /EHESP - European University of Brittany- Rennes
- Sept 2011 **Master 2: sport-health-movement**
Applied biomechanics, Laboratory M2S,
University of Rennes 2-UFR STAPS (Faculty of Sport Sciences)

- July 2009 **Medical doctoral thesis**
The interest of the functional exercise test in the management of metabolic myopathies in Physical and Rehabilitation Medicine
- 2008-2009 **Master 1 health: Biosciences Chemistry-Health; field: Sciences-Technologies-Health**
University of Reims
- 2007-2008 **Inter-university diploma: pathophysiology of exercise and functional explorations of effort**
(University of Strasbourg, Montpellier, Paris 7, Paris 13)
- 2006-2007 **University Diploma: cardiovascular and effort-based rehabilitation** University Hospital of Creteil
- 2005-2006 University Diploma: **Medicine and biology of sport**, University hospital of Reims
- June 2005 **Medical National exam:** classified 1254/4308
Choice: medical specialty at Reims University / DES physical medicine and rehabilitation

IT skills

MRI software: SPM12, MRICron, Itksnape
Statistical software: SPSS

Languages

French native speaker
English Upper-intermediate

Teaching/organizations

SOFPEL member (French society of balance and locomotion)
SOFMER member (PRM French society)
Scientific committee **Kap Ouest Congress** (2012-2019)

Teaching medical students
Committee for report presentations of physiotherapists
Teaching PRM 3rd-cycle medical studies

Awards

Mobility Grant of the regional Council of Brittany 2019
Thesis Grant of the 'Fondation de l'avenir' 2017-2020
Support grant of the 'Fond de dotation Kerpape' 2017-2019
Research subvention INCR 2017
Award for young researcher 2010 of 'Société Francophone Posture Equilibre'

Activities and Interests

Mindfulness
Rowing
Kitesurfing

Publications

Combining prism and neck vibration for postural recovery after stroke: a randomized multicentric study

Authors

Leplaideur S, Allart E, Chochina L, Perennou D, Rode G, Boyer FC, Paysant J, Yelnik A, Jamal K, Duché Q, Combès B, Bannier E, Bonan I

In submission

Postural asymmetry and hemiplegia post-stroke: a systematic review and meta-analysis

Jamal K, **Leplaideur S**, Lucas T, Butet S, Cogne M, Bonan I

Gait an posture, in proof reviewing sept 2021

The neural bases of egocentric spatial representation for extra-corporeal and corporeal tasks: an fMRI study

Leplaideur S, Moulinet-Raillon AL, Duché Q, Chochina L, Jamal K, Ferré JC, Bannier E* and Bonan I*

Brain Sci. 2021 Jul 22;11(8):963. doi: 10.3390/brainsci11080963

The effects of repetitive neck-muscle vibration on postural disturbances after a chronic stroke

Jamal K, **Leplaideur S**, Rousseau Chloé, Chochina L, Moulinet Raillon A, Butet S, Bonan I

Clinical Neurophysiology. 2020 <https://doi.org/10.1016/j.neucli.2020.01.005>

The effects of neck muscle vibration on postural and spatial perception: a systematic review

Jamal K, **Leplaideur S**, Leblanche F, Moulinet Raillon A, Honoré T, Bonan I

Clinical Neurophysiology 2019, <https://doi.org/10.1016/j.neucli.2019.10.003>

Disturbances of spatial reference frame and postural asymmetry after a chronic stroke.

Jamal K, **Leplaideur S**, Rousseau C, Chochina L, Moulinet-Raillon A, Bonan I.

Exp Brain Res. août 2018;236(8):2377-85.

Difference between Individuals with Left and Right Hemiparesis in the Effect of Gluteus Medius Vibration on Body Weight Shifting

Bonan I, Butet S, Jamal K, Yelnik A, Tasseel Ponche S, **Leplaideur S**.

Clinical Neurophysiology. 2017 <https://doi.org/10.1016/j.neucli.2017.08.002>.

Short term effects of neck muscle vibration on postural disturbances in stroke patients.

Exp Brain Res, 2016 (234) 2643-2651

Leplaideur S, Leblong E, Jamal K, Moulinet-Raillon A, Coignard P, Damphousse M, Bonan I.

The effect of optokinetic and galvanic vestibular stimulations in reducing post-stroke postural asymmetry.

Clin Neurophysiol 2016 (127) 842:847

Bonan IV, Leblong E, **Leplaideur S**, Laviolle B, Tassel Ponche S, Yelnik AP.

Effect of sensorial stimulations on postural disturbances related to spatial cognition disorders after stroke.

Clin Neurophysiol 2015 (45) 297 : 303

Bonan I, Chochina L, Moulinet-Raillon A, leblong E, **Challois-Leplaideur S**.

Actualités dans la prise en charge de l'AVC Septembre 2010 édition Sauramps medical Montpellier-paris

Perception de la verticalité après AVC : 143-149

I Bonan, J Baglione, **S Leplaideur**

Rééducation instrumentale de l'équilibre après accident vasculaire cérébral : 151-156

I Bonan, **S Leplaideur**, J Baglione

Syndrome post-poliomyélite : actualités thérapeutiques

Lettre de médecine Physique et de réadaptation 2009 ; 25 :144-9

A Rapin, L Percebois, C Supper, **S Leplaideur**, JM Coulon , P Mouret, F Boyer

Oral Communication

Effet de l'adaptation prismatique combinée ou non à des vibrations des muscles du cou sur l'asymétrie posturale après AVC

récent : Résultats Préliminaires d'un essai randomisé contrôlé - SOFMER 2019

S Leplaideur, K Jamal, M Rousseaux, L Chochina, D Perennou, G Rode, FC Boyer, J Paysant, A Yelnik, I Bonan

Relation entre la perception spatiale et les troubles de l'équilibre suite un Accident vasculaire cérébral en phase chronique.

Jamal K , **Leplaideur S** , Chochina L , Moulinet-Raillon AL , Senal N , Bonan I

SOFMER 2017

Les effets des stimulations sensorielles par vibrations répétées des muscles du cou sur les perturbations posturales chez des patients victimes d'un AVC en phase chronique

Jamal K , **Leplaideur S** , Chochina L , Moulinet-Raillon AL , Senal N , Bonan I
SOFMER 2017

Cortical activity and egocentric representation: An fMRI study

Raillon Moulinet A, Chochina L, **Challois Leplaideur S**, Bannier E, Ferré JC, Bonan I
SOFMER 2016

Effect of neck muscles and gluteus medius vibrations on standing balance in healthy subjects.

Challois Leplaideur S , Jamal K, Leblong E, Chochina L, Bonan I
Congrès SOFMER 2015

Effects of vibration on the bearing asymmetry walking in chronic stroke patients.

Leblong E, Cordillet S, **Challois-Leplaideur S**, Cretual A, Chochina L, Jamal K, Bonan I
Congrès SOFMER 2015

Neck Muscle Vibration and stroke patients .

S Challois Leplaideur, E Leblong, P Coignard, I Bonan
ESPRM 2014

Effet immédiat des vibrations appliquées sur le muscle gluteus medius sur l'équilibre postural statique chez l'hémiplégique chronique ,

E Leblong, **S Challois Leplaideur**, I Bonan
SOFPEL 2014

Actualités en rééducation : pathologies de l'immobilité, complications thrombo-emboliques

S Leplaideur, I Bonan
Journées des Réseaux Neuro-Bretagne

Equilibre et intégration sensorielle après AVC

I Bonan, **S Leplaideur**, P Carson
Journées de neurologie de langue Française 27-30 Avril 2010, Lyon

AVC et MPR, actualité en 2010

I Bonan, P Carson, **S Leplaideur**
24e Journée de l'Association Nationale des Médecins Spécialistes de Médecine Physique et de Réadaptation ANMSR 2010

Fatigue générale, fatigabilité : que ressentent nos patients ?

R Brissot, **S Leplaideur**
8e Journées Francophones Alvéole (Société de Pneumologie de langue Française),
12-13 Mars 2010, Lyon

Posters

Effect of prism adaptation and neck muscle vibration on body weight asymmetry after recent right hemisphere stroke: a multicentre randomized controlled study

World congress NeuroRehabilitation October 2020
S Leplaideur, K Jamal, E Allart, L Chochina, D Perennou, G Rode, FC Boyer, J Paysant, A Yelnik, I Bonan

Short Term effects of neck muscle vibration on balance control of stroke patients: a preliminary study.

European Congress of Physical and Rehabilitation Medicine, 2012
S Challois-Leplaideur, A Raillon, E Leblong, M Damphousse, P Coignard, I Bonan

Etude de l'effet immédiat de vibrations cervicales sur l'équilibre de patients cérébrlésés droits et gauches

Congrès APE, 2011
S Challois-Leplaideur, M Damphousse, E Leblong, P Coignard, I Bonan

Programme ambulatoire de natation après accident vasculaire. Exemple de coopération hospitalo-associative.

Congrès SOFMER, 2010
P Carson, V Daniel, V Cahagne, **S Leplaideur**, P Rochcongar, I Bonan

Evaluation de la dépense énergétique après réentrainement à l'exercice musculaire des patients victimes d'accident vasculaire cérébral. Mesure par SenseWear Pro 3 Armband.

Congrès SOFMER, 2010

P Carson, V Daniel, G Nicolas, L Godet, **S Leplaideur**, P Rochcongar, I Bonan

Statut vitaminique D à l'admission en service de Médecine Physique et Réadaptation : état des lieux, influence de la gravité de l'atteinte fonctionnelle, conduite à tenir en pratique

Congrès SOFMER, 2010

C Le Meur, **S Leplaideur**, P Gallien, P Le Cavorzin, P Guggenbuhl, I Bonan

Différentes évaluations de l'effort en médecine physique et réadaptation : quels objectifs ?

Congrès SOFMER, 2009

S Leplaideur, C Supper, N Morel, P Mouret, F Boyer

Négligence spatiale unilatérale droite et accidents vasculaires cérébraux : à propos de 4 cas

Congrès SOFMER, 2009

A Potet, E Regrain, **S Leplaideur**, G Belassian, F Boyer

Mesure isocinétique longitudinale de la force musculaire quadriceps / ischiojambiers chez des personnes dystrophiques myotonique.

Congrès SOFMER, 2009

N Bayle, **S Leplaideur**, A Rapin, A Chéné, ML Baudrillart, D Jolly, JL Novella, F Boyer

Méningo-radiculite révélatrice d'un lymphome B, à propos de deux observations.

Congrès Français de Rhumatologie ,2008

S Leplaideur, C Varoquier, A Giraud Morelet, MP Chaunu, B Goudot, B Seignon, P Brochot, JP Eschard

Titre : Bases neurales de la représentation spatiale égocentrique et de l'effet de vibrations cervicales sur la cognition spatiale, chez les sujets sains et cérébrolésés droits.

Mots clés : référentiel égocentré, accident vasculaire cérébral, équilibre, IRM fonctionnelle

Résumé : Les troubles de l'équilibre impactent le pronostic des patients après un AVC. Ces troubles sont au moins en partie liés à la perturbation de la cognition spatiale probablement en lien avec le référentiel égocentré, notamment chez les patients AVC droits. Nous avons donc étudié quelles zones cérébrales étaient activées en IRM fonctionnelle pendant deux tâches égocentrées. Dix-sept sujets sains ont réalisé une tâche de droit devant subjectif (SSA) et une tâche de plan corporel longitudinal subjectif (SLB) en IRMf. Ces tâches activent des aires pariétales supérieures et inférieures et le cortex occipital latéral avec une prédominance droite. Les résultats préliminaires de 14 patients post AVC droit distinguent trois patterns de réorganisation d'activations : péri lésionnelles, contra lésionnelles et bilatérales. La question sous-jacente est la prise en charge

spécifique de ces troubles, car aucun traitement portant sur la composante cognitive de l'équilibre n'est actuellement couramment utilisé. A la suite d'études préliminaires, les stimulations proprioceptives par vibrations cervicales (NMV) sont apparues comme un traitement prometteur. Nous avons étudié l'effet cumulatif de séances de NMV sur l'asymétrie posturale de 89 patients dans les 9 mois après un AVC droit. L'amélioration de la déviation mediolaterale immédiatement après la première séance de NMV ne s'est pas maintenue après les interventions. De plus, la combinaison avec l'adaptation prismatique n'a pas montré d'effet bénéfique. Les perspectives de recherche portent sur l'inclusion de patients plus précocement après l'AVC en utilisant des marqueurs plus spécifiques de la cognition spatiale : SSA et SLB.

Title : The neural basis of egocentric spatial representation and neck muscle vibration effects on spatial cognition, in healthy subjects and patients who had a right stroke

Keywords : egocentric referential frame, stroke, balance, functional MRI

Abstract : Balance disorders affect the prognosis of stroke, increasing the risk of falls and gait disorders. As they are partly related to spatial cognition disorders, we studied the correlates of the egocentric referential frame. Using functional MRI, we analysed 17 healthy subjects' brain activations during the subjective straight-ahead task (SSA) and the subjective longitudinal body plan task (SLB). They activated superior and inferior parietal areas and the lateral occipital cortex with a right predominance. The same analysis was performed on 14 patients who had a right stroke. We distinguished three patterns of activation reorganisation: perilesional, contra-lesional and bilateral. The underlying question is the specific management of these spatial cognition disorders after stroke. Despite the primary issue of managing

balance disorders, no treatment addressing the cognitive component of balance is commonly used. Preliminary studies have shown that sensory stimulation by neck muscle vibration (NMV) is a promising treatment for postural disorders. We studied the cumulative effect of NMV sessions on postural asymmetry in 89 patients within nine months of a right stroke. However, the improvement in mediolateral deviation immediately after the first NMV session was not sustainable after the interventions on day 14. Furthermore, the combination with prismatic adaptation did not show any beneficial effect. Future research will focus on including patients earlier after stroke using specific markers of spatial cognition: SSA and SLB.