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L'effet hypoalgésique de la manipulation vertébrale

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L'effet hypoalgésique de la manipulation vertébrale

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LISTE DES ABBRÉVIATIONS

MV : Manipulation vertébrale

PAG : Substance grise périaqueducale

RVM : Médulla rostroventromédiale

PPT : Seuil de la douleur à la pression (en anglais « *pressure pain threshold* »)

INTRODUCTION

Les douleurs de dos sont une cause très fréquente de handicap dans le monde **[1]**, et sont un des premiers motifs de consultation en thérapie manuelle. La manipulation vertébrale (MV) est un type de thérapie manuelle communément utilisé par différentes professions de la santé **[2]**, en raison de son effet positif sur les douleurs musculo-squelettiques **[3]**.

Cependant, la littérature scientifique ne propose aujourd'hui que des hypothèses à propos du lien entre la MV et la diminution de la douleur, et très peu de travaux expérimentaux ont été conduits dans ce domaine. Ce projet doctoral a donc pour objectif de contribuer à l'étude de l'effet hypoalgésique des MV.

CADRE THÉORIQUE

1. La douleur

1.1 Concepts et modèle

La douleur est un phénomène complexe et multidimensionnel, qui résulte de quatre composantes : nociceptive (détection de la douleur), sensori-discriminative (perception de la douleur), motivo-affective (souffrance) et cognitivo-comportementale **[4]**. Le modèle actuel de la douleur est considéré comme « circulaire », et « dynamique », où ces quatre composantes peuvent chacune moduler la perception douloureuse, et interagir entre elles **[5]**.

1.2. Transmission de la douleur

Les messages nociceptifs périphériques tissulaires, activés par exemple par une blessure, sont transmis à la corne dorsale de la moelle épinière par des fibres neuronales myélinisées A Delta (de grand calibre, vitesse de transmission rapide, responsables de la douleur aiguë et transitoire) ou des fibres amyélinisées C (de petit calibre, vitesse de transmission plus lente, responsables de la douleur

diffuse et prolongée). Au niveau de la corne dorsale de la moelle épinière, un premier neurone sensitif fait synapse avec un deuxième neurone **[6]**, entraînant à son niveau la libération de glutamate et de substance P pro inflammatoires **[7]**. Ce second neurone peut emprunter deux trajets ascendants différents vers le cortex sensitif : la voie spinothalamique (latérale), et la voie spinoréticulaire (médiale). Durant ce trajet, d'autres synapses peuvent s'effectuer, notamment au niveau de la substance grise périaqueducale (PAG) et de la médulla rostroventromédiale (RVM), toutes les deux impliquées dans la modulation de la douleur **[8]**.

Une deuxième synapse avec un troisième neurone a lieu dans les noyaux du thalamus vers le cortex somato-sensoriel pour l'aspect somatique de la douleur (localisation, durée et intensité), et la région préfrontale ainsi que le système limbique (l'insula et cortex cingulaire antérieur) pour l'aspect affectif et émotionnel de la douleur **[9]**.

D'autres voies de transmission, via des connexions neuronales dans le noyau du nerf trijumeau et le noyau para-brachial latéral vers l'amygdale, semblent également avoir un rôle dans les composantes nociceptive et affective impliquées dans la douleur chronique **[10]**.

1.3. Modulation endogène de la douleur clinique

Il existe différents systèmes de modulation endogène de la perception douloureuse : facilitateurs ou inhibiteurs. Plusieurs zones du système nerveux central sont impliquées conjointement dans ces systèmes, dont les principales sont le cortex préfrontal, la PAG et la RVM. Ces structures coopèrent afin de maintenir un état d'équilibre **[11][12]**. Les principaux médiateurs sont à ce niveau les monoamines (sérotonine, norépinephrine, dopamine) **[13]**.

De nombreuses études cliniques portant sur la fibromyalgie **[14]**, l'arthrose ou encore la polyarthrite rhumatoïde **[15]** ont mis en évidence une dysfonction des systèmes d'inhibition endogène de la douleur qui serait responsable du passage à la chronicité. Des facteurs psychologiques et contextuels peuvent également modifier la gestion de ces systèmes, entraînant selon les cas une réponse placebo

ou nocébo [16].

Les fibres A Beta (bien que non-transmetteurs d'influx nociceptif et responsables de perception de vibration, mouvement ou effleurement) peuvent être également stimulées et bloquer brièvement l'influx nerveux, en recrutant des interneurons inhibiteurs de l'influx nociceptif [17].

Au niveau supra spinal, les connexions neuronales entre le cortex cingulaire antérieur et la PAG va entraîner deux phénomènes : i) la stimulation de la RVM, qui, par une décharge de sérotonine, inhibe l'influx nociceptif au niveau des cornes dorsales spinales, ii) la stimulation de deux types de cellules ON/OFF au sein de la RVM [7] qui alors peuvent augmenter (« hyperalgésie »), réduire (« hypoalgésie ») ou inhiber (« analgésie ») l'influx nociceptif.

Parallèlement, au niveau spinal, on peut observer un maintien de la stimulation nociceptive (sensibilisation centrale) par le biais d'une décharge continue de glutamate au niveau des neurones spinaux [8]. Cette sensibilisation augmente l'excitabilité des neurones, qui provoque une augmentation de la douleur. Plus spécifiquement, en cas de stimulus nociceptif, cette augmentation de la douleur est appelée « hyperalgésie », et en cas de stimulus non nociceptif, cette augmentation est appelée « allodynie ».

1.4. Douleur expérimentalement induite et son intérêt

Une douleur expérimentale peut être induite de nombreuses façons (chaud, froid, crème irritante, pression...) dans des conditions (durée, intensité...) contrôlées en laboratoire. L'une des plus courantes est la douleur induite par la pression, via le seuil de douleur à la pression. Différents types de sujets (douloureux ou non douloureux) peuvent être étudiés, afin d'observer leurs réactions et de déterminer, par exemple, l'efficacité d'un traitement donné sur la perception douloureuse. Lorsqu'une douleur est induite selon un protocole expérimental précis, et donc dépourvu de tout danger, il est important de noter qu'elle n'engendrera pas le même ressenti psychologique ni le même investissement motivationnel qu'une douleur clinique. En conséquence, notre travail sur la

douleur ne s'est pas intéressé à contrôler ces aspects psychologiques.

1.4.1. Le seuil de douleur à la pression, une mesure de la douleur expérimentalement induite

Ce seuil douloureux, en anglais « *pressure pain threshold* » (PPT) est la pression minimale appliquée sur la peau qui provoque une douleur ou un inconfort **[18]**. Dans le cadre d'une intervention, l'étude de la variation du PPT renseigne sur une potentielle modification de la perception douloureuse avant et après l'intervention, et donc sur un éventuel mécanisme d'action impactant la transmission de la douleur via les fibres C et A delta. Le PPT est différent du seuil de tolérance, défini comme le niveau maximum de douleur qu'un sujet est capable de tolérer **[19]** car il ne fait pas intervenir l'aspect émotionnel ni les facteurs psychologiques associés à la douleur, ce qui en fait un outil précieux d'exploration. Le PPT est testé à l'aide d'un algomètre, appareil de mesure de la pression exacte appliquée à un endroit spécifique, et qui permet de déterminer le seuil de survenue de la douleur avec précision. Plusieurs travaux ont validé la fiabilité de l'algomètre **[20]**, sa sensibilité **[21]** et sa spécificité **[21]** ce qui en fait un outil simple et efficace à utiliser, après la formation de l'évaluateur **[21]**. Tous les individus ont un seuil de douleur que l'on peut déterminer, quel que soit leur niveau de douleur spontanée lors du test. C'est pourquoi le PPT peut également être utilisé sur des sujets indolores (asymptomatiques).

1.4.2. Population de sujets asymptomatiques

Le recours à des sujets indolores dans les études expérimentales assure la présence d'un système de gestion endogène fonctionnel de la douleur. Des sujets souffrants de douleur chronique sont en effet susceptibles de présenter un dysfonctionnement des mécanismes inhibiteurs de la douleur **[22]** qui pourrait alors modifier la perception de la douleur expérimentalement induite.

De plus, il est important de noter qu'il existe une diminution naturelle de la sensibilité à la douleur avec l'âge (*débutant autour de l'âge de 60 ans*) **[23]**. C'est pourquoi les études purement expérimentales sont le plus souvent réalisées sur des sujets jeunes et asymptomatiques.

2. L'effet d'un traitement

2.1. Définition

Afin d'étudier la validité d'un traitement, par exemple sur la douleur, il est nécessaire de comparer son résultat avec celui d'un autre traitement qui s'est avéré efficace. Tester l'effet *spécifique* de ce traitement nécessite en revanche de le comparer avec une procédure placebo.

Dans un premier temps, il est possible de mesurer les différences pré et post intervention **intra-groupes**, soit **(A)** la différence entre la mesure de suivi du groupe de traitement et sa mesure de référence, et **(B)** la différence entre la mesure de suivi du groupe « placebo » et sa mesure de référence. Cependant, ces comparaisons de mesures **intra-groupes** ne sont pas suffisantes pour représenter l'effet du traitement seul. En effet, il se peut que les changements dans les mesures obtenues surviennent à cause d'une amélioration spontanée chez le sujet ou d'un effet placebo. L'effet *spécifique* d'un traitement **(C)** est donc défini comme étant la différence **inter-groupes** entre les deux résultats **(A)** et **(B)**. **(Figure 1)**.

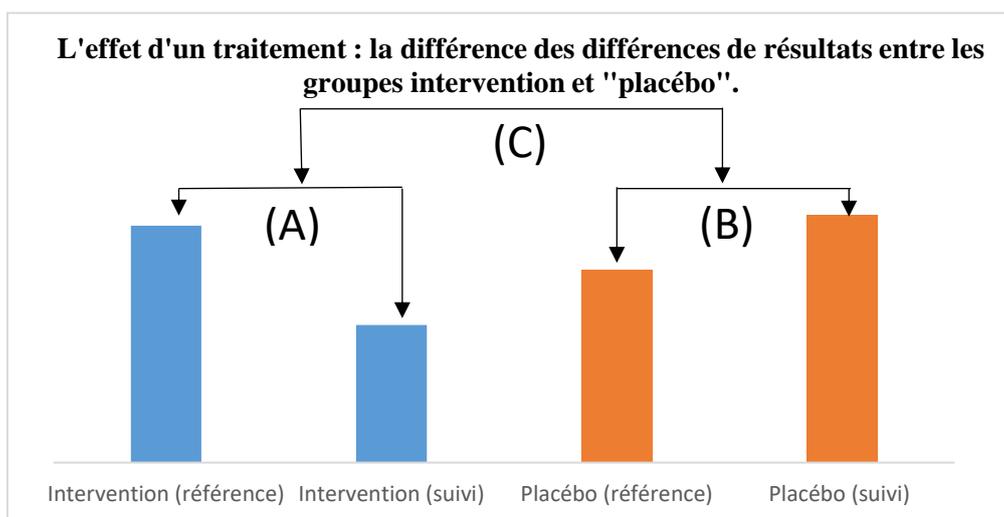


Figure 1. L'effet spécifique d'un traitement correspond à la différence des différences entre les mesures des groupes. **(A)** la mesure de suivi du groupe intervention moins la mesure de référence du groupe intervention, puis **(B)** la mesure de suivi du groupe placebo moins la mesure de référence du groupe placebo. Ensuite, **(C)**

la différence entre ces deux différences, correspondant à l'effet spécifique du traitement.

Cependant, la signification statistique ne renseigne que sur l'existence d'un effet *spécifique* d'un traitement. Elle n'est pas une indication de la signification clinique. En effet, la réduction de la douleur observée doit aussi être notable pour le patient. C'est pourquoi, en plus de la p valeur, il est nécessaire de renseigner la taille de cet effet (en anglais « *effect size* ») et son évolution dans le temps.

2.2. Description d'un effet : sa taille et sa durée

La taille d'un effet est révélatrice de l'importance de l'efficacité du traitement. Elle renseigne sur sa potentielle utilité en clinique. Plus l'effet du traitement est grand, plus l'on s'attend à ce que le patient détecte une différence, et rapporte une amélioration.

Comme la comparaison entre les études est rendue compliquée par l'utilisation de différentes méthodes et unités de mesures, des indices sont souvent utilisés afin de rapporter la taille de l'effet, il s'agit des coefficients d de Cohen ou g de Hedge. Afin de relier ces coefficients au concept de signification clinique, Cohen a créé une échelle qui peut être utilisée pour les coefficients d ou g . Selon cette échelle, une taille d'effet de 0,2 représente un chevauchement entre les populations comparées dans leurs distributions de moyennes d'environ 85%, ce qui, selon Aron [24], pourrait être comparé à une différence de taille entre les filles de 15 et 16 ans, et donc considéré comme « *petit* ». Une taille d'effet de 0,5 représente un chevauchement d'environ 67%, ce qui, de la même manière, pourrait être interprété comme une différence de taille entre les filles de 14 et 18 ans, donc considérée comme « *moyenne* ». Une taille d'effet de 0,8 (ou plus) correspond à un chevauchement de 53% (ou moins) et représente une différence de taille entre les filles de 13 et 18 ans, donc considérée comme « *grande* ». Comme autre exemple, Cohen suggère que la différence de QI entre les titulaires d'un doctorat et un « étudiant de première année typique » est comparable à une taille d'effet de 0,8 [25]. Le coefficient d de Cohen est généralement calculé en soustrayant la moyenne

du groupe expérimental de la moyenne du groupe témoin et en divisant ce résultat par l'écart-type. Cependant, cette équation doit être utilisée dans des conditions spécifiques, qui sont décrites en détails dans la littérature, mais sans consensus clair. Par conséquent, la taille de l'effet peut être calculée de différentes manières et à moins qu'elle ne soit clairement décrite, il y a place pour des erreurs et de la confusion. C'est pourquoi notre travail a cherché à détailler les différentes méthodes de calculs de la taille d'effet de la MV selon les différentes conditions spécifiques des études sur le sujet. (Voir **ANNEXE 1** pour plus de détails).

Enfin, l'efficacité d'un traitement s'évalue également dans le temps. C'est la durée pendant laquelle l'effet du traitement est statistiquement significatif.

L'effet d'un traitement est donc décrit par sa taille et sa durée.

2.3. L'effet placebo

Un placebo est une substance ou une intervention qui n'a pas d'effet thérapeutique spécifique dans la pathologie étudiée [26]. L'effet placebo fait référence à tous les effets thérapeutiques non spécifiques associés à l'administration d'un placebo. Idéalement, un placebo doit être complètement comparable à un traitement actif. En dehors des traitements pharmacologiques, cette condition est relativement complexe à réaliser. Dans le cas d'un traitement manuel, une procédure «*placebo*» doit imiter le mieux possible le traitement, sans en contenir l'élément actif. Comme avec un traitement placebo pharmacologique, il ne faut pas que les sujets soient au courant de leur répartition dans les groupes (intervention/placebo) ou qu'ils puissent deviner quelle intervention ils ont reçue. Cette condition est fondamentale pour garantir la validité des résultats, au risque de surestimer (jusqu'à 44%) [27] l'efficacité d'un traitement, et d'entraîner une mauvaise interprétation. Il est donc impératif de vérifier l'aveuglement des sujets après l'intervention.

2.3.1. Particularité de l'effet placebo dans la thérapie manuelle

En thérapie manuelle, la mise au point d'une procédure placebo «*crédible*» est difficile. La littérature récente a conceptualisé deux aspects pour une procédure placebo crédible : i) le placebo doit être

psychologiquement acceptable (c'est-à-dire que les sujets sont naïfs et aveugles) et répondre à la question « *les sujets peuvent-ils repérer la différence entre la « vraie » intervention et le placebo ?* », et ii) le placebo doit être physiologiquement acceptable (les deux procédures « intervention » et « placebo » sont similaires en exécution) répondant à la question « *les aspects physiques de la procédure placebo ressemblent-ils à la « vraie » intervention?* » [28] [29] [30]. Une procédure placebo totalement crédible réunirait ces deux aspects fondamentaux.

3. La manipulation vertébrale

3.1. Définition et intérêt clinique

La manipulation vertébrale (MV) est un type de thérapie manuelle. Elle peut être définie comme une manœuvre forcée de haute vitesse mais de faible amplitude, appliquée sur des articulations rachidiennes, et accompagnée parfois d'un bruit de craquement caractéristique [31]. Elle peut être comparée à une mobilisation, qui est également définie comme un type de thérapie manuelle, avec une exécution similaire, mais appliquée plus lentement et/ou de manière répétitive, sur les articulations rachidiennes [32]. Il a été démontré que la MV et la mobilisation avaient parfois un impact clinique dans le traitement de la douleur musculo squelettique [33], et plusieurs théories ont été émises afin de tenter d'expliquer cet effet.

3.2. Quelques théories sur l'effet de la manipulation vertébrale sur la douleur

Les principales théories sur les mécanismes d'action des MV sont historiquement : i) biomécanique et ii) neurophysiologique. Cependant, leur exploration reste partielle, et reposent sur très peu d'essais expérimentaux.

3.2.1. Théorie biomécanique

Cette théorie est l'une des plus anciennes cherchant à expliquer l'action hypoalgésique de la MV. La MV ciblerait des « anomalies » de fonction au niveau de structures articulaires et tissulaires de la colonne vertébrale, telles qu'une « raideur » ou une « limitation de mouvement » dans la palpation passive de la vertèbre [34], et qui seraient responsables des douleurs ressenties par le patient. Il est

alors supposé que l'hypoalgésie dépende de la correction de ces « anomalies » biomécaniques par la MV. Cependant, il existe de nombreuses limites à cette théorie, comme le manque de fiabilité de la palpation de ces « anomalies » biomécaniques [35] et plus particulièrement la similarité de résultats cliniques entre le traitement des zones « dysfonctionnelles » et des zones choisies au hasard [36]. Il serait alors acceptable de tester l'effet biomécanique sans chercher à trouver une zone « dysfonctionnelle ».

Cependant, à notre connaissance, il n'existe aucun travail expérimental sur la relation entre les modifications biomécaniques observées suite aux MV et leur potentiel intérêt clinique. Ce domaine de recherche reste encore à être investigué.

3.2.2. Théorie neurophysiologique

La MV serait responsable d'une modification de la concentration de substances (réduction de cytokines pro-inflammatoires [37], augmentation de sérotonine, Beta endorphines [38] et endocannabinoïdes [39]) impliquées dans les mécanismes endogènes de gestion de la douleur. Cependant, ces résultats sont très partiels. En effet, la limite principale à ces études est très souvent l'absence de comparaison avec un groupe contrôle et/ ou un placebo. C'est pourquoi ces résultats ne permettent pas non plus d'exclure un mécanisme d'action des MV semblables à ceux impliqués lors d'un placebo.

La MV serait également capable de réduire les seuils de perception douloureuse à la pression régionalement et à distance, chez des sujets avec des douleurs musculo-squelettiques et asymptomatique [40] [41] suggérant un mécanisme d'action segmentaire et supra-spinal, médié par les fibres C et A Delta.

3.3. Exploration de l'effet régional de la manipulation vertébrale sur le seuil de douleur

Afin de déterminer l'existence ou non d'un mécanisme de la MV, une revue systématique des publications portant sur l'effet de la MV sur la douleur induite expérimentalement chez des sujets asymptomatiques [41] a montré que la MV pouvait réduire de manière significative et plus constante

la douleur induite par la pression, par opposition à d'autres types de douleurs induites, du moins lors du test de la douleur dans la même zone que la zone manipulée, ou le long du même dermatome (« régional »). Plus précisément, 12/20 des études incluses dans la revue ont montré un effet immédiat positif sur le PPT mesuré régionalement [41]. Malheureusement, aucune de ces études ne comportait d'évaluation de la qualité de l'aveuglement des sujets, ce qui altère la fiabilité de ces résultats. De plus, les auteurs de la revue n'ont renseigné ni sa taille ni sa durée (au-delà d'un effet à court terme).

RÉSUMÉ

Il est possible d'utiliser le seuil de la douleur expérimentale à la pression induite chez des sujets jeunes asymptomatiques pour rechercher la présence d'un effet hypoalgésique *spécifique* d'un traitement en le comparant avec un groupe « placebo » validé à postériori. Cet effet se décrit également en renseignant sa taille et sa durée. Dans la littérature, l'effet régional *spécifique* de la manipulation vertébrale sur le seuil de la douleur à la pression dans la population asymptomatique n'a pas encore été déterminé, pas plus que sa taille ni sa durée spécifique.

PROBLÉMATIQUE GÉNÉRALE

En conclusion, deux questions doivent être posées :

i) Existe-t-il un effet régional *spécifique* de la manipulation vertébrale sur le seuil de la douleur dans une population de sujets asymptomatiques ?

ii) S'il y a un effet, quelle en est sa taille, et quelle en est sa durée ?

Les réponses à ces questions ont été obtenues par deux revues de la littérature et une étude expérimentale, présentées ci-dessous.

MÉTHODE ET RÉSULTATS

CONTRIBUTIONS DE RECHERCHE

Les contributions scientifiques sont organisées autour de **A)** deux revues de la littérature et **B)** un essai randomisé.

1- ARTICLE 1 : L'effet régional de la manipulation vertébrale sur le seuil de la douleur chez des sujets asymptomatiques.

La première contribution scientifique est une revue systématique et critique de la littérature, dont l'objectif était d'effectuer une mise à jour des données scientifiques sur le sujet, tout en analysant la qualité des procédures placebo utilisées dans les études. La version intégrale de cet article est disponible en **ANNEXE 2**.

2- ARTICLE 2 : La durée et la taille de l'effet régional de la manipulation vertébrale sur le seuil de la douleur chez des sujets asymptomatiques.

La deuxième contribution scientifique est une analyse additionnelle des articles inclus dans la première revue, rapportant la durée et la taille de l'effet régional de la MV sur le PPT dans la population asymptomatique. La version intégrale de cet article est disponible en **ANNEXE 3**.

Les études incluses dans les deux revues sont identiques, et par conséquent les questions de recherche, la méthode et les résultats d'analyses de ces articles seront rapportés conjointement.

a) Questions de recherche

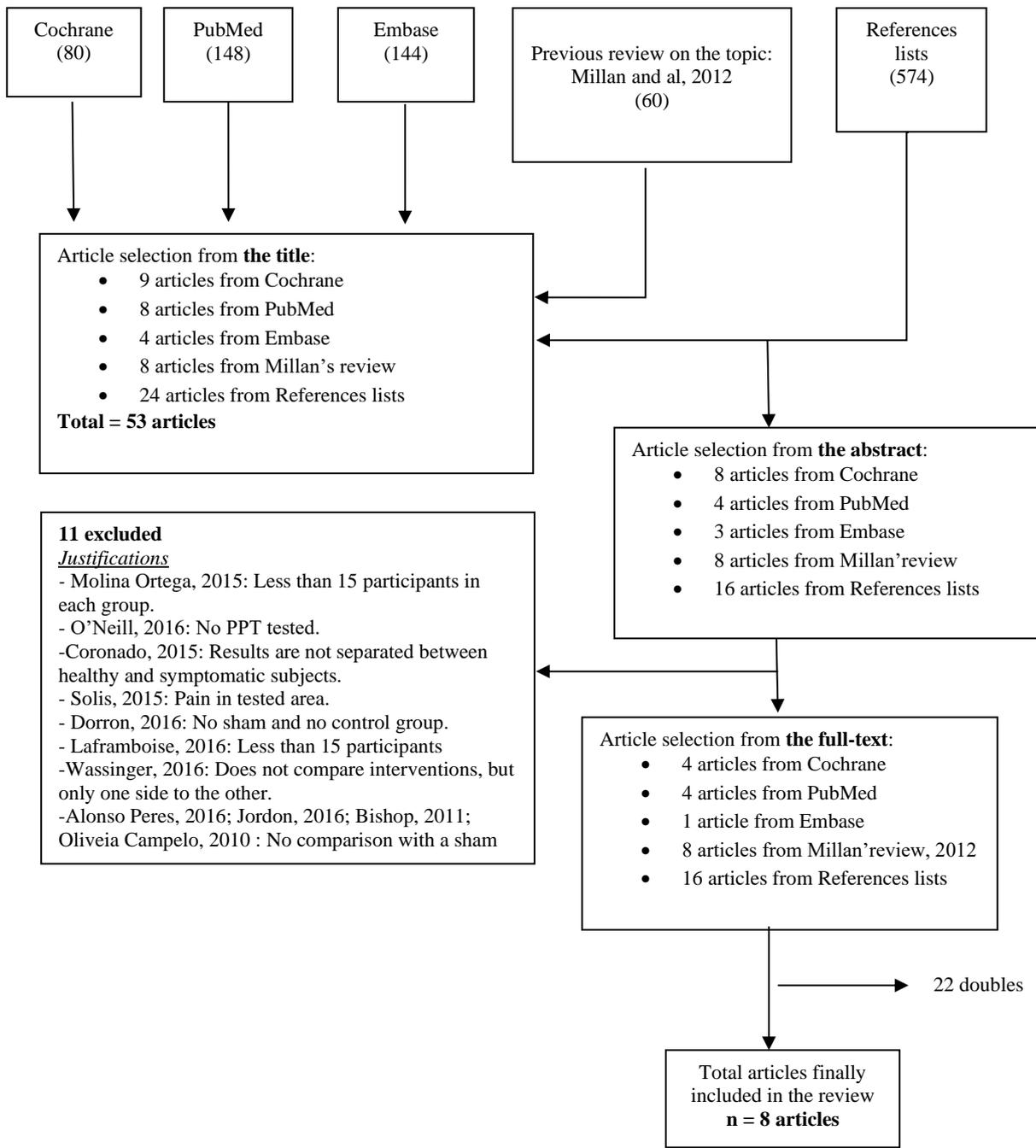
- Existe-t-il un effet régional *spécifique* de la manipulation vertébrale sur le seuil de la douleur dans la population de sujets asymptomatiques ? **(Article 1)**
- S'il existe, quelle en est sa taille, et quelle en est sa durée ? **(Article 2)**

b) Méthodes de l'article 1 et l'article 2

Pour ces revues systématiques, une recherche bibliographique a été effectuée dans les bases de

données *PubMed*, *Embase* et *Cochrane*, avec un enregistrement sur *PROSPERO* daté du 27 février 2017 (reçu [58207]). La méthode PRISMA a été utilisée pour rapporter la sélection des articles inclus (Figure 2).

Figure 2. Organigramme rapportant le processus de sélection des articles sur l'effet régional de la manipulation vertébrale sur le seuil de la douleur chez des sujets asymptomatiques pour les deux revues systématiques et critiques de la littérature de notre projet doctoral [42].



Les critères de sélection ont été les suivants :

Critères d'inclusion

Les études incluses sont des essais randomisés contrôlés comparant la MV avec un groupe placebo. La MV est produite manuellement et/ou mécaniquement assistée au niveau de la colonne vertébrale ; les mesures du PPT sont prises dans une région sans douleur et le même jour que la MV. Les données brutes des valeurs de PPT doivent être fournies.

Critères de non-inclusion et d'exclusion

Les études uniquement sur la mobilité ou la tension du rachis n'ont pas été incluses, et les études de moins de 15 participants dans chaque groupe ont été exclues.

Recherche, sélection et extraction des données

La recherche d'articles s'est faite avec l'aide d'une bibliothécaire (Université Paris Saclay). La sélection des articles ainsi que l'extraction des données dans des grilles de lecture se sont faites en aveugle et de manière objective en suivant les critères d'inclusion et d'exclusion, par les deux premiers auteurs. S'il y avait un désaccord, le troisième auteur pouvait être consulté.

Analyse des données

Pour **l'article 1**, trois grilles de lecture ont été créées par les auteurs. Le but était de décrire puis d'évaluer la qualité et de rapporter les résultats des études incluses afin de conclure sur nos objectifs. Chaque grille a été fournie avec un descriptif de chaque item et une justification du score (**ANNEXE 2**). Les articles ont été listés en fonction du score de qualité (de bons à mauvais), sans mettre une limite pour 'non acceptable' (**Tableau 1**). La grille de qualité a été basée sur les critères CONSORT et les grilles d'une revue précédente sur le même sujet de *Millan et al, 2012 [41]*. Nous avons fait spécialement attention à la qualité du placebo, déterminée par deux aspects :

- sa crédibilité psychologique (sujets sont naïfs et aveugles)

- le placebo doit ressembler le plus possible physiologiquement au traitement (la position du sujet et du thérapeute ainsi que son contact ; le mouvement/rotation du torse ; « *thrust* » ou impulsion mécanique appliquée au sujet sur la zone de traitement ; et le son de craquement produit par la manœuvre [28]).

Pour **l'article 2**, de nouvelles grilles de lecture ont dû être créées, basées sur les multiples recommandations du créateur de l'index de taille de l'effet [43] et d'auteurs contemporains [44], supportées par d'autres textes récents sur le sujet [25] [45]. Cependant, aucun score de qualité n'a été proposé pour **l'article 2**, car il n'y a aucun consensus sur le sujet. L'analyse préliminaire a montré qu'aucune étude ne rapportait la taille de l'effet en comparant les résultats *entre* les groupes. Ces études ont donc uniquement rapporté la taille de la différence *intra*-groupe. En revanche, les valeurs brutes des PPT étaient disponibles, ce qui nous a permis de calculer nous-mêmes la taille de l'effet de chaque article dans une grille de résultats. Ces résultats ont été vérifiés par une deuxième personne. Pour associer la taille de l'effet au concept de signification clinique, nous avons suivi l'échelle de Cohen et l'interprétation de Aron [24].

Résultats de l'article 1 et de l'article 2

- *Existe-t-il un effet régional spécifique de la manipulation vertébrale sur le seuil de la douleur dans la population de sujets asymptomatiques ? (Article 1)*

Après la recherche et la sélection des articles, uniquement 8 essais randomisés contrôlés par un placebo sur 946 articles ont été inclus (**Figure 2**). Le niveau de qualité des études était généralement moyen à bon. La procédure placebo a été jugée crédible psychologiquement pour 6 études [46][47][48][49][50][51], physiologiquement acceptable pour 2 articles [46][48], et les deux aspects crédibles (à la fois psychologiquement et physiologiquement) par 2 études [46][48]. Seulement deux études ont été considérées comme inacceptables à la fois psychologiquement et physiologiquement [52][53] (**Table 1**).

Les limites méthodologiques les plus communément rencontrées dans les articles sont la gestion de leurs données potentiellement manquantes, l'aveuglement du statisticien, et le plus important, aucune étude n'a utilisé de questionnaire post-intervention afin de vérifier l'aveuglement des sujets au placebo. Nous avons observé que lorsque le placebo était considéré comme complètement crédible, les résultats étaient en faveur de la MV. Cependant, les limites méthodologiques des études, et plus spécifiquement l'aveuglement uniquement supposé et non vérifié des sujets, peuvent compromettre les résultats de cette revue.

Table 1. Tableau modifié et traduit en français issu de la revue systématique et critique sur l'effet régional de la manipulation vertébrale sur le seuil de la douleur chez des sujets asymptomatiques [42] montrant l'existence ou non d'une différence significative dans les résultats entre les groupes dans 8 études comparant la manipulation vertébrale à un placebo, incluant des informations sur la crédibilité du placebo.

Premier auteur Année	- Sujets naïfs ? (Oui/Non) -Questionnaires post-intervention (Oui/Non) -Placebo considéré psychologiquement (Acceptable/Pas acceptable) ?	Placebo considéré physiologiquement (Acceptable/Pas acceptable), c'est à dire l'exécution des deux interventions se ressemblent-elles)?	En conclusion, le placebo complètement crédible ? (Oui/Non)	Qualité générale de l'article	Différence statistiquement significative entre les groupes ?
Ruiz Saez, 2007 [47]	-Oui - Non -Acceptable	Pas acceptable	Non	Bonne	Oui
Srbely, 2013 [48]	-Oui -Non -Acceptable	Acceptable	Oui	Bonne	Oui
Fernandez de las Penas, 2008 [49]	-Oui -Non -Acceptable	Pas acceptable	Non	Moyenne	Oui
Fernandez de la Penas 2007 [50]	-Oui -Non -Acceptable	Pas acceptable	Non	Moyenne	Oui
Hamilton, 2007 [50]	-Oui -Non -Acceptable	Pas acceptable	Non	Moyenne	Non
Yu, 2012 [46]	-Oui -Non -Acceptable	Acceptable	Oui	Bonne	Oui
Thompson 2009 [52]	-Non -Non -Pas acceptable	Pas acceptable	Non	Moyenne	Non
Fryer, 2004 [53]	-Non -Non Pas acceptable	Pas acceptable	Non	Moyenne	Non

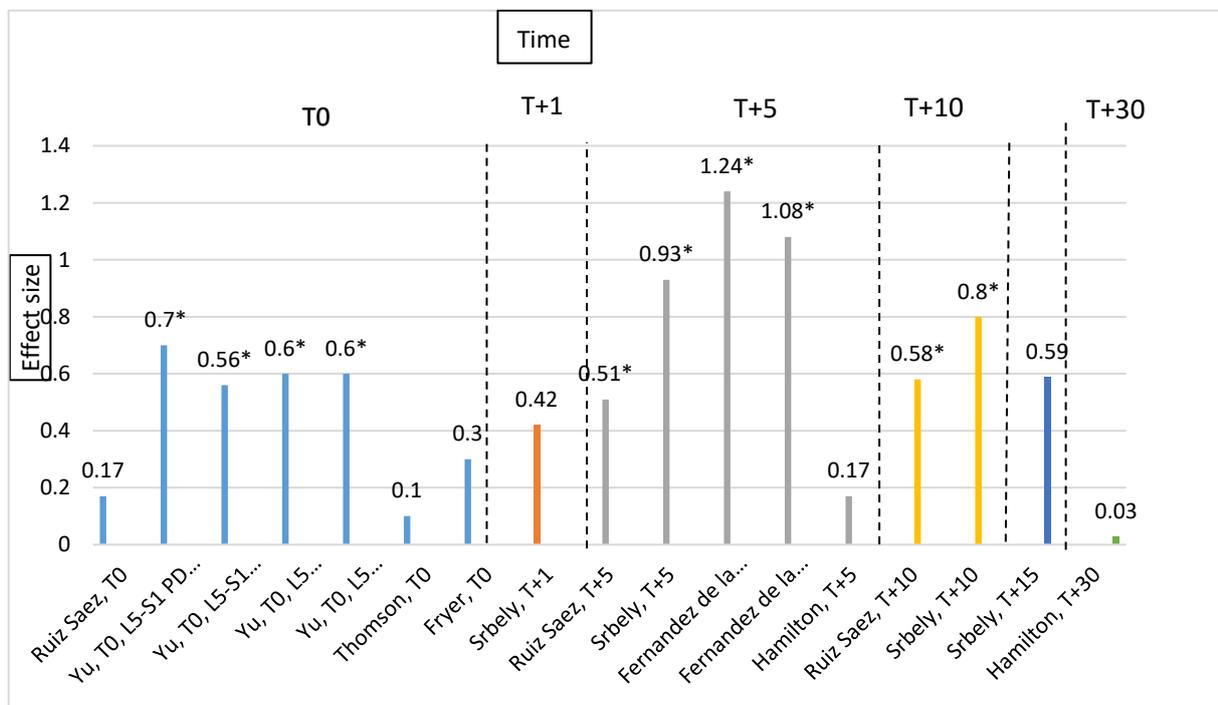
- Quelle est la taille et la durée de l'effet régional de la manipulation vertébrale sur le seuil de la douleur chez des asymptotiques ? (Article 2)

Les 8 études incluses sont les mêmes que pour l'article 1, leur qualité générale est donc classée de « moyenne à bonne ». Ces articles ont rapporté le PPT après les interventions à différents temps de mesures : quatre études immédiatement après, une étude T+1 minute après, cinq études T+5 minutes après, deux études T+10 minutes après et une étude T+15 minutes et T+30 minutes. Nos calculs ont montré que l'effet de la MV sur le PPT peut passer de « moyen » à « important » dans les cinq premières minutes, mais semble diminuer à nouveau dans les dix minutes après l'intervention. Illustration des résultats en Figure 3.

Figure 3 issue de l'analyse additionnelle de la taille d'effet de la manipulation vertébrale comparée à un groupe placebo sur le seuil de la douleur chez des sujets asymptotiques à différents temps de mesure [54]

Temps étudiés : Immédiatement après (T0), une minute après (T+1), cinq minutes après (T+5), dix minutes après (T+10), quinze minutes après (T+15) et trente minutes après l'intervention (T+30).

* : Différence statistiquement significative entre les groupes manipulation vertébrale et placebo.



A ce stade, la MV semble avoir un effet régional sur le PPT chez les personnes asymptomatiques mais la taille de l'effet est moyenne, et la durée de l'effet est très courte. Aucune des études n'a vérifié l'aveuglement des sujets par des questionnaires post-intervention, il convient de vérifier ces résultats avec un essai expérimental.

3- ARTICLE 3 : L'effet régional de la manipulation vertébrale sur le seuil de la douleur chez des sujets asymptomatiques, comparé à un placebo validé.

La troisième contribution scientifique est un essai randomisé contrôlé par placebo, avec l'objectif de vérifier l'effet de la MV dans la région de la zone manipulée, en la comparant à une procédure placebo validée par questionnaire post-intervention. La version intégrale de cet article est disponible en **ANNEXE 4**.

a) Questions de recherche de l'article 3

- Existe-t-il un effet régional *spécifique* de la manipulation vertébrale sur le seuil de la douleur dans la population de sujets jeunes et asymptomatiques ?
- S'il existe un effet, quelle en est sa taille, et quelle en est sa durée ?

b) Méthode de l'article 3

Schéma d'étude, comité éthique et immatriculations

L'étude est un essai croisé randomisé contrôlé par placebo. L'expérimentation a eu lieu de septembre 2017 à Octobre 2018, et fait partie d'une plus large expérimentation investiguant également les effets de la MV sur le système nerveux autonome chez des sujets asymptomatiques. L'étude a été approuvée par le comité éthique EA 4532 de l'Université Paris Sud UFR STAPS, Orsay (Octobre 2016) (**ANNEXE 5**), a été enregistrée sur www.clinicaltrials.gov (Registration NCT03776708), et assurée par HDI global assurance (N°01012787-14009) (**ANNEXE 6**).

Protocole d'étude

L'expérimentation s'est déroulée sur deux sessions séparées de 48h. Durant la première session, les sujets sont randomisés en deux groupes, afin de recevoir soit la MV soit un placebo, en choisissant une enveloppe scellée et non transparente dans une boîte opaque. Lors de la deuxième session, les sujets reçoivent la deuxième intervention, MV ou placebo, celle qu'ils n'ont pas reçue lors de la première session (**Figure 4**). La seconde session a été programmée au même moment de la journée que la première session, et durait environ une heure.

Chaque session a été précédée d'une période de repos. Les mesures de PPT ont été prises au niveau du rachis thoracique, avant et après chaque intervention. Ces mesures ont été répétées toutes les 12 minutes, quatre fois après chaque intervention pour une période totale de 45 minutes (**Figure 5**).

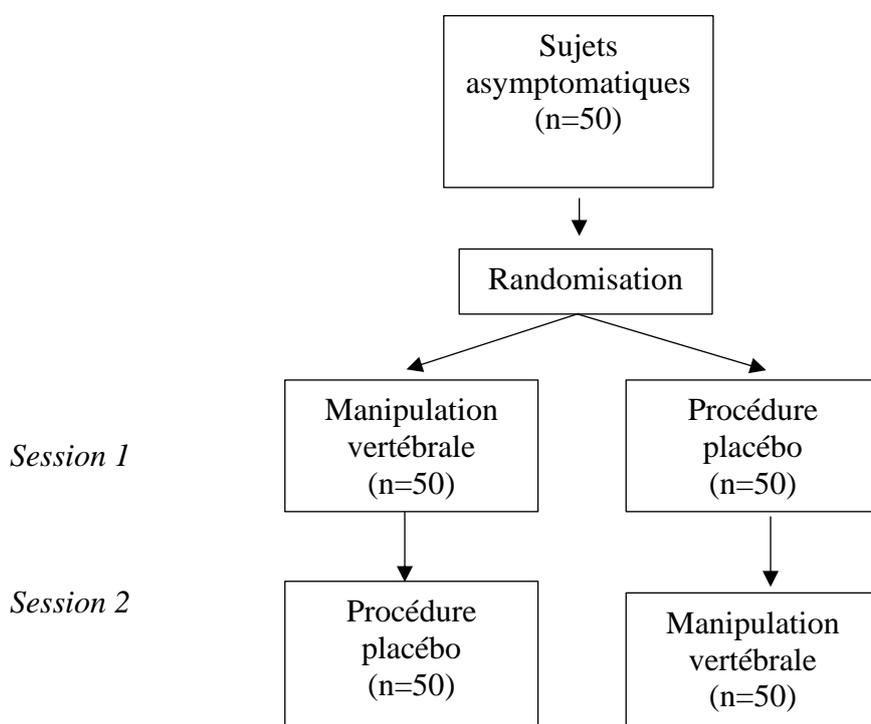


Figure 4 modifiée et traduite en français issue de l'essai randomisé croisé contrôlé par placebo sur l'effet de la manipulation vertébrale sur le seuil de la douleur chez des sujets asymptotiques [55] montrant l'expérimentation en deux sessions, séparées de 48h. Tous les sujets (n=50) ont reçu les deux interventions (manipulation/placebo).

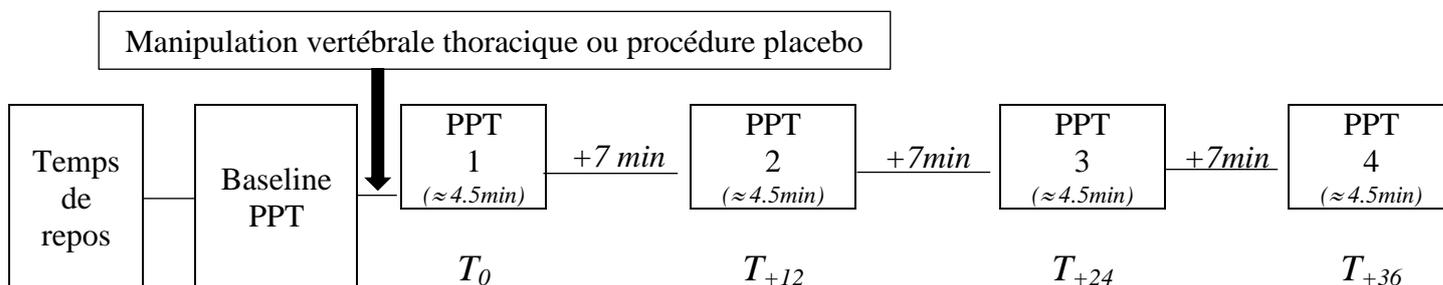


Figure 5 modifiée et traduite montrant les prises de mesure du seuil de la douleur à différents temps (pré-intervention puis toutes les douze minutes, post-interventions) [55]

Seuil de la douleur (PPT); PPT 1 est mesuré immédiatement (T_0 à $T+4.5min$) après l'intervention, PPT 2 est mesuré douze minutes ($T+12$ à $T+16.5min$) après l'intervention, PPT 3 est mesuré vingt-quatre minutes ($T+24$ à $T+28.5 min$) après l'intervention, et PPT 4 est mesuré trente-six minutes ($T+36$ à $T+40.5min$) après l'intervention.

Sujets d'étude

Les sujets sont des jeunes étudiants en chiropraxie de première année de l'Institut Franco Européen de Chiropraxie d'Ivry sur Seine. Les étudiants ont reçu une lettre d'information sur les risques potentiels et leur droit à se retirer à tout moment de l'étude, ainsi qu'un formulaire de consentement éclairé à signer pour faire partie de l'étude.

Critères d'inclusion et non inclusion

Les sujets inclus devaient être de jeunes (de 18 à 30 ans) volontaires et asymptomatiques, c'est-à-dire ne pas avoir de douleurs dans la zone testée. Ils ne devaient pas avoir ressenti de douleur au niveau de la colonne vertébrale depuis plus d'un mois, avoir pris des médicaments antidouleurs 24h avant l'étude ou avoir reçu un traitement manuel 48h avant les sessions. Aucun sujet avec des contre-indications à la thérapie manuelle (instabilité, fracture, malformations, fragilité ligamentaire ou osseuse, inflammation locale) n'était inclus.

La manipulation vertébrale et la procédure placebo

La MV était réalisée sur la colonne vertébrale, entre les omoplates, dans une zone sans douleur à la palpation légère. La manipulation était donnée dans la direction postéro-antérieure avec un mouvement rapide et de petite amplitude, avec un contact sur les zones des processus transverses des vertèbres thoraciques choisies.

La procédure placebo était faite avec un contact sur la partie médiale de l'omoplate droite avec les deux mains. Après avoir mis une légère pré-tension sur les tissus, un mouvement de « poussée » était effectué, respectant les plans de glissement de l'omoplate sur le grill costal. Aucune tension sur la colonne vertébrale thoracique n'était ainsi appliquée. Une procédure similaire a auparavant été validée sur des sujets migraineux, sur 12 sessions de traitement sur une période de 3 mois, et a montré son efficacité à aveugler les sujets [56]. De plus, dans notre étude, des questionnaires post-interventions ont été utilisés à chaque session, afin de vérifier que l'aveuglement des sujets avait réussi.

Aveuglement des sujets

Les sujets de l'étude étaient des étudiants de première année en chiropraxie. Tout au long de leurs études de premier cycle, ces étudiants seront exposés à plusieurs types de manipulations de la colonne vertébrale. Ceci rend essentielle la question de leur aveuglement. Cependant, au cours de leur première année d'étude, il est peu probable qu'ils aient suffisamment de connaissances et d'expérience en matière de manipulation pour connaître les différents types existants et qu'il est donc peu probable de découvrir une procédure placebo bien réalisée. Ces sujets ont été informés que l'objectif de l'étude était d'évaluer les résultats de différentes techniques efficaces utilisées dans les thérapies manuelles et qu'ils recevraient le même type d'intervention lors des deux sessions. Lors de la répartition aléatoire, ils avaient le choix entre six enveloppes (pour renforcer l'idée, il y avait de

nombreuses possibilités d'interventions). Ils n'étaient également pas au courant de leur traitement attribué tout au long de l'étude.

Nous voulions manipuler la cinquième vertèbre thoracique, parce qu'elle est proche de l'omoplate où la procédure placebo a été donnée, de sorte que les deux interventions se ressemblent considérablement. En outre, ils ont répondu à un questionnaire à la fin de chaque session pour connaître leurs convictions quant à l'efficacité des deux interventions (voir **ANNEXE 7**). Un sujet complètement aveugle aurait les mêmes convictions pour les deux interventions, et pourrait même supposer que la procédure placebo serait plus efficace que la vraie MV. Donc, théoriquement, ils seraient aveugles à nos types d'intervention et naïfs aux objectifs exacts de notre étude.

Les mesures de seuil de douleur à la pression

Les mesures de PPT ont été prises par un testeur aveugle à l'allocation des groupes avec un algomètre. Comme déjà expliqué, cet appareil de mesure a une bonne sensibilité, spécificité et fiabilité [20] [21]. Les données statistiques ont été traitées en aveugle par le statisticien, à qui l'on a caché l'allocation des groupes.

b) Résultats de l'article 3

- Est-ce que les sujets de l'étude ont été aveugles ? (Questionnaires)

Les questionnaires ont montré que 78% des sujets avaient les mêmes convictions pour les deux interventions ou pensaient que le placebo était supérieur à la MV, indiquant un aveuglement réussi (**Table 2**, lignes A, B et C).

Table 2. Attentes des sujets entre les deux sessions de l'expérimentation, issu de l'article 3 [55]

	Beliefs regarding SM or sham	Total of subjects (n/50)	Percentage (%)	Are the subjects considered completely blinded? (Yes/No)
A	Subjects had same beliefs for SM and sham	32/50	64%	Yes (78 %)
B	Subjects thought that both interventions were effective and Sham > SM	1/50	2%	
C	Subjects did not know if SM was effective but thought that the Sham was effective	6/50	12%	
D	Subjects thought that both interventions were effective and SM > Sham	2/50	4%	No (22%)
E	Subjects did not know if the sham was effective but thought that SM was effective	3/50	6%	
F	Subjects did not know if the SM was effective but thought that the Sham was ineffective	3/50	6%	
G	Subjects thought that SM was effective and Sham ineffective	3/50	6%	

SM : spinal manipulation

Notes:

-Sham > SM means stronger certainty for the Sham.

-SM > Sham means stronger certainty for the SM.

- Existe-t-il un effet régional spécifique de la manipulation vertébrale sur le seuil de la douleur dans la population de sujets asymptotiques ?

Nous n'avons pas trouvé de différence significative entre la MV et la procédure placebo régionalement (au niveau des thoraciques) à aucun moment dans le temps.

- S'il existe un effet, quelle est la taille et la durée de l'effet de la manipulation vertébrale sur le seuil de la douleur à la pression chez des sujets asymptotiques ?

Comme nous n'avons pas trouvé d'effet de la MV sur le PPT dans cette population, aucune taille d'effet ni de durée d'effet n'ont pu être rapportées.

DISCUSSION GÉNÉRALE

L'objectif de cette thèse était de déterminer s'il existe un effet spécifique régional de la manipulation vertébrale sur la perception douloureuse induite expérimentalement.

1. Synthèse des résultats

-Existe-t-il un effet régional spécifique hypoalgésique de la manipulation vertébrale sur la douleur induite par la pression dans la population de sujets asymptomatiques ?

Notre première revue systématique de la littérature (**ANNEXE 2 – Revue 1**) s'est intéressée à l'effet régional de la MV sur le PPT au sein d'une population asymptomatique, c'est-à-dire sans troubles de la modulation de la perception douloureuse [22]. La majorité des études ont rapporté un effet hypoalgésique de la MV, au niveau du rachis cervical et lombaire. Les résultats de notre première contribution scientifique sont donc en accord avec la précédente revue systématique sur le même sujet [41]. Cependant, aucune de ces deux revues n'apportent plus d'informations descriptives sur cet effet. La deuxième revue systématique de la littérature (**ANNEXE 3 – Revue 2**) a ainsi été effectuée, sous forme d'une analyse additionnelle des 8 essais randomisés contrôlés inclus dans la première revue. L'objectif était de déterminer la taille et la durée de l'effet de la MV sur le PPT. La MV aurait donc un effet hypoalgésique moyen (interprété comme semblable à une différence de taille entre les filles âgées de 14 à 18 ans [24] et de très courte durée (moins de 30 minutes). Nous avons intégré une analyse de la qualité des placébos des études incluses et avons observé que lorsque le placebo était considéré comme complètement « crédible », les résultats rapportés étaient en faveur de la MV.

Cependant, notre essai croisé randomisé contrôlé par placebo et validé par des questionnaires post-intervention (**ANNEXE 4 – Essai expérimental**) n'a pas réussi à reproduire un effet, comme les résultats des revues l'avaient précédemment indiqué. Devant les résultats

contradictoires entre nos contributions scientifiques, il convient d'observer les conditions méthodologiques et matérielles dans lesquelles elles ont été réalisées, afin de tenter d'expliquer pourquoi il existe cette différence entre nos résultats.

2. Considérations méthodologiques

2.1. Cette contradiction serait-elle due à l'évaluation de l'efficacité du placebo ?

La notion de procédure placebo en thérapie manuelle a connu une évolution récente, en intégrant le concept de placebo « *actif* » ressemblant le plus possible à la thérapie [28]. Un modèle de procédure placebo « *actif* » en thérapie manuelle a même été validé à plus de 80% à travers 12 sessions de traitements pour les migraines, sur une période de 3 mois [56]. Nous avons donc l'idée que l'effet placebo pouvait être décrit selon des critères psychologiques (*la naïveté des sujet et leur aveuglement*) ainsi que des critères physiologiques (*le placebo doit ressembler le plus possible en termes de procédure à la MV*). Cette approche nous a permis d'observer qu'aucune des études incluses dans la revue n'a vérifié l'aveuglement des sujets, au moyen de questionnaires post-intervention (**ANNEXE 2 - Revue 1**). Il n'est donc pas exclu que les sujets aient pu comprendre dans quel groupe (*intervention ou placebo*) ils étaient, et que les résultats des études aient pu être compromis, voire modifiés par les sujets. Par conséquent, les résultats rapportés dans notre première revue sont très probablement surestimés. Il semble que la vérification de l'aveuglement des sujets soit fondamentale pour assurer la validité des résultats.

Rétrospectivement, nous avons émis des réserves sur les conclusions de notre revue (**ANNEXE 4 – Essai expérimental**) car si l'on intégrait notre essai expérimental dans les grilles de lecture utilisées dans notre première contribution scientifique, nous aurions compris que les critères de jugement concernant l'aveuglement des sujets étaient primordiaux, et nous aurions donc conclu à une absence d'effet *spécifique* de la MV sur le PPT. De plus, notre essai expérimental est la seule étude qui justifie d'une procédure placebo semblable validée précédemment [56], puis validée

durant l'étude expérimentale.

Enfin, les résultats de notre étude sont en accord avec les récents travaux sur les populations douloureuses. En effet, aucun effet *spécifique* n'a été trouvé dans la population avec des douleurs musculo-squelettiques [57] ni dans la population migraineuse comparé à une procédure placebo semblable [56]. Ainsi, lorsque les sujets ne savent pas qu'ils ne sont pas traités, les résultats de la MV et du placebo sont identiques. En revanche, il est intéressant de noter que Chaibi et al, 2013 ont trouvé une différence significative lorsque la MV était comparée à *un contrôle inactif* [56]. Dans ce cas, les sujets savaient qu'ils ne recevaient aucun traitement. La différence observée est donc peut-être due à un effet *nocebo* dans le contrôle groupe.

Nous avons effectué une analyse sommaire des caractéristiques des procédures placebo et de la crédibilité des études incluses dans les revues systématiques les plus récentes à ce sujet sur la population symptomatique [58] et asymptomatique [42], tout en rajoutant notre essai croisé randomisé (ANNEXE 4). Nous avons alors observé que, lorsqu'il y avait des procédures placebo non validés et non vérifiés, les résultats des études étaient mitigés. Cependant, lorsque les études validaient et vérifiaient « l'efficacité » de leur procédure placebo, il n'y avait systématiquement aucun effet *spécifique* de la MV sur le PPT, dans aucune de ces deux populations [55] [59] [60] (Table 3).

Table 3. Les caractéristiques du placebo dans les études sur l'effet de la manipulation vertébrale sur le seuil de la douleur chez i) des sujets asymptomatiques et ii) des sujets douloureux musculo-squelettiques

Populations	Auteurs	Caractéristiques de la procédure placebo			Est-ce que la différence entre la manipulation vertébrale et le placebo est statistiquement significative ? (Oui/Non)
		Utilisation d'une procédure placebo précédemment validée dans la littérature ?	L'étude a-t-elle elle-même validé sa procédure placebo (Questionnaires) ?	L'étude a-t-elle validé sa procédure placebo et a montré que l'aveuglement a été maintenu ?	
Asymptomatiques dans la revue de Honoré et al, 2018 [42]	Srbely	Oui	Non	Non	Oui
	Fernandez de la Penas (2008)	Non	Non	Non	Oui
	Fernandez de la Penas (2007)	Non	Non	Non	Oui
	Fryer	Non	Non	Non	Non
	Ruiz Saez	Non	Non	Non	T0: Non T+5: Oui T+10: Oui
	Thomson	Non	Non	Non	Non
	Hamilton	Non	Non	Non	T+5: Oui T+30 : Non
	Yu	Non	Non	Non	Oui
Ajout de notre troisième contribution scientifique	Honoré (2020)	Oui	Oui	Oui	Non
Symptomatiques dans la revue de Aspinall et al, 2019 [57]	Bialosky	Non	Oui	Oui	Non
	Packer	Non	Non	Non	Non
	Mansilla Farragut	Non	Non	Non	Oui
	Kardouni	Oui	Oui	Oui	Non
	Fernandez Carnero	Non	Non	Non	Oui

2.2. Considérations sur l'exécution de la procédure placebo

La littérature récente recommande l'utilisation d'une procédure placebo qui ressemble autant que possible à la MV sans faire bouger le rachis [28]. Par conséquent, la procédure placebo utilisée lors de notre essai expérimental consistait en une tension produite avec les deux mains sur la partie inféro-médiale de l'omoplate droite, suivie d'une « poussée » ressemblant autant que possible à

l'intervention réelle. On pourrait soutenir que le mouvement de « poussée » sur l'omoplate ressemble trop à une mobilisation ou une manipulation, avec une composante active capable de modifier la perception de la douleur chez les sujets. Cependant, la partie « poussée » s'est faite sur l'omoplate, c'est-à-dire en dehors de la colonne vertébrale thoracique. Elle ne peut donc être considérée ni comme une forme de mobilisation ni de manipulation de la colonne vertébrale, à cause de l'absence de mouvement direct sur ces articulations rachidiennes.

3. Autres considérations méthodologiques

3.1. A propos des études incluses dans les revues

Dans un premier temps, il est intéressant de noter qu'il existe très peu d'articles publiés sur l'effet de la MV sur le PPT comparé à un placebo chez les asymptomatiques (uniquement 8 articles avec nos critères). Il n'y a eu qu'une seule nouvelle étude publiée [48] depuis la parution de la première revue systématique de *Millan et al* en 2012 [41]. Concernant les articles inclus dans les revues, nous avons pu identifier les problèmes les plus communément rencontrés, outre la vérification de l'aveuglement des sujets comme précédemment évoqué, la gestion de leurs données potentiellement manquantes, la méthode de dissimulation de l'allocation des groupes et l'aveuglement du statisticien. L'analyse additionnelle des articles a permis de voir qu'aucune étude n'avait calculé la taille de l'effet correctement, en rapportant les résultats de différences pré-post intervention à l'intérieur de chaque groupe, sans les comparer entre eux. Cependant, les auteurs ont tous fourni leurs données brutes, ce qui nous a permis de produire leur analyse correcte.

Il est important de noter que malgré notre regard critique sur ces articles, leur qualité générale était tout à fait acceptable, et a été évaluée de « moyenne » à « bonne ». C'est pourquoi nous proposons, pour ce type d'études, que le niveau de qualité générale des articles tienne tout particulièrement compte de l'aveuglement correct des sujets concernant l'allocation des groupes « intervention/placebo ».

3.2. A propos de notre travail sur les revues

L'une de nos limites, qui est commune à toutes les revues de la littérature, est la sélection des articles. Il est possible que tous les articles sur notre sujet n'aient pas été trouvés, malgré la recherche bibliographique dans trois bases de données fournie par une bibliothécaire universitaire, le croisement des références pour chacun des articles inclus et une sélection en aveugle par au moins deux des auteurs de chaque revue.

L'analyse de la qualité des études de la première revue s'est basée sur la grille de lecture de Cochrane pour les essais cliniques randomisés (*Cochrane Risk of bias Tool*), tout en incorporant les éléments correspondant à notre thème de recherche, notamment sur les spécificités de la procédure placebo. Cette approche non standardisée est cependant acceptable car l'analyse des biais considérés comme essentiels par Cochrane sont intégrés (biais de sélection, biais de performance, biais de détection, biais de report de donnée, biais d'attribution) (*Cochrane Collaboration's tool for assessing risk of bias adapted from Higgins and Altman 13*) [61]. Nous avons inclus le raisonnement pour chaque item expliqué pour permettre de reproduire l'extraction des données (**ANNEXE 2**).

3.3. A propos de notre essai expérimental

3.3.1. Les sujets inclus dans notre étude

Un problème potentiel spécifique de notre étude était que nos sujets étaient des étudiants en chiropraxie (*biais de performance potentiels*). Ils étaient probablement déjà familiarisés avec la MV et souhaitaient montrer des résultats « positifs » en faveur de la MV.

Pour contrer cela, nous avons inclus uniquement les étudiants de première année. Ces étudiants seraient sensibilisés à la MV, mais n'auraient probablement pas les connaissances nécessaires pour faire la différence entre la MV et un placebo « actif ». Ces sujets ont été informés que l'objectif de l'étude était d'évaluer les résultats de différentes techniques efficaces utilisées dans

les thérapies manuelles dans le temps, et qu'ils recevraient le même type d'intervention lors des deux sessions. Lors de la répartition aléatoire, ils avaient le choix entre six enveloppes (pour renforcer l'idée qu'il y avait de nombreuses possibilités d'intervention). Ils n'étaient également pas au courant de la nature de leur traitement attribué tout au long de l'étude. Nous avons choisi de manipuler une vertèbre thoracique proche de l'omoplate où la procédure placebo a été donnée, de sorte que les deux interventions se ressemblent, mais aussi parce que c'est une zone facile à traiter, et évaluée comme peu risquée chez des personnes jeunes. En outre, ils ont répondu à un questionnaire à la fin de chaque session pour connaître leurs convictions quant à l'efficacité des deux interventions (**ANNEXE 7**). Un sujet complètement aveugle aurait les mêmes convictions pour les deux interventions et pourrait même supposer que le placebo serait plus efficace que la vraie MV. Donc, théoriquement, ils seraient aveugles à nos types d'interventions et naïfs aux objectifs exacts de notre étude. Cette vérification par questionnaires a montré que la vaste majorité (78%) des sujets avait les mêmes convictions pour les deux interventions ou pensait que le placebo était plus efficace que la vraie MV. En d'autres termes, nous avons réussi à « *blinder* » nos étudiants de première année en chiropraxie quant à savoir s'ils étaient traités « correctement » ou avec une procédure placebo.

Nos questionnaires ont demandé si les étudiants pensaient qu'ils avaient reçu un traitement "efficace" ou non pour modifier les variables que l'on cherchait. Il pourrait être argumenté que d'autres questionnaires cherchant explicitement à savoir si les sujets avaient reconnu la procédure placebo (*de-blinding questionnaires*) auraient pu être utilisés. Cependant, à cause de la population étudiée et le design de l'étude (*essai croisé organisé en deux sessions séparées de 48h avec 50 individus*), il a été jugé trop risqué d'évoquer directement avec eux la possibilité d'un groupe placebo. Ce choix est lié au risque de compromettre les résultats des étudiants qui pourraient prévenir leurs camarades et futurs sujets de notre étude. Aussi, à notre connaissance, il n'existe pas de questionnaire standardisé que nous aurions pu utiliser. Étant donné que les sujets de l'étude étaient

tous des étudiants en chiropraxie, même si cela n'affectait pas leur capacité à faire la différence entre une intervention et un placebo, il est toujours possible que ces résultats ne puissent pas être transposables à la population générale asymptomatique (*potentiel biais de recrutement*). Cependant, on pourrait également soutenir que, les résultats n'étant pas favorables à la MV, ce facteur de recrutement inhérent à la sélection de cette population n'a peut-être pas été significatif dans cette étude. De plus, ces résultats sont concordants avec ceux trouvés dans la population avec des douleurs musculo-squelettiques, dans une étude qui a utilisé le même type de procédure *placebo* approprié [58].

3.3.2. Les autres participants à l'étude

Les autres sources d'erreurs potentielles ont également été évitées en veillant à ce que l'évaluateur ne connaisse pas le type d'intervention effectué (en sortant de la salle) et à ce que le clinicien et l'évaluateur soient tous deux expérimentés. Nous avons assuré l'aveuglement du statisticien en rendant anonyme le nom des groupes (A/B). Les données manquantes et leur exclusion ont été signalées et expliquées, mais trop peu nombreuses pour changer les résultats.

3.3.3. Le seuil de la douleur à la pression

Le PPT est une variable objective et valide de la perception douloureuse [21]. Cette technique est la plus communément utilisée dans les études expérimentales. Cependant, le PPT ne mesure pas l'aspect affectif et émotionnel de la douleur. Il renseigne uniquement d'un effet *spécifique* ou non d'un traitement, sur une variable objective, et d'un potentiel mécanisme d'action supra spinal médié par les fibres C et A Delta. De fait, il ne renseigne pas d'une modification de l'expérience de la douleur clinique, ce qui ne représente par conséquent pas l'entièreté de la réalité clinique. Cela signifie que ces travaux ne sont pas transposables à une situation clinique, et que nos résultats ne peuvent pas non plus être extrapolés à d'autres variables.

4. Interprétation des résultats

La manipulation vertébrale n'a pas d'effet spécifique sur la perception douloureuse à la pression dans la population asymptomatique. La littérature récente indique que c'est également le cas dans la population symptomatique [57]. Les mécanismes d'action de la MV sur la douleur sont donc probablement similaires à ceux impliqués lors d'une manœuvre placebo.

CONCLUSION

Ce projet doctoral a cherché à évaluer si la manipulation vertébrale avait un effet hypoalgésique sur la douleur induite par la pression dans la population asymptomatique. Bien que la littérature indique que tel est le cas, lorsque l'on utilise une procédure placebo appropriée, aucun effet *spécifique* sur ce type de perception douloureuse n'a pu être trouvé. Par conséquent, l'importance principale de ce travail est d'avoir montré l'importance de l'effet placebo et comment les résultats d'un essai peuvent dépendre de la manière dont l'intervention placebo est réalisée et évaluée.

RECOMMANDATIONS

- La validité du placebo est primordiale dans l'étude des effets des thérapies manuelles. Il est nécessaire que l'intervention active et le placebo se ressemblent le plus possible, afin d'assurer l'aveuglement des sujets. De même, il est fondamental de toujours vérifier cet aveuglement au moyen de questionnaires.
- Nous recommandons aussi que les études sur l'efficacité des thérapies manuelles sur des populations cliniques se fassent en comparant le traitement avec des procédures placebos validées et vérifiées.
- Il existe une confusion dans l'analyse de la taille d'effet des traitements dans la littérature. Ceci rend très difficile la comparaison entre les études. Il est à noter que la taille d'un effet se calcule toujours *entre* les groupes. Nous recommandons la totale transparence des méthodes de calculs.

- Enfin, il faudrait reproduire notre étude expérimentale afin de vérifier nos résultats.

PERSPECTIVES

Une priorité de recherche pourrait être d'étudier les populations qui répondent ou non à la thérapie manuelle, et les circonstances dans lesquelles le placebo est le plus efficace. De même, il serait intéressant de comparer la manipulation vertébrale avec d'autres traitements.

RÉFÉRENCES

1. Buchbinder R, Blyth FM, March LM, Brooks P, Woolf AD, Hoy DG. Placing the global burden of low back pain in context. *Best Pract Res Clin Rheumatol*. 2013 Oct ;27(5):575–589.
2. Hurwitz, E. L. (2012). Epidemiology: Spinal manipulation utilization. *Journal of Electromyography and Kinesiology*, 22(5), 648–654. doi: 10.1016/j.jelekin.2012.01.006
3. Bialosky, J. E., Beneciuk, J. M., Bishop, M. D., Coronado, R. A., Penza, C. W., Simon, C. B., & George, S. Z. (2018). Unraveling the Mechanisms of Manual Therapy: Modeling an Approach. *Journal of Orthopaedic & Sports Physical Therapy*, 48(1), 8–18. doi:10.2519/jospt.2018.7476
4. Loeser JD (1980). Perspectives on pain. In: Turner P, Padgham C, & Hedges A (Eds.), *Clinical pharmacology & therapeutics* (pp. 313–316). London : Palgrave Macmillan. https://doi.org/10.1007/978-1-349-05952-2_34
5. Marchand S (2012). *The phenomenon of pain*. IASP Press
6. Fields HL, *Pain*, New York, McGraw-Hill Book Compagny, 1987, p.354
7. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annu Rev Neurosci* 1984 ;7:309-338
8. Marchand S, *Le Phénomène de la douleur*, 2008
9. Ossipov MH, Morimura K, Porreca F. 2014. Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care*. 2014 Jun;8(2):143-51. doi: 10.1097/SPC.000000000000055.
10. Kato, F., Sugimura, Y. K., & Takahashi, Y. (2018). Pain-Associated Neural Plasticity in the Parabrachial to Central Amygdala Circuit. *Advances in Experimental Medicine and Biology*, 157–166. doi:10.1007/978-981-13-1756-9_14)
11. Vanegas H, Schaible HG. Descending control of persisting pain: inhibitory or facilitatory? *Brain Res Rev*. 2004; 46 :295-309. [PubMed: 19146877
12. You HJ, Lei J, Sui MY, et al, Endogenous descending modulation: spatiotemporal effect of dynamic imbalance between descending facilitation and inhibition of nociception. *J Physiol* 2010 ; 588 :4177-4188. [PubMed : 20837643]
13. Benarroch, E. E. (2008). Descending monoaminergic pain modulation: Bidirectional control and clinical relevance. *Neurology*, 71(3), 217–221. doi: 10.1212/01.wnl.0000318225.51122.63).
14. Ablin JN, Buskila D. Fibromyalgia syndrom: novel therapeutic targets. *Maturitas*. 2013 ; 75 :335-340.[PubMed : 23742873])
15. Meeus M, Hermans L, Ickmans K, et al. Endogenous pain modulation in response to exercise in patients with rheumatoid arthritis, patients with chronic fatigue syndrom and comorbid fibromyalgia, and healthy controls: a double blind randomized controlled trial. *Pain Pract*. 2014
16. Brody H. The placebo response. *J Fam Pract* 2000 ; 49 :649-54).
17. Melzack, R., & Wall, P. D. (1965). *Pain Mechanisms: A New Theory*. *Science*, 150(3699), 971–978. doi:10.1126/science.150.3699.971
18. Laura Frank PM, Vaughan B. The repeatability of pressure algometry in asymptomatic individuals over consecutive days. *Int J Osteopathic Med*. 2013;16(3):143–52.]
19. D.C. Turk, A. Okifuji, Pain terms and taxonomies of pain, in: F.M. Fishman, J.C. Ballantyne, J.P. Rathmell (Eds.), *Bonica's management of pain*, fourth ed., Lippincott Williams & Wilkins, Philadelphia, 2009, pp. 13–24)
20. Chesterton, L. S., Sim, J., Wright, C. C., & Foster, N. E. (2007). Interrater Reliability of Algometry in Measuring Pressure Pain Thresholds in Healthy Humans, Using Multiple Raters. *The Clinical Journal of Pain*, 23(9), 760–766. doi:10.1097/ajp.0b013e318154b6ae]

21. Kinser, A. M., Sands, W. A., & Stone, M. H. (2009). Reliability and Validity of a Pressure Algometer. *Journal of Strength and Conditioning Research*, 23(1), 312–314. doi:10.1519/jsc.0b013e31818f051c]
22. Staud, R. (2012). Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Review of Neurotherapeutics*, 12(5), 577–585. doi:10.1586/ern.12.41)
23. Lautenbacher, S., Peters, J. H., Heesen, M., Scheel, J., & Kunz, M. (2017). Age changes in pain perception: A systematic-review and meta-analysis of age effects on pain and tolerance thresholds. *Neuroscience & Biobehavioral Reviews*, 75, 104–113. doi:10.1016/j.neubiorev.2017.01.039)
24. Aron. *Statistics for psychology*. 2nd ed: Prentice Hall; 1999. p. 229–30.],
25. Coe Robert. It's the effect size, stupid. What effect size is and why it is important. Annual conference of the British Research Association, University of Exeter England, 12–14. September 2002.]
26. Arthur K Shapiro, Elaine Shapiro, *The powerful placebo : from ancient priest to modern physician*, Baltimore, Johns Hopkins University Press, 1997, pp. xi, 280, (0-8018-5569-1)).
27. Wood L, Egger M, Gluud LL, et al: Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008; 336:601Y5)
28. Aaron A. Puhl, Christine J Reinhart, Jon B. Doan, Howard Vernon, The quality of placebos used in randomized, controlled trials of lumbar and pelvic joint thrust manipulation – a systematic review., *The Spine Journal* (2016), <http://dx.doi.org/doi: 10.1016/j.spinee.2016.11.003>
29. Vernon H, Puhl A, Reinhart C. Systematic review of clinical trials of cervical manipulation: control group procedures and pain outcomes. *Chiropr Man Therap*. 2011; 19 (1): 3
30. Machado LAC, Kamper SJ, Herbert RD, Maher CG, McAuley JH. Imperfect placebos are common in low back pain trials: a systematic review of the literature. *Eur J Spine*. 2008; 17: 889-904.).
31. Bergmann TF. High-velocity low-amplitude manipulative techniques. In: Haldeman S, editor. *Principles and practice of chiropractic*. 3rd ed. USA:McGraw-Hill; 2005. p. 755–66)
32. Gross A, Langevin P, Burnie SJ, Bédard-Brochu MS, Empey B, Dugas E, Faber662 Dobrescu M, Andres C, Graham N, Goldsmith CH, Brønfort G, Hoving JL, LeBlanc F. Manipulation and mobilisation for neck pain contrasted against an inactive control or another active treatment. *Cochrane Database of Systematic Reviews* 2015, Issue 9. Art. No.: CD004249. doi: <https://doi.org/10.1002/14651858.CD004249.pub4>.
33. Bialosky JE, Beneciuk JM, Bishop MD, Coronado RA, Penza CW, Simon CB, George SZ. Unraveling the mechanisms of manual therapy: modeling an approach. *J Orthop Sports Phys Ther*. 2018;48(1):8–18. <https://doi.org/102519/jospt.2018.7476>.)
34. Maitland GD, Hengeveld E. *Maitland's Vertebral Manipulation*. Butterworth-Heinemann, Oxford, UK (2001)
35. Pattyn E, Rajendran D. Anatomical landmark position – can we trust what we see? Results from an online reliability and validity study of osteopaths. *Man. Ther*. 19(2), 158–164 (2014)
36. (Kent, P., Marks, D., Pearson, W., & Keating, J. (2005). Does Clinician Treatment Choice Improve the Outcomes of Manual Therapy for Nonspecific Low Back Pain? A Metaanalysis. *Journal of Manipulative and Physiological Therapeutics*, 28(5), 312–322)
37. Teodorczyk-Injeyan JA, Injeyan HS, Ruegg R. Spinal manipulative therapy reduces inflammatory cytokines but not substance p production in normal subjects. *J. Manipulative Physiol. Ther*. 29(1), 14–21 (2006)
38. Vernon HT, Dhami MS, Howley TP, Annett R. Spinal manipulation and beta-endorphin: A controlled study of the effect of a spinal manipulation on plasma beta-endorphin levels in normal

- males. *J. Manipulative Physiol. Ther.* 9(2), 115–123 (1986)
39. Mcpartland JM, Giuffrida A, King J et al. Cannabimimetic effects of osteopathic manipulative treatment. *J. Am. Osteopath. Assoc.* 105(6), 283–291 (2005)
 40. Coronado RA, Gay CW, Bialosky JE et al. Changes in pain sensitivity following spinal manipulation: A systematic review and meta-analysis. *J. Electromyogr. Kinesiol.* 22(5), 752–767 (2012)
 41. Millan, M., Leboeuf-Yde, C., Budgell, B., & Amorim, M.-A. (2012). The effect of spinal manipulative therapy on experimentally induced pain: a systematic literature review. *Chiropractic & Manual Therapies*, 20(1), 26. doi:10.1186/2045-709x-20-26
 42. Honoré, M., Leboeuf-Yde, C., & Gagey, O. (2018). The regional effect of spinal manipulation on the pressure pain threshold in asymptomatic subjects: a systematic literature review. *Chiropractic & Manual Therapies*, 26(1). doi:10.1186/s12998-018-0181-3
 43. Cohen J. The earth is round ($p < .05$). *Am Psychol.* 1994;49(12):997–1003.
 44. Ray JW, Shadish WR. How interchangeable are different estimators of effect size? *J Consult Clin Psychol.* 1996;64(6):1316–25. <https://doi.org/10.1037/0022-006x.64.6.1316>.
 45. Cuijpers P, Weitz E, Cristea IA, Twisk J. Pre-post effect sizes should be avoided in meta-analyses. *Epidemiology and Psychiatric Sciences.* 2016; 26(04):364–8. <https://doi.org/10.1017/s2045796016000809>.
 46. Yu X, Wang X, Zhang J, Wang Y. Changes in pressure pain thresholds and basal electromyographic activity after instrument-assisted spinal manipulative therapy in asymptomatic participants: a randomized, controlled trial. *J Manip Physiol Ther.* 2012;35(6):437–45.)
 47. Ruiz-Saez M, Fernandez-de-las-Penas C, Blanco CR, Martinez-Segura R, Garcia-Leon R. Changes in pressure pain sensitivity in latent myofascial trigger points in the upper trapezius muscle after a cervical spine manipulation in pain-free subjects. *J Manip Physiol Ther.* 2007;30(8):578–83),
 48. Srbely JZ, Vernon H, Lee D, Polgar M. Immediate effects of spinal manipulative therapy on regional antinociceptive effects in myofascial tissues in healthy young adults. *J Manip Physiol Ther.* 2013;36(6):333–41
 49. Fernandez-de-Las-Penas C, Alonso-Blanco C, Cleland JA, Rodriguez-Blanco C, Albuquerque-Sendin F. Changes in pressure pain thresholds over C5-C6 zygapophyseal joint after a cervicothoracic junction manipulation in healthy subjects. *J Manip Physiol Ther.* 2008;31(5):332–7
 50. Fernandez-de-las-Penas C, Perez-de-Heredia M, Brea-Rivero M, Miangolarra- Page JC. Immediate effects on pressure pain threshold following a single cervical spine manipulation in healthy subjects. *The Journal of orthopaedic and sports physical therapy.* 2007;37(6):325–9)
 51. Luke Hamilton CB, Fryer G. The effects of high-velocity, low-amplitude manipulation and muscle energy technique on suboccipital tenderness. *International Journal of Osteopathic Medicine.* 2007
 52. Thomson O, Haig L, Mansfield H. The effects of high-velocity low-amplitude thrust manipulation and mobilisation technique on pressure pain threshold on the lumbar spine. *Int J Osteopath Med.* 2009;12(2):56–62
 53. Fryer G, Mclver JCS. The effect of manipulation and mobilisation on pressure pain thresholds in the thoracic spine. *Journal of Osteopathic Medicine.* 2004
 54. Honoré M, Leboeuf-Yde C, Gagey O, Wedderkopp N. How big is the effect of spinal manipulation on the pressure pain threshold and for how long does it last? - secondary analysis of data from a systematic review. *Chiropr Man Therap.* 2019 Apr 24;27:22. doi: 10.1186/s12998-019-0240-4. eCollection 2019
 55. Honoré M, Picchiottino M, Wedderkopp N, Leboeuf-Yde C Gagey O. What is the effect of spinal manipulation on the pressure pain threshold in young, asymptomatic subjects? A randomized

- placebo-controlled trial, with a cross-over design. *Chiropr Man Therap*. 2020 Feb 7;28(1):6. doi: 10.1186/s12998-020-0296-1
56. Aleksander Chaibi, Jūratė Šaltytė Benth & Michael Bjørn Russell Validation of Placebo in a Manual Therapy Randomized Controlled Trial *Scientific Reports* 5:11774 Doi: 10.1038/srep11774
 57. Aspinall SL, Leboeuf-Yde C, Etherington SJ, Walker BF. Manipulation-induced hypoalgesia in musculoskeletal pain populations: a systematic critical review and meta-analysis. *Chiropr Man Ther*. 2019;27(1). <https://doi.org/10.1186/718s12998-018-0226-7>.)
 58. Aspinall SL, Jacques A, Leboeuf-Yde C, Etherington SJ, Walker BF. No difference in pressure pain threshold and temporal summation after lumbar spinal manipulation compared to sham: a randomised controlled trial in adults with low back pain. *Musculoskelet Sci Pract*. 2019. <https://doi.org/10.1016/j.msksp.2019.05.011>.)
 59. Mansilla-Ferragut P, Fernández-de-las Peñas C, Alburquerque-Sendín F, Cleland JA, Boscá-Gandía JJ. Immediate effects of atlanto-occipital joint manipulation on active mouth opening and pressure pain sensitivity in women with mechanical neck pain. *J Manip Physiol Ther*. 2009;32(2):101–6
 60. Kardouni JR, Shaffer SW, Pidcoe PE, Finucane SD, Cheatham SA, Michener LA. Immediate changes in pressure pain sensitivity after thoracic spinal manipulative therapy in patients with subacromial impingement syndrome: a randomized controlled study. *Man Ther*. 2015;20(4):540–6.)
 61. Higgins, J. P. T., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., ... Oxman, A. D. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 343(oct18 2), d5928–d5928. doi:10.1136/bmj.d5928).

TABLE DES ILLUSTRATIONS

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ANNEXE 1. Calcul de la taille de l'effet.

Calculation of the effect size index

There are several ways to calculate the “between-group” effect size, as reported by Ellis and al in 2009 [24], but all with specific conditions of utilization. The most commonly reported is the Cohen’s d coefficient [25], which is the subtraction of the mean of the experimental group from the mean of the control group ($M_E - M_C$), and the division of the result by the standard deviation (SD) (Equation 1). However, the utilization of this equation is on the condition of a homogeneity of both the number of participants per group ($N_E = N_C$) and of their standard deviations ($SD_E = SD_C$).

$$\text{Equation 1: Cohen's } d = \frac{(M_E - M_C)}{SD}$$

When this is not the case, one of two scenarios can be selected.

1) When the sizes of each population remain equal ($N_E = N_C$), but with different SDs ($SD_E \neq SD_C$), then a different calculation of a pooled SD (SD^*) is required [24] (Equation 2).

$$\text{Equation 2: } SD^* = \sqrt{\frac{SD_E^2 + SD_C^2}{2}}$$

2) When, on the other hand, the size of each population is not equal ($N_E \neq N_C$), also with different SDs ($SD_E \neq SD_C$), then the Hedges’ g coefficient could be used, according to [24] (Equation 3) with yet another calculation of a pooled SD (SD_{Pooled}) (Equation 4) [26]

$$\text{Equation 3: Hedge's } g = \frac{(M_E - M_C)}{SD_{\text{Pooled}}}$$

$$\text{Equation 4: } SD_{\text{pooled}} = \sqrt{\frac{(N_E - 1)SD_E^2 + (N_C - 1)SD_C^2}{N_E + N_C - 2}}$$

The Hedges’ g coefficient can also be calculated from the Cohen’s d coefficient [24] (Equation 5).

$$\text{Equation 5: } g = d \left(1 - \frac{3}{4(N_E + N_C) - 9}\right)$$

Finally, it is not enough only to report the effect size (Cohen’s d or Hedges’ g coefficients) [9].

Indeed, its 95% interval of confidence (95% CI) (Equation 6) and standard deviation (SD) (d)

(Equation 7) should also be reported [27].

Equation 6: 95% CI: $[d - 1.96 \times \text{SD}(d); d + 1.96 \times \text{SD}(d)]$

$$\text{Equation 7: } \text{SD}(d) = \sqrt{\frac{N_E + N_C}{N_E \times N_C} + \frac{d^2}{2(N_E + N_C)}}$$

References :

9. Cohen, J. (1994). **The earth is round ($p < .05$)**. *American Psychologist*, 49(12), 997-1003
24. Ellis, P.D. (2009). “**Effect size equations**,” website:
[http://www.polyu.edu.hk/mm/sizeeffectsizefaq/effect_size_equations2.html] accessed on [September 2018]
25. Cohen. **Statistical power analysis for the behavioral sciences**. 2nd edition. 1988. Page 43
26. Hedge LV, Olkin . **Statistical methods for meta-analysis**. Orlando, Academic Press Inc. 2014, p.86
27. Hedges LV. **Distribution theory for Glass’s estimator of effect size and related estimators**. *Journal of Educational Statistics*, 1981. 6(2):106-128. Page 110. → 27

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REVIEW

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The regional effect of spinal manipulation on the pressure pain threshold in asymptomatic subjects: a systematic literature review

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Abstract

Background: Spinal manipulation (SM) has been shown to have an effect on pain perception. More knowledge is needed on this phenomenon and it would be relevant to study its effect in asymptomatic subjects.

Objectives: To compare regional effect of SM on pressure pain threshold (PPT) vs. sham, inactive control, mobilisation, another SM, and some type of physical therapy. In addition, we reported the results for the three different spinal regions.

Method: A systematic search of literature was done using PubMed, Embase and Cochrane. Search terms were ((spinal manipulation) AND (experimental pain)); ((spinal manipulative therapy OR spinal manipulation) AND ((experimental pain OR quantitative sensory testing OR pressure pain threshold OR pain threshold)) (Final search: June 13th 2017). The inclusion criteria were SM performed anywhere in the spine; the use of PPT, PPT tested in an asymptomatic region and on the same day as the SM. Studies had to be experimental with at least one external or internal control group. Studies on only spinal motion or tenderness, other reviews, case reports, and less than 15 invited participants in each group were excluded. Evidence tables were constructed with information relevant to each research question and by spinal region. Results were reported in relation to statistical significance and were interpreted taking into account their quality.

Results: Only 12 articles of 946 were accepted. The quality of studies was generally good. In 8 sham controlled studies, a psychologically and physiologically "credible" sham was found in only 2 studies. A significant difference was noted between SM vs. Sham, and between SM and an inactive control. No significant difference in PPT was found between SM and another SM, mobilisation or some type of physical therapy. The cervical region more often obtained significant findings as compared to studies in the thoracic or lumbar regions.

Conclusion: SM has an effect regionally on pressure pain threshold in asymptomatic subjects. The clinical significance of this must be quantified. More knowledge is needed in relation to the comparison of different spinal regions and different types of interventions.

Keywords: Spinal manipulation, Experimental pain, Pressure pain threshold, Asymptomatic, Systematic review

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RESUME

But: Un effet de la manipulation vertébrale a été observé sur la perception de la douleur. Plus de connaissances sont nécessaires sur ce phénomène et il serait pertinent d'étudier cet effet sur les sujets asymptomatiques.

Objectifs: Evaluer l'effet régional de la MV sur le seuil de douleur à la pression (SDP) comparé à un placebo, un groupe contrôle, la mobilisation, une autre MV, et un autre type de physiothérapie. De plus, nous avons rapporté les résultats pour les régions cervicale, dorsale et lombaire.

Méthode: La revue systématique de la littérature a été faite en utilisant PubMed, Embase et Cochrane. Les termes de recherche étaient ((manipulation vertébrale) ET (douleur expérimentale)); ((thérapie manuelle spinale OU manipulation spinale) ET (douleur expérimentale OU test quantitatif sensoriel OU seuil de douleur à la pression OU seuil de douleur)). (La recherche finale date du 13 juin 2017). Les critères d'inclusion étaient MV exécutées à n'importe quel niveau de la colonne vertébrale; l'utilisation du SDP, testé dans une région asymptomatique et le même jour que la MV. Les études devaient être expérimentales avec au moins un groupe externe à la MV ou un groupe contrôle interne. Les études uniquement sur le mouvement de la colonne vertébrale, tensions des tissus paravertébraux, les autres revues, les études de cas et des études avec moins de 15 participants dans chaque groupe ont été exclues. Des tables d'évidence ont été construites avec les informations appropriées à chaque question de recherche et reportées par régions. Les résultats ont été rapportés avec leur signification statistique et ont été interprétés en tenant compte de leur qualité.

Résultats: Seulement 12 articles sur 946 ont été acceptés. La qualité des études est, en général, bonne. Sur les 8 études contrôlées par placebo, un placebo psychologiquement et physiologiquement « crédible » a été trouvé seulement dans 2 études. Une différence significative a été notée entre MV et le placebo, et entre MV et contrôle inactif. Aucune différence significative dans SDP n'a été trouvée entre MV et une mobilisation, une autre MV, ou un autre type de physiothérapie. Des résultats significatifs ont été trouvés plus souvent dans la région cervicale comparé aux études aux niveaux thoraciques et lombaires.

Conclusion: La manipulation vertébrale a un effet régional sur le seuil de la douleur à la pression chez des sujets asymptomatiques. Sa différence clinique doit être quantifiée. Plus de connaissance est nécessaire à propos de la comparaison des différentes régions spinales et différents types d'interventions.

Mots clés: Manipulation vertébrale, Douleur expérimentale, Seuil de douleur à la pression, Sujets asymptomatiques, Revue systématique

Background

Spinal manipulation (SM) is a therapeutic tool used by several health care professions [1]. It is reasonably inexpensive [2] and recognized to have a clinically significant impact on musculoskeletal pain [3]. Nevertheless, its indications and mechanisms of action are still not well established for example in relation to pain reduction.

Spinal manipulation**Definition**

SM can be performed manually, resulting in a passive high velocity low amplitude movement that separates the vertebral joint surfaces [4]. Various positions of the therapist and angles of his hands can be used to obtain this result. Regardless, it is often accompanied by a cracking sensation and sound [5]. SM takes the targeted joint beyond its passive amplitude without causing an anatomical lesion [6]. It is a mechanical event that seems to decrease briefly the intra-discal pressure and to stretch the surrounding muscles, thus causing their relaxation [7]. It can be differentiated from mobilisation, where the movement would be

one or several low velocity low amplitude actions on the joints by the therapist, usually not accompanied by the "crack".

SM can also be mechanically assisted with an instrument called "activator". It can be set to produce a high velocity low amplitude force directly over a joint, just as the classical manual type of SM. In research on SM, the activator is often used as a sham procedure, with the instrument set on zero force, but still producing the same sound as when at normal force.

These two types of SM are traditionally used as interchangeable by chiropractors, although they may of course have different mechanisms. For the purpose of this review, we shall consider both of them as equally representative of SM.

Impact on clinical pain

Patients often report immediate improvement of pain after SM. For example, 63% of 984 patients with low back pain reported immediate improvement in a multicenter study [8], and according to the results of a meta-

analysis, SM has better outcome compared with exercises, education of the patient, and other forms of manual therapies (physiotherapy) in relation to experimentally induced pain [9]. This hypoalgesic effect is the object of several theories and models, and has been tested using experimentally induced pain.

Spinal manipulation and experimental pain

Pressure pain threshold

To examine this hypoalgesic effect, studies have used experimentally induced pain on asymptomatic subjects, to avoid the presence of co-morbidity and/or a central pain inhibitory effect likely to be present with ongoing pain.

The perception of pain is a complex phenomenon that can be induced by various external stimuli, such as pressure or temperature. A systematic review of the literature on asymptomatic healthy subjects published in 2012 showed that SM has an effect on pain induced by pressure, by increasing the pain threshold. It would seem that SM acts more on the pain produced by pressure than by temperature [10]. Pain on pressure is often tested via the pressure pain threshold (PPT), which is defined as the minimal pressure which provokes a pain or a discomfort [11]. It has the advantage to be objective and valid, with a good reliability [12]. It is present in all individuals and, thus, possible to be estimated for everybody. The PPT can be relatively easily determined by the means of an algometer, a device making it possible to measure exactly the applied pressure and in a precise zone.

Concerning the regional testing

Although many studies report an immediate effect on pain perception following SM [10], the literature seems undecided as to whether this effect is purely local or if it extends also into other anatomical areas. According to a systematic critical review of the effect of SM on asymptomatic tissues, local and regional effects were often reported. However, all studies reporting a distant effect failed to use a blinded design [10]. The differentiation between "local" and "regional" is not always clear, but it seems likely that any pain-reducing effect would follow the nerve supply of the manipulated segment rather than occurring only directly in the manipulated area.

Spinal manipulation and experimental groups

Sham procedure and inactive control

To determine the effect of SM on experimental pain, SM must be compared to a sham procedure, or possibly an inactive control. A sham procedure is used in order to induce a placebo effect, with the intent to "fool" the subjects and to make them believe they received an active treatment. As it is relatively easy for study subjects to differentiate between a real SM and various attempted sham maneuvers, the subjects should be as naïve to SM

as possible. An inactive control is when the subjects are resting, and nothing is done to them. However, in such a situation, study subjects are well aware of not being treated, so it is not comparable to a successful sham procedure. If there would be no physiological effect of SM (i.e. no increased PPT), one would expect there to be no difference in PPT readings between SM and a successful sham. However, an unsuccessful sham treatment and a control treatment would be expected to result in higher PPT values for the SM group, as the study subjects would be likely to realize that this is the active procedure, which could result in a placebo effect. Therefore, it is relevant to compare the results in studies with credible shams vs. those without and also, results in purely passive control groups.

Spinal manipulation vs. mobilisation

Results from a systematic review on healthy subjects indicated that there was no difference in results between studies that concentrated on the crack and those that did not [10]. Similarly and perhaps for this reason, there is a doubt concerning the physiological effect of SM compared to mobilisation, and one study in the systematic review even found that mobilisation had a stronger effect than SM [13]. Therefore, it would be relevant to investigate also the difference of outcome between SM and mobilisation.

Spinal manipulation vs. other spinal manipulation

The literature indicates that SM may be more effective in certain regions than others, without giving a clear answer [10], for which reason a comparison between SM in different spinal regions is relevant as well.

Spinal manipulation vs. some type of physical therapy

A recent meta-analysis showed a significant "effect" of SM on the PPT, as compared to other interventions, such as exercise, education of the patient, and physiotherapy [9], but the difference is rather small, making also this an interesting topic of investigation.

Aims and search questions

Because of the gaps in our understanding of the effect of SM as compared to sham and other types of treatments, and because more articles have been published on this topic since 2012, it would be timely to update the previous review and enlarge our scope of approach. Therefore, in this systematic literature review we investigated if SM influences the PPT in symptomatic subjects, i.e. in subjects without symptoms in the tested area. A "tested area" was defined as the immediate anatomical site (i.e. within the dermatome) where SM was given and PPT testing took place. In addition to the previous survey, we compared the outcome between SM and different comparison groups.

We had five specific research questions in relation to the regional effect on the PPT after SM.

Research questions 1–2

Is there a statistically significant effect on the PPT levels when comparing (i) SM to sham, and/or (ii) SM to an inactive control?

Research questions 3–5

Are there any statistically significant differences of outcomes in the PPT when SM is compared to (i) mobilisation, (ii) another type of SM or SM in another spinal region, and/or (iii) some type of physical therapy?

In addition, we noted the results for the different spinal regions.

Method

Design

This systematic critical review consists of an update and extension of previous work on almost the same topic [10], and was registered in Prospero on February 27, 2017 (receipt [58207]).

Search strategy

We did a systematical literature search of PubMed, Embase and Cochrane using the search terms [(spinal manipulation) AND (experimental pain)]; [(spinal manipulative therapy OR spinal manipulation) AND ((experimental pain OR quantitative sensory testing OR pressure pain threshold OR pain threshold)]. We generally used the same search terms as the previous systematic review conducted on the same topic [10]. We also searched reference lists of relevant articles including those in the previous review [10]. The present search was performed between 2011.01.01 and 2017.06.13.

In the screening process, our inclusion criteria were SM performed manually and/or mechanically assisted, anywhere in the spine; the use of PPT, in an asymptomatic region and on the same day as SM, reported in experimental studies with at least one external or internal control group. Studies on only spinal motion or tenderness, other reviews, case reports and studies with less than 15 invited participants in each group were excluded. We used the preferred reporting item for systematic reviews and meta-analysis (PRISMA) flow chart (Fig. 1) to record our screening of the articles for inclusion and to report the flow of the review.

Extraction of data

We created our own evidence checklists, based on concepts described in CONSORT statements and the previous review [10]. All items were extracted from the [Method](#) and [Results](#) sections only.

The extraction of data was done blindly by the first author and one supervisor with extensive experience in systematic reviews. Both were chiropractors and were able to interpret the information in articles in relation to how SM and sham treatments were performed. Then, they compared the data and, if there were any disagreements, a third person could intervene and decide. Clear definitions and the rationale for the descriptive and the quality checklists items have been described in Tables 1 and 2. Results were reported in Table 3 and Table 4. Finally, the outcomes were noted for each article as significant or not significant (Table 5); exact estimates and effect size to be reported elsewhere.

Classifying articles by their quality

The selected articles were checked for each quality item. We took a special interest in the sham procedure and determined two specific approaches, investigating if the sham was both psychologically and physiologically credible. For the psychological aspect, the study had to include naïve subjects and the sham should resemble the intervention, and/or it had to be assessed and found to “work”, with the use of a post-study questionnaire.

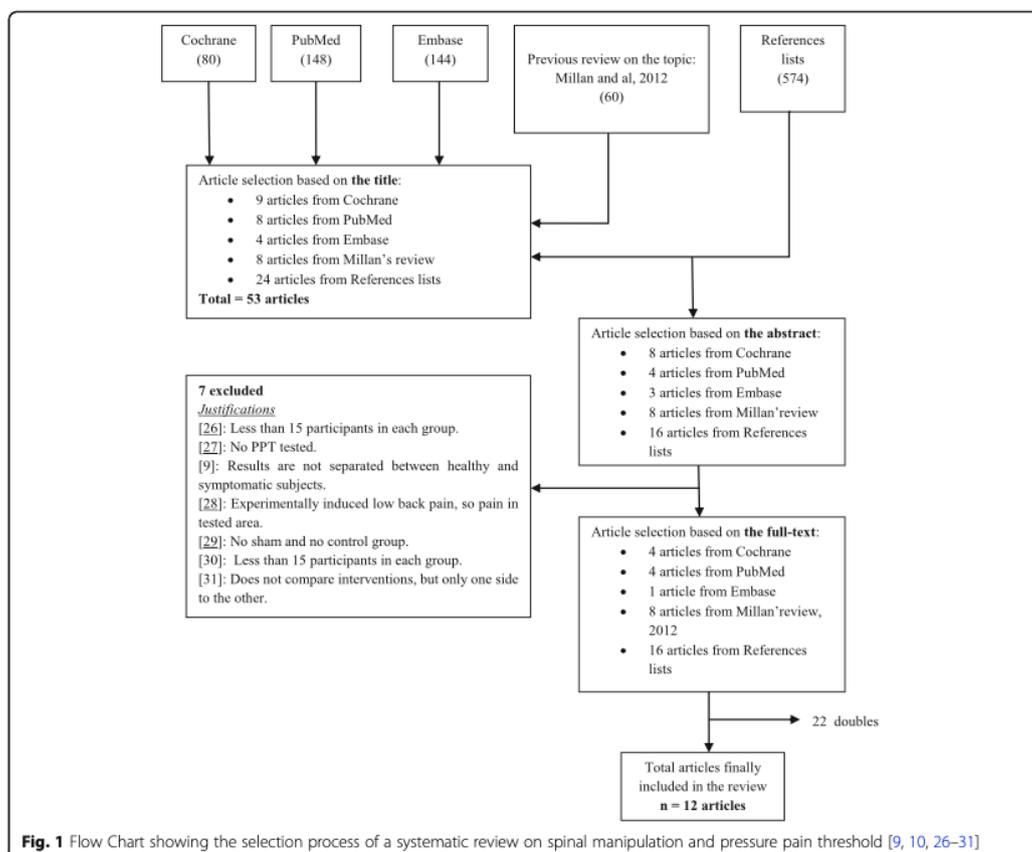
For the physiological approach, we expected there to be some type of tension, but not directly over the spinal column, to mimic closely the real intervention. It would be associated with a low velocity low amplitude sham “thrust”, to imitate the same mechanical components of a manual SM but without a direct action on the spinal column [14]. This type of procedure has been shown to confuse study participants and to do so over a whole treatment program [14]. For the mechanically assisted SM, the same characteristics as with the “active” (activator) treatment are expected, but with the activator set with no force at all and producing the same sound as the real intervention. In conclusion, the sham would be considered completely “credible” only if both aspects (psychological and physiological) were fulfilled.

Thereafter, we created a quality score, by giving one point for each fulfilled item. This score was arbitrarily divided into “high”, “medium” and “low”, to indicate the general quality of the articles (Table 6). Articles were listed in descending order based on the quality score in the result checklists. For the sham studies, we also separated them into “sham credible” and “sham not credible”.

Data synthesis

The evidence tables were used in a systematic fashion to obtain answers to our research questions, by taking into account the general quality of the articles and in the case of the sham studies, the credibility of the sham procedure in relation to the psychological and physiological aspects, both independently and in combination.

Although many studies report an immediate effect on [swell](#) [10], for which reason a comparison between SM



Results

In all, 148 potentially relevant articles titles were found in the PubMed search, 80 in Cochrane, 144 in Embase, and 60 were selected from the previous review on the same topic. At the end of the screening process, the hand search of the reference lists of all selected articles resulted in 574 potential articles. Only 12 articles were finally selected. Please see Fig. 1.

Description of studies

As it can be seen in Table 7, eight articles reported on SM vs. sham, with five articles measuring the PPT in the cervical, one in the thoracic, and two in the lumbar region. Only three articles tested SM vs. inactive control, with two articles in the cervical region, and one in the thoracic region. Two articles were found testing SM vs. SM, one in the cervical region and the other for both the cervical and lumbar regions. We found three articles on SM vs. mobilisation, one in the cervical region, one in the thoracic

region, and one in the lumbar region; and three articles on SM vs. some type of physical therapy, two in the cervical region and one in the thoracic region.

The level of quality was generally medium to high, except for one article that we considered to be of low quality (Table 4). The sham procedure was found psychologically acceptable for six articles ([15–20]), physiologically acceptable for two articles ([15, 17]) and both aspects were acceptable for two articles ([15, 17]), thus classified by us as completely “credible”. Only two were classified by us to be unacceptable both psychologically and physiologically (Table 7).

Examples of methodological weaknesses were that none of the twelve studies reported a detailed definition of the statistical imputation method, or reported on the blindness of the statistician, and none assessed the credibility of the placebo procedure with a post-study questionnaire. Only half of the studies reported on losses and exclusions of study subjects in their experiments.

Table 1 Description and interpretation of items used in a systematic review on spinal manipulation and pressure pain threshold

Descriptive items	Design	Sham Control Comparison with other treatment	Source of study sample	Age of participants Mean (range)	N subjects 1/invited 2/final analysis 3) per treatment group 4) (M/F)	Intervention groups: Types and area	Treatment area - "Lesion" - Standard	Pain measured where in relation to SM? Regional Remote	PPT measured when?
Interpretation	Randomized controlled trial and/or cross over studies	Description of the group of comparison	General population, volunteers, students to estimate if they were naïve		Describes size of study and indicates if there were losses or exclusions during the study.	Treatment group was indicated in relation to area of spine manipulated and comparison groups were described as Sham and Control with an indication of the area where the sham was given	"Lesion": The treating clinicians decides where to apply the SM based on clinical examination. "Standard": All study subjects receive the SM in a predetermined area	"Regional" was defined as an area within the dermatome of the area of SM. "Remote" was defined as an area outside this dermatome	PPT could be measured at base-line and at various time intervals after the intervention

M/F: number of Males and Females in the study/SM: Spinal Manipulation/PPT: Pressure Pain Threshold

Table 2 Quality items, rationale for inclusion in quality assessment, interpretation and scoring used in a systematic review on spinal manipulation and pressure pain threshold

Quality items	Description of the random allocation: 1)Randomization method 2)Concealment	Treatment performed by appropriate and experienced person?	Is the intervention described? 1. SM 2. Sham 3.Comparison 4. Control	Is the assessment blinded? 1. Assessor/ intervention 2. Statistician/ intervention	The sham procedure: (Yes/No/NA) 1. Naïve subjects 2. In the same position as SM? 3. Assessed Conclusion: Is the sham psychologically acceptable (1 pt), possibly acceptable (0.5 pt), not acceptable (0 pt)	If no sham procedure, at least are the subjects naïve? (Yes/No/NA)	Is the measurement procedure described?	Is reliability of the outcome variables reported? Were pain readings taken more than once at each point?	After the study started, are losses and exclusions of study subjects reported or evident?	
Rationale for inclusion in quality assessment	1)Ensuring equal distribution of study subjects 2) Prevent risk of cheating during group allocation and risk of bias during assessment	Ensuring interventions are appropriately administered	Ensuring that study can be reproduced	1)Preventing risk of assessor bias 2.Preventing "data massage"	Assuring the credibility of the sham both from a psychological and physiological aspect	Ensuring that there is no risk of participant bias	Ensuring that study can be reproduced	As validity is difficult to obtain, ensuring that, at least, the outcome variable is reliable	More than one reading is needed to avoid unrepresentative data	Making it possible to detect risk of exclusion/attrition bias
Interpretation details (where relevant)	1)as it said that participants were allocated into groups in a random fashion? 2) Was it stated that groups were concealed during random allocation?	Appropriate: practitioner with training in SM We believed the study when authors reported some sort of expertise or the treating clinicians	If we understood what had been done in the experiment, we considered this acceptable	This had to be stated in the text	1-3. A sham procedure may be able to "fool" a study subject but...	This had to be stated in the text	If we understood the procedure, we considered this acceptable	This could be reported with a reference to previous study or a reliability study could be reported in the Result section	This had to be stated in the Method or Result section	This had to be stated or obvious from Information given in Tables or Result section
Scoring	1. 0.5 pt. 2. 0.5 pt	1 pt	1 pt	1. 0.5 pt. 2. 0.5 pt	1 or 2: 0.5 pt 1 + 2: 1 pt 3 found acceptable: 1 pt 3 not found acceptable: 0 pt. Conclusion: Is the sham psychologically acceptable (when 1 pt is given), possibly acceptable (when 0.5 pt. is given), not acceptable (when 0 pt. is given)	Yes: 1 pt. No: 0 pt. If NA, this case is not taken into account.	1 pt	1 pt	1 pt	1 pt

SM Spinal Manipulation, NA Not Applicable

Table 3 Description of 12 studies included in a systematic review on spinal manipulation and pressure pain threshold

1st author Year Country [ref #]	Design	Sham Control Comparison with other treatment	Source of study sample	Age of participants Mean (range)	N subjects 1/invited 2/final analysis 3/ per treatment group 4) (M/F)	Intervention groups: Types and area	Treatment area - "Lesion" - Standard	Pain measured where in relation to SM? Regional Remote	PPT measured when?
Fryer 2004 Australia [21]	RCT	Sham Comparison	Students	- (19-34)	1) 96 2) - 3) 3 x 32 4) 39/57	1) SM thoracic 2) Thoracic Mobilization 3) Sham laser	Lesion	Regional	Before and after SM
Ruiz-Saez 2007 Spain [16]	RCT	Sham	Volunteers, general population with palpatory pain in trapezius	31 (19-45)	1) 72 2) 72 3) 2 x 36 4) 26/46	1) Cervical SM 2) Sham cervical	Lesion	Regional	Before and 1,5 and 10 min after SM
Fernandez de las Penas 2007 Spain [19]	RCT cross over	Sham Control Comparison	Students in physical therapy, occupational therapy, rehabilitation, and physical medicine	21 (19-25)	1) 15 2) 15 3) 7 for Right SM 8 for Left SM 4) 7/8	1) Cervical SM on the right or left 2) Sham cervical 3) Control	Standard	Regional	Before and 5 min after SM
Hamilton 2007 Australia [20]	RCT	Sham Comparison	Students and teaching body of university	23 (-)	1) 90 2) - 3) 35;25;30 4) 29/61	1) SM cervical 2) Sham thoracic 3) Muscle energy technique (suboccipital and trapezius muscles)	Standard	Regional	Before 5 and 30 min after SM
Fernandez de las Penas 2008 Spain [18]	RCT	Sham Comparison	Volunteers from general population	26 (19-35)	1) 30 2) 30 3) 3 x 10 4) 13/17	1) Cervico-thoracic SM (dominant side) 2) Cervico-thoracic SM (non-dominant side) 3) Sham cervical	Standard	Regional	Before and 5 min after SM
Thomson 2009 Sweden [13]	RCT	Sham Comparison	Osteopathic students and teachers	27	1) 50 2) 50 3) 18;19;13 4) 29/21	1) Lumbar SM 2) Lumbar mobilization 3) Sham lumbar laser	Lesion	Regional	Before and immediately after SM
Oliveira Campelo 2010 Spain [22]	RCT	Control Comparison	Volunteers from school of technology with palpatory pain in jaw muscle	20 (18-30)	1) - 2) 122 3) 40; 41; 41 4) 31/91	1) Cervical SM 2) Soft tissue 3) Control	Standard	Regional	Before and 2 min after SM
Bishop 2011 USA [24]	Randomized experimental design	Control Comparison	Volunteers recruited by posters	23 (-)	1) 90 2) - 3) 3 x 30 4) 24/66	1) SM Cervico-Thoracic region 2) Cervical exercises 3) Control	Standard	Regional and remote	Before and immediately after SM
Yu 2012 China [15]	RCT cross- over	Sham	General population and medical students	24 (-)	1) 30 2) 30 3) 30 x 2 4) 19/11	1) SM lumbar (activator) 2) Sham (detuned activator)	Lesion using activator protocol	Regional and remote	Before and after SM

Table 3 Description of 12 studies included in a systematic review on spinal manipulation and pressure pain threshold (Continued)

1st author Year Country [ref #]	Design	Sham Control Comparison with other treatment	Source of study sample	Age of participants Mean (range)	N subjects 1/invited 2/final analysis 3) per treatment group 4) (M/F)	Intervention groups: Types and area	Treatment area - "Lesion" - Standard - Remote	Pain measured where in relation to SM? Regional Remote	PPT measured when?
Sibely 2013 Canada [17]	RCT	Sham	Volunteer university students	29 for treatment 27 for sham (-)	1) 44 2) 33 3) 18 for SM and 18 for sham 4) 19/17	1) SM cervical 2) Sham cervical	Standard	Regional and remote	Before, 1,5,10 and 15 min after SM
Jordan 2016 USA [23]	RCT	Control Comparison	University community	22 (18-32)	1) 57 2) 54 3) 18;19;17 4) 25/32	1) Rest 2) Lumbar + Cervical SM 3) Cervical + Lumbar SM	Standard	Regional and remote	Before and after SM
Alonso Perez 2016 Spain [22]	RCT	Comparisons	University population	29 (-)	1) 83 2) 74 3) 25;24;25 4) 39/36	1) Cervical SM 2) Cervical mobilization 3) Cervical glide mobilization	Standard	Regional	Before and after SM

RCT randomized controlled trial, SM spinal manipulation

Table 4 Quality items and scores of 12 studies included in a systematic review on spinal manipulation and pressure pain threshold

First author Year Country [ref #]	Is there a description of the random allocation? 1) Randomization method 2) Concealment	Is treatment performed by experienced person?	Is the intervention described? 1. SM 2. Sham 3. Comparison 4. Control	Is the assessment blinded? 1. Assessor/ intervention 2. Statistician/ intervention	The sham procedure: (Yes/No/NA) 1. Naive subjects 2. In the same position as SM? 3. Assessed Conclusion: Is the sham psychologically acceptable (1 pt), possibly acceptable (0.5 pt), not acceptable (0 pt)	If comparison interventions are the subjects naïve? (Yes/No/NA)	Is the measurement procedure described?	Is reliability of the outcome variables reported?	Were pain readings taken more than once at each point?	After the study started, are losses and exclusions of study subjects reported or evident?	Score for sham studies	Score for comparison studies
Fryer 2004 Australia [21]	1) Yes 2) No	No	1) Yes 2) Yes 3) Yes 4) NA	1) Yes 2) No	1. No 2. No 3. No Conclusion: Not acceptable	No	Yes	Yes	Yes	No		
Ruiz-Saez 2007 Spain [16]	0.5 1) Yes 2) No	0 Yes	1 1) Yes 2) Yes 3) NA 4) NA	0.5 1) Yes 2) No	0 1. Yes 2. Yes 3. No Conclusion: Acceptable	0 NA	1 Yes	1 Yes	1 Yes	0 Yes	5/9	5/9
Fernandez de las Penas 2007 Spain [19]	0.5 1) No 2) No	1 Yes	1 1) Yes 2) Yes 3) Yes 4) Yes	0.5 1) Yes 2) No	1 1. Yes 2. Yes 3. No Conclusion: Acceptable	Yes Yes	Yes Yes	1 Yes	1 Yes	1 No	8/9	NA
Hamilton 2007 Australia [20]	0 1) Yes 2) No	1 Yes	1 1) Yes 2) Yes 3) Yes 4) NA	0.5 1) Yes 2) No	1 1. Yes 2. No 3. No Conclusion: Possibly acceptable	1 Yes	1 Yes	1 Yes	1 Yes	0 No	6.5/9	6.5/9
	0.5	1	1	0.5	0.5	1	1	1	1	0	6.5/9	7/9

Table 4 Quality items and scores of 12 studies included in a systematic review on spinal manipulation and pressure pain threshold (Continued)

First author Year Country [ref #]	Is there a description of the random allocation? 1) Randomization method 2) Concealment	Is treatment performed by experienced person? 1. SM 2. Sham 3. Comparison 4. Control	Is the intervention described? 1. Assessor/ intervention 2. Statistician/ intervention	The sham procedure: (Yes/No/NA) 1. Naive subjects 2. In the same position as SM? 3. Assessed Conclusion: Is the sham psychologically acceptable (1 pt), possibly acceptable (0.5 pt), not acceptable (0 pt)	If comparison between interventions are the subjects naïve? (Yes/No/NA)	Is the measurement procedure described?	Is reliability of the outcome variables reported?	Were pain readings taken more than once at each point?	After the study started, are losses and exclusions of study subjects reported or evident?	Score for sham studies	Score for comparison studies	
Fernandez de las Penas 2008 Spain [18]	1) Yes 2) No	1) Yes 2) Yes 3) Yes 4) Yes	1) Yes 2) No	1. Yes 2. Yes 3. No Conclusion: Acceptable	Yes	Yes	Yes	Yes	No	7/9	7/9	
Thomson 2009 Sweden [13]	1) Yes 2) No	1) Yes 2) Yes 3) Yes 4) NA	1) Yes 2) No	1. No 2. No 3. No Conclusion: Not acceptable	No	Yes	Yes	Yes	No	6/9	6/9	
Oliveira Campelo 2010 Spain [22]	1) Yes 2) No	1) Yes 2) NA 3) Yes 4) Yes	1) Yes 2) No	NA Conclusion: Not acceptable	Yes	Yes	Yes	Yes	Yes	NA	8/9	
Bishop 2011 USA [24]	1) Yes 2) No	1) Yes 2) NA 3) Yes 4) Yes	1) No 2) No	NA Conclusion: Not acceptable	Yes	Yes	No	No	No	NA	3.5/9	
	0.5	0	0	0	1	1	0	0	0	0	NA	3.5/9

Table 4 Quality items and scores of 12 studies included in a systematic review on spinal manipulation and pressure pain threshold (Continued)

First author Year Country [ref#]	Is there a description of the random allocation? 1) Randomization method 2) Concealment	Is the treatment performed by experienced person?	Is the intervention described? 1. SM 2. Sham 3. Comparison 4. Control	Is the assessment blinded? 1. Assessor/ intervention 2. Statistician/ intervention	The sham procedure: (Yes/No/NA) 1. Naive subjects 2. In the same position as SM? 3. Assessed	If comparison between interventions are the subjects naïve? (Yes/No/NA)	Is the measurement procedure described?	Is reliability of the outcome variables reported?	Were pain readings taken more than once at each point?	After the study started, are losses and exclusions of study subjects reported or evident?	Score for sham studies	Score for comparison studies	
Yu 2012 China [15]	1) Yes 2) No	Yes	1) Yes 2) Yes 3) NA 3) NA	1) Yes 2) No	1. Yes 2. Yes 3. No	NA	Yes	Yes	Yes	Yes			
Srbely 2013 Canada [17]	0.5 1) Yes 2) Yes	1 Yes	1 1) Yes 2) Yes 3) NA 4) NA	0.5 1) Yes 2) No	1 1. Yes 2. Yes 3. No	NA	1 Yes	1 No	1 Yes	1 Yes	8/9	NA	
Jordan 2016 USA [23]	1 1) Yes 2) Yes	1 Yes	1 1) Yes 2) NA 3) Yes 4) Yes	0.5 1) Yes 2) No	1 NA	Yes	1 Yes	0 Yes	1 No	1 Yes	7.5/9	NA	
Alonso Perez 2016 Spain [22]	1 1) Yes 2) Yes	1 Yes	1 1) Yes 2) NA 3) Yes 4) NA	0.5 1) Yes 2) No	NA	Yes	1 Yes	0 Yes	1 Yes	1 Yes	NA	7.5/9	
	1	1	1	0.5		1	1	1	1	1	1	NA	8.5/9

NA Not applicable, SM Spinal manipulation

Table 5 Results from 12 studies included in a systematic review on spinal manipulation and pressure pain threshold

First author Year Country [#ref]	Area of SM	Regional: (.....)	Sign. diff. SM vs. Sham? Was the sham credible? (Yes/No)	Sign. diff. SM vs. Control	Sign. diff. SM vs. Other SM (.....)	Sign. diff. SM vs. Mobilization. (.....)	Sign. diff. SM vs. Other therapy (.....)	Quality Score (for sham and comparison groups)
Srbely 2013 Canada [17]	Cervical (bilateral)	Regional: (Infraspinatus muscle)	Regional: Yes Sham procedure: Yes					7.5/9 for sham
Yu 2012 China [15]	Lumbar	Regional: - (L5-S1 over apophyseal joints) - (L5 dermatome)	Regional: Yes Sham procedure: Yes					8/9 for sham
Thomson 2009 Sweden [13]	Lumbar	Regional: (Spinous process of L3)	Regional: No Sham procedure: No			No (Mobilization lumbar spine)		6/9 for sham 6/9 for comparison
Fernandez de las Penas 2008 Spain [18]	Cervical	Regional: (C5-C6 level at dominant and non-dominant side)	Regional: Yes Sham procedure: No		No (SMT dominant side vs. non-dominant side)			7/9 for sham 7/9 for comparison
Ruiz Saez 2007 Spain [16]	Cervical	Regional: (Upper trapezius latent trigger points)	Regional: Yes Sham procedure: No					8/9 for sham
Fernandez de las Penas 2007 Spain [19]	Cervical	Regional: (Ipsilateral and contralateral epicondyle)	Regional: Yes Sham procedure: No	Yes				6.5/9 for sham 6.5/9 for comparison
Fryer 2004 Australia [21]	Thoracic	Regional: (Thoracic spinous process between T1 and T4)	Regional: No Sham procedure: No			No (Extension mobilization of thoracic spine)		5/9 for sham 5/9 for comparison
Bishop 2011 USA [24]	Thoracic	Regional: (Between first and second fingers)		Regional: No Remote: No			No (Exercise)	3.5/9 for comparison
Oliveira Campelo 2010 Spain [22]	Cervical	Regional: (Masseter and temporalis latent trigger points)		Regional: - Masseter: Yes - Temporalis: Yes				8/9 for comparison
Hamilton 2007 Australia [20]	Cervical	Regional: (Between C2 and C0)	Regional: No Sham procedure: No				No (Muscle energy technique)	6.5/9 for sham 7/9 for comparison
Jordan 2016 USA [23]	Cervical and Lumbar	Regional: (Lateral epicondyle of humerus and upper trapezius bilaterally)			Regional: No			7.5/9 for comparison
Alonso Perez 2016 Spain [22]	Cervical	Regional: (Cervical process of C7, bilateral Trapezius muscle, epicondyle region)			Regional: No between groups results but within groups results presented			8.5/9 for comparison

Table 6 Summary of quality scores and quality classification for 12 articles included in a systematic review on spinal manipulation and pressure pain threshold

	First Author, Year [ref]	Score	Quality scale
SHAM STUDIES	Yu, 2012 [15]; Ruiz Saez, 2007 [16]	8/9	High
	Srbely, 2013[17]	7.5/9	High
	Fernandez de la Penas, 2008 *[18]	7/9	Medium
	Fernandez de la Penas, 2007 [19]; Hamilton [20]	6.5/9	Medium
	Thomson, 2009 [13]	6/9	Medium
	Fryer, 2004 [21]	5/9	Medium
COMPARISON STUDIES	Alonso Peres, 2016 [22]	8.5/9	High
	Oliveira Campelo, 2010 [23]	8/9	High
	Jordon, 2016 [24]	7.5/9	High
	Hamilton, 2007 [20]; Fernandez de las Penas, 2008 [18]	7/9	High
	Fernandez de la Penas, 2007 [19]	6.5/9	Medium
	Thomson, 2009 [13]	6/9	Medium
	Fryer, 2004 [21]	5/9	Medium
	Bishop, 2011 [25]	3.5/9	Low

Classification: Low: 0–4.5pts; Medium: 5–6.5pts; High: 7-9pts. *Some articles were listed twice in the table, as they used a sham procedure and compared a spinal manipulation to another intervention

Spinal manipulation vs. sham

Significant difference in PPT readings

Out of eight articles on SM vs. sham, all of high to medium quality, two were of us considered completely credible, and both of these reported a significant effect on the PPT. Another three were considered only psychologically credible, and three of these reported a significant difference in favor of the treatment group. The three studies with a sham considered by us to be unsuccessful in relation to both aspects did not find such differences (Table 7).

Difference between regions

Four of the five studies that measured the PPT in the cervical spine had positive findings. One out of two studies

measuring outcome in the lumbar spine reported a significant difference, whereas the only study to concentrate on the thoracic spine had no significant findings. For further information relating to general quality and credibility of sham, please see Table 7.

Spinal manipulation vs. inactive control

Significant difference in PPT readings

Out of the three articles that addressed this matter, two of high and medium quality, reported a significant difference in PPT readings whereas the third article, considered not to be of good quality, found no significant difference. See Table 8.

Table 7 Significant difference of outcomes between-groups in 8 studies that compared a spinal manipulation to a sham procedure, including information on the sham and areas tested included in a systematic review on spinal manipulation and pressure pain threshold

Regions	First author, year [ref]	Psychologically acceptable sham	Physiologically acceptable sham	In conclusion, was the sham completely credible? (Yes/No)	General quality classification of articles	Significant difference of outcomes between groups (Yes/No)
Cervical	Ruiz-Saez, 2007 [16]	Acceptable	Not acceptable	No	High	Yes
	Srbely, 2013 [17]	Acceptable	Acceptable	Yes	High	Yes
	Fernandez de las Penas, 2008 [18]	Acceptable	Not acceptable	No	Medium	Yes
	Fernandez de la Penas, 2007 [19]	Acceptable	Not acceptable	No	Medium	Yes
	Hamilton, 2007 [20]	Possibly acceptable	Not acceptable	No	Medium	No
Lumbar	Yu, 2012 [15]	Acceptable	Acceptable	Yes	High	Yes
	Thompson, 2009 [13]	Not acceptable	Not acceptable	No	Medium	No
Thoracic	Fryer, 2004 [21]	Not acceptable	Not acceptable	No	Medium	No

Table 8 Significant difference of outcomes between -groups of 3 studies that compared a spinal manipulation to an inactive control included in a systematic review on spinal manipulation and pressure pain threshold

Regions	First Author, Year [ref]	General quality classification of articles	Significant difference of outcomes between groups (Yes/No)
Cervical	Fernandez de la Penas, 2007 [19]	Medium	Yes
	Oliveira Campelo, 2010 [22]	High	Yes
Thoracic	Bishop, 2011 [25]	Low	No

Difference between regions

The two studies on the cervical spine reported a significant difference, whereas the study on the thoracic spine did not (Table 8).

**Spinal manipulation vs. mobilisation
Significant difference in PPT readings**

Three studies compared SM vs. mobilisation, all of medium to high quality. One did not report between-group results and the other two found no significant difference. See Table 9.

Difference between regions

The thoracic and lumbar regions were investigated in respectively two studies, none of which detected a significant difference (Table 9).

**Spinal manipulation vs. another spinal manipulation
Significant difference in PPT readings**

Two articles investigated SM performed in different parts of the spine, both of high quality. No difference was found. None compared different techniques. See Table 10.

Difference between regions

Two studies on the cervical spine found no difference in outcomes between areas of treatment. The third study investigated if the order of treatment (neck before or after low back) affected the outcome, which it did not (Table 10).

Table 9 Significant difference of outcomes between- groups of 3 studies that compared a spinal manipulation to a mobilisation included in a systematic review on spinal manipulation and pressure pain threshold

Regions	First Author, Year [ref]	General quality classification of articles	Significant difference of outcomes between groups (Yes/No)
Cervical	Alonso Peres, 2016 [22]	High	No between groups results
Thoracic	Fryer, 2004 [21]	Medium	No
Lumbar	Thompson, 2009 [13]	Medium	No

Table 10 Significant difference of outcomes between- groups of 2 studies that compared a spinal manipulation to another spinal manipulation included in a systematic review on spinal manipulation and pressure pain threshold

Regions	First author, Year [ref]	General quality classification of articles	Significant difference of outcomes between groups (Yes/No)
Cervical	Fernandez de la Penas, 2008 [18]	High	No
Cervical and Lumbar	Jordon, 2016 [23]	High	No

**Spinal manipulation vs. some type of physical therapy
Significant difference in PPT readings**

Three articles reported on the comparison of SM vs. some type of physical therapy; two were of high quality and one was not. One article had contradictory results, both positive and absence of positive findings, whereas the others found no significant difference. See Table 11.

Difference between regions

Two studies reported on the cervical spine and one on the thoracic region. Only one of the cervical studies reported some significant findings (Table 11).

Discussion

Summary

This systematic review consisting of 12 relevant articles studied the regional effect of SM on PPT in asymptomatic subjects. Such an effect was found when SM was compared to a sham and an inactive control, but there were generally no difference in outcome when compared to mobilisation, another SM, or some type of physical therapy. In relation to the region, the majority of the studies of the cervical region obtained significant findings as compared to studies on the other regions. Our review consists of four additional studies on PPT as compared to two systematic reviews from 2012 [9, 10], in which eight articles on PPT were identical to ours. Our findings were similar to their conclusions that SM under experimental conditions has an effect on PPT.

Explanations

It would not be surprising that a treatment, in comparison with an inactive control, results in better results, as the study subjects in the control group would be able to guess that they did not receive an active treatment. Interestingly, we found that when the sham was credible, the results were more likely to be significant than when the sham lacked credibility. This finding, therefore, contradicts the placebo effect, which would have been expected to occur rather in studies with poorly concealed

Table 11 Significant difference of outcomes between- groups of 3 studies that compared a spinal manipulation to some type of physical therapy included in a systematic review on spinal manipulation and pressure pain threshold

Regions	First Author, Year [ref]	General quality classification of articles	Significant difference of outcomes between groups (Yes/No)	
Cervical	Hamilton, 2007 [20]	High	No	
	Oliveira Campelo, 2010 [22]	High	Yes: Masseter	No: Temporalis
Thoracic	Bishop, 2011 [25]	Low	No	

inactive treatments. Therefore, our findings point in the direction of a true effect of SM on PPT in asymptomatic subjects.

When SM was compared to other types of intervention, such as mobilisation, SM in another area, and some type of physical therapy, there was no significant difference, indicating that they probably all have an “effect”, as they all increased the PPT levels on asymptomatic subjects.

Our results raise the question, as to whether the cervical spine is more sensitive to this type of experimentation. This could be explained by the possibility that mechanoreceptors are distributed unevenly through the body, and that the cervical spine tends to have more of them than the thoracic and lumbar spine. However, in order to investigate if there is a true difference between spinal regions, specific studies will have to be designed that specifically test several areas. In this review, no such studies were found.

Methodological considerations of our own review

We created our own checklists to answer our research questions, but we did follow the CONSORT statements and the previous review on the same topic [10]. We kept searching the main sites (PubMed, Embase, and Cochrane) regularly to capture recent publications. However, our university did not have access to all search databases, so it is possible that we missed out on some studies.

Both readers were blind during the process of selecting articles and extracting data in the checklists. In case of a disagreement, a third reviewer could intervene, but this was never needed, indicating that our procedure was user friendly.

In our review, one of the quality criteria was that PPT measurements should have been made at least twice at each anatomical region. However, it may well be possible that this is in fact not necessary [32].

Various types of SM and mobilisation were used and they could, theoretically, have different modes of action, which was not taken into account in this analysis, nor do other authors seem to have dealt with this issue. The same could be argued for different sham procedures, as these were not identical between studies, and different approaches could have different effects.

The concept of the sham treatment was dealt with from two angles in this review. Firstly, we were interested to see how often researchers truly cared about the psychological

aspect of the sham treatment. This was either determined by us (i.e. we considered that it seemed credible or not) or, better, by the researchers through a post study questionnaire. Secondly, though, we attempted to determine if the sham treatment also had a physiological element to it that resembled the real treatment. Nevertheless, we could not fully exploit this information, because there were too few studies for further analysis.

Methodological consideration of the reviewed studies

In relation to weaknesses of the reviewed studies, the three most commonly omitted quality items were how authors dealt with missing data, such as their statistical imputation methods for missing data. They also failed to use a blinded statistician, and none performed a post-intervention assessment of the sham. All these omissions could severely compromise the veracity of the data.

Of the eight studies that used a sham procedure, only three were neither psychologically nor physiologically acceptable, and none of these found a significant difference between SM and a sham procedure. However, such significant difference was found for the other five articles. Further, some studies mistakenly used the term “control” to describe a procedure that instead should have been described as an attempt at a sham procedure, as it was stated that they tried to “fool” the subjects.

Unfortunately, one study failed to report between-group results, which made comparison of outcomes impossible for this study.

Generally, however, the quality was quite high, with only one study scoring low. Also, inclusion in a review does not necessarily mean that studies have the same study objectives as the review, which can have a negative effect on the quality scoring without really reflecting badly on the study in question, which may have been perfectly well conducted for its original purposes just not well suited for the reviewers’ specific research questions.

Conclusion

In asymptomatic subjects, SM does have an effect on PPT but there appears to be no obvious difference in outcome between various types of manual approaches. It was not possible to compare the effect of SM on different spinal regions, as there were not enough data.

Perspectives

Our finding that “credible” sham studies had “better” results should be challenged in clinical studies on SM as well as in other areas, to see if this is a common moderator of results. Most importantly though is that the clinical significance, such as level of pain reduction or increased pressure pain threshold, should be quantified as well as duration of the effect.

Abbreviations

NA: Not Applicable; PPT: Pressure Pain Threshold; RCT: Randomized Controlled Trial; SM: Spinal Manipulation

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Authors' contributions

All authors helped to plan the review. MH and CLY systematically and critically reviewed, analysed and interpreted the data. All authors contributed in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

All authors consented to publication.

Competing interest

All authors declare that they have no competing interests.

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References

- Hunwittz EL. Epidemiology: spinal manipulation utilization. *J Electromyogr Kinesiol.* 2012;22(5):648–54.
- Phelan SP, Armstrong RC, Knox DG, Hubka MJ, Ainbinder DA. An evaluation of medical and chiropractic provider utilization and costs: treating injured workers in North Carolina. *J Manip Physiol Ther.* 2004;27(7):442–8.
- Bronfort G, Haas M, Evans R, Leininger B, Triano J. Effectiveness of manual therapies: the UK evidence report. *Chiropr Osteopat.* 2010;18:3.
- Vernon H, Mrozek J. A revised definition of manipulation. *J Manip Physiol Ther.* 2005;28(1):68–72.
- Herzog W. The biomechanics of spinal manipulation. *J Bodyw Mov Ther.* 2010;14(3):280–6.
- Horowitz SH. Peripheral nerve injury and causalgia secondary to routine venipuncture. *Neurology.* 1994;44(5):962–4.
- Maigne JY, Vautravers P. Mechanism of action of spinal manipulative therapy. *Joint Bone Spine.* 2003;70(5):336–41.
- Malmqvist S, Leboeuf-Yde C, Ahola T, Andersson O, Ekstrom K, Pekkarinen H, Turpeinen M, Wedderkopp N. The Nordic back pain subpopulation program: predicting outcome among chiropractic patients in Finland. *Chiropr Osteopat.* 2008;16:13.
- Coronado RA, Gay CW, Bialosky JE, Carnaby GD, Bishop MD, George SZ. Changes in pain sensitivity following spinal manipulation: a systematic review and meta-analysis. *J Electromyogr Kinesiol.* 2012;22(5):752–67.
- Millan M, Leboeuf-Yde C, Budgell B, Amorim MA. The effect of spinal manipulative therapy on experimentally induced pain: a systematic literature review. *Chiropr Osteopat.* 2012;20(1):26.
- Laura Frank PM, Vaughan B. The repeatability of pressure algometry in asymptomatic individuals over consecutive days. *International Journal of Osteopathic Medicine.* 2013;16(3):143–52.
- Fischer AA. Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold. *Pain.* 1987;30(1):115–26.
- Oliver Thomson LH, Mansfield H. The effects of high-velocity low-amplitude thrust manipulation and mobilisation techniques on pressure pain threshold in the lumbar spine. *International Journal of Osteopathic Medicine.* 2009.
- Chaibi A, Salyte Benth J, Bjørn Russell M. Validation of placebo in manual therapy randomized controlled trial. *Nature, Sci Rep.* 2015;5:11774. <https://doi.org/10.1038/srep11774>.
- Yu X, Wang X, Zhang J, Wang Y. Changes in pressure pain thresholds and basal electromyographic activity after instrument-assisted spinal manipulative therapy in asymptomatic participants: a randomized, controlled trial. *J Manip Physiol Ther.* 2012;35(6):437–45.
- Ruiz-Saez M, Fernandez-de-las-Penas C, Blanco CR, Martinez-Segura R, Garcia-Leon R. Changes in pressure pain sensitivity in latent myofascial trigger points in the upper trapezius muscle after a cervical spine manipulation in pain-free subjects. *J Manip Physiol Ther.* 2007;30(8):578–83.
- Srbely JZ, Vernon H, Lee D, Polgar M. Immediate effects of spinal manipulative therapy on regional antinociceptive effects in myofascial tissues in healthy young adults. *J Manip Physiol Ther.* 2013;36(6):333–41.
- Fernandez-de-Las-Penas C, Alonso-Blanco C, Cleland JA, Rodriguez-Blanco C, Albuquerque-Sendin F. Changes in pressure pain thresholds over C5–C6 zygapophyseal joint after a cervicothoracic junction manipulation in healthy subjects. *J Manip Physiol Ther.* 2008;31(5):332–7.
- Fernandez-de-las-Penas C, Perez-de-Heredia M, Brea-Rivero M, Miangolarra-Page JC. Immediate effects on pressure pain threshold following a single cervical spine manipulation in healthy subjects. *J Orthop Sports Phys Ther.* 2007;37(6):325–9.
- Luke Hamilton CB, Fryer G. The effects of high-velocity, low-amplitude manipulation and muscle energy technique on suboccipital tenderness. *International Journal of Osteopathic Medicine.* 2007.
- Fryer JC G, McIver S. The effect of manipulation and mobilisation on pressure pain thresholds in the thoracic spine. *Journal of Osteopathic Medicine.* 2004.
- Jose Luis Alonso-Perez AL-L, La Touche R, Lerma-Lara S, Suarez E, Rojas J, Bishop MD, Villafane JH, Fernandez-Carnero J. Hypoalgesic effects of three different manual therapy techniques on cervical spine and psychological interaction: a randomized clinical trial. *J Bodyw Mov Ther.* 2017;21(4):798–803. <https://doi.org/10.1016/j.jbmt.2016.12.005>.
- Oliveira-Campelo NM, Rubens-Rebelatto J, Marti N-Vallejo FJ, Albuquerque-Sendin NF, Fernández-de-Las-Peñas C. The immediate effects of Atlanto-occipital joint manipulation and suboccipital muscle inhibition technique on active mouth opening and pressure pain sensitivity over latent myofascial trigger points in the masticatory muscles. *J Orthop Sports Phys Ther.* 2010;40(5).
- Max K Jordon PFB, D'Urso S, Scriven S. Spinal manipulation does not affect pressure pain thresholds in the absence of neuromodulators: a randomized controlled trial. *J Man Manip Ther.* 2016.
- Bishop MD, Benecluk JM, George SZ. Immediate reduction in temporal sensory summation after thoracic spinal manipulation. *Spine J.* 2011;11(5):440–6.
- Molina-Ortega F, Lomas-Vega R, Hita-Contreras F, Plaza Manzano G, Achalandabaso A, Ramos-Morcillo AJ, Martinez-Amat A. Immediate effects of spinal manipulation on nitric oxide, substance P and pain perception. *Man Ther.* 2014;19(5):411–7.
- O'Neill S, Odegaard-Olsen O, Sovde B. The effect of spinal manipulation on deep experimental muscle pain in healthy volunteers. *Chiropr Man Therap.* 2015;23:25.
- Solis F. Effect of spinal manipulation and body based interventions in a model of experimentally induced low back. *Pain.* 2015.

29. Dorrón SL, BEL PDD, Walker BF. Effect of lumbar spinal manipulation on local and remote pressure pain threshold and pinprick sensitivity in asymptomatic individuals: a randomised trial. *Chiropr Man Therap*. 2016;24:47.
30. Laframboise Michelle HV, Srbely J. Effect of two consecutive spinal manipulations in a single session on myofascial pain pressure sensitivity: a randomized controlled trial. *J Can Chiropr Assoc*. 2016;60(2):2016.
31. Wassinger CA, Rich D, Cameron N, Clark S, Davenport S, Lingelbach M, Smith A, Baxter GD, Davidson J. Cervical & thoracic manipulations: acute effects upon pain pressure threshold and self-reported pain in experimentally induced shoulder pain. *Man Ther*. 2016;21:227–32.
32. Balaguier R, Madeleine P, Vuillerme N. Is One Trial Sufficient to Obtain Excellent Pressure Pain Threshold Reliability in the Low Back of Asymptomatic Individuals? A Test-Retest Study. *PLoS One*. 2016 Aug 11; 11(8):e0160866. <https://doi.org/10.1371/journal.pone.0160866>.

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ANNEXE 3 – Revue systématique et critique de la littérature : La durée et la taille de l'effet régional de la manipulation vertébrale sur le seuil de la douleur à la pression chez des sujets asymptomatiques

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SYSTEMATIC REVIEW

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How big is the effect of spinal manipulation on the pressure pain threshold and for how long does it last? – secondary analysis of data from a systematic review



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Abstract

Background: Spinal manipulation (SM) has been shown in a systematic review to have a statistically significant effect on the pressure pain threshold (PPT) in asymptomatic subjects, when SM is compared to a sham intervention. The magnitude and duration of this effect is unclear.

Objectives: To determine the effect-size of SM in asymptomatic subjects and its duration.

Method: This is a secondary analysis of data from a previous review. We sought to compare the effect-sizes in the various articles but had to calculate them ourselves, at different follow-up time measurements. Effect-sizes (Cohen's *d* or Hedge's *g* coefficient) were considered low, medium, and large, at the cut points of 0.2, 0.5, and 0.8, respectively.

Results: Effect-sizes were reported in 6/8 studies, but all had calculated 'within-group' changes, not 'between-group' differences. Immediately after SM, only one study of four (with four measurements) had a statistically significant 'medium' effect size ($d = 0.56$; 95% CI: 0.04–1.08 to $d = 0.70$; 95% CI: 0.18–1.22). Five minutes after SM, 4/5 studies found a statistically significant 'medium to large' effect-size ($d = 0.51$; 95% CI: 0.04–0.98 to $d = 1.24$; 95% CI: 0.28–2.20). Ten minutes after SM, two studies reported a 'medium' effect-size with statistical significance ($d = 0.58$; 95% CI: 0.11–1.05 to $d = 0.80$; 95% CI: 0.12–1.48). We drew no conclusions for the effect-sizes at one minute and thirty minutes after SM, as no between-group statistical difference was found.

Conclusion: Authors need to revise their approach to 'effect size'. Our calculations showed that the effect-size of SM on PPT may go from 'medium' to 'large' within the first five minutes but appears to diminish again within ten minutes. Research of this type should collect information for longer periods and compare results to other interventions to put results into perspective.

Keywords: Effect size, Duration, Spinal manipulation, Pressure pain threshold, Asymptomatic subjects

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Resume

Contexte: Une revue systématique a montré que la manipulation vertébrale (MV) avait un effet statistiquement significatif sur le seuil de douleur à la pression (SDP) chez les sujets asymptomatiques, lorsque la MV était comparée à une manœuvre placebo. Cependant, l'ampleur et la durée de cet effet n'ont pas été clairement rapportées.

Objectifs: Déterminer la taille d'effet de la MV chez les sujets asymptomatiques et sa durée.

Méthode: Il s'agit d'une deuxième analyse des données de notre précédente revue systématique de la littérature. Nous avons cherché à comparer les tailles d'effet dans les différents articles, mais nous avons dû nous résoudre à les calculer, à différents temps de mesures. La taille d'effet rapportée (comme les coefficients *d de Cohen* ou *g de Hedge*) était considérée comme faible, moyenne et grande, aux seuils respectifs de 0,2, 0,5 et 0,8.

Résultats: Nous avons constaté que 6 études sur 8 montraient le calcul de la taille d'effet, mais que toutes étaient fondées sur des changements « intra-groupe », et non sur des différences « intergroupes ». Immédiatement après la MV, seule une étude sur quatre (avec quatre mesures) présentait une taille d'effet « moyenne » statistiquement significative ($d = 0,56$ [IC à 95%: 0,04 à 1,08] à $d = 0,70$ [IC à 95%: 0,18 à 1,22]). Cinq minutes après la MV, quatre études sur cinq ont révélé une taille d'effet « moyenne à grande » statistiquement significative ($d = 0,51$ [IC à 95%: 0,04–0,98] à $d = 1,24$ [IC à 95%: 0,28–2,20]). Dix minutes après la MV, deux études ont indiqué une taille d'effet « moyenne » statistiquement significative ($d = 0,58$ [IC à 95%: 0,11–1,05] à $d = 0,80$ [IC à 95%: 0,12–1,48]). Aucune conclusion n'a été tirée des résultats une minute et trente minutes après la MV car la différence entre les groupes n'était pas statistiquement significative.

Conclusion: Les auteurs doivent revoir leur approche de la « taille d'effet ». Nos calculs ont montré que l'effet de la manipulation vertébrale sur le seuil de la douleur à la pression peut passer de « moyen » à « important » dans les cinq premières minutes mais semble diminuer à nouveau dans les dix minutes. Les recherches de ce type devraient collecter des informations sur des périodes plus longues et comparer les résultats à ceux d'autres interventions afin de les mettre en perspective.

Mots-clés: Taille d'effet; durée; manipulation vertébrale; seuil de douleur à la pression; sujets asymptomatiques.

Introduction

The effect of treatment

In order to study the validity of a treatment, it is necessary to compare its outcome with the outcome of another treatment. However, in order to test the specific effect of this treatment, it would be necessary to compare it with a well masked placebo.

Measuring the effect

The effect of a treatment is, in fact, the difference between the differences in outcome in these two interventions, i.e. (i) the follow-up measurement of the treatment group minus the baseline measurement is estimated and also (ii) the follow-up measurement of the placebo group minus the baseline measurement. Thereafter, (iii) the difference between these two differences is subjected to a test for statistical significance. However, if the baseline measurements in the two groups is more or less identical, then there is no need to take the baseline measurements into account, and it would be sufficient to test only if the difference between the outcome measurements is statistically significant.

Statistical significance vs. clinical significance

However, the statistical significance (i.e *p-value*) is not an indication of the clinical significance. The clinical

significance can be judged by comparing the estimates of the treatment and placebo groups and by calculating, for example, the numbers needed to treat, in clinical studies. In experimental studies, the clinical significance would often be assessed by calculating what is called an 'effect size'.

Effect size

To show how big an effect of a particular treatment might be, one could proceed to calculate the 'difference of differences', as explained above. However, it would be difficult to compare studies that used different methods and units. Therefore, an index is often used, such as the Cohen's *d* or Hedge's *g* coefficients.

To relate the effect size to the concept of clinical significance, Cohen created a scale that can be used for either the *d* or the *g* coefficients. According to this scale, an effect size of 0.2 represents an overlap between the compared populations in their distributions of means of about 85%, which Aron [1] suggests could be compared to a difference of height between 15 and 16 years old girls, thus considered 'small'. An effect size of 0.5 represents an overlap of about 67%, which, in the same way, could be interpreted as a difference of height between 14 and 18 years old girls, thus considered 'medium'. An effect size of 0.8 (or above) is an overlap of 53% (or less)

and represents a difference of height between 13 and 18 years old girls, thus considered 'large'. As another example, Cohen suggests that the difference in IQ between holders of a PhD degree and a 'typical college freshman' is comparable to an effect size of 0.8 [2].

Calculation of the effect size

The Cohen's *d* coefficient is commonly calculated by the subtraction of the mean of the experimental group from the mean of the control group, and the division of this result by the standard deviation. However, this equation should be used under specific conditions, which are described extensively in the literature albeit without a clear consensus. Therefore, the effect size can be calculated in different ways and unless it is clearly described, there is room for errors and confusion. (Please, see Additional file 1 for more details).

The regional effect of spinal manipulation on experimentally induced pain in asymptomatic subjects

Spinal manipulation

Spinal manipulation (SM) is used for its beneficial effect on musculoskeletal pain. It is reported to very quickly soothe musculoskeletal pain in some patients [3] but its mechanisms are not yet well understood. Nevertheless, according to a previous systematic review, SM has been reported in some studies to have a hypoalgesic effect in asymptomatic subjects exposed to experimentally induced pain, such as increasing the pressure pain threshold (PPT) [4]. However, not all studies used proper sham-controlled studies to control for the placebo effect.

Pressure pain threshold

Pressure pain threshold (PPT) is a type of quantitative sensory testing that can be used to understand the somato-sensory profiles of people in pain [5], but also in asymptomatic subjects [6]. It is defined as the minimal pressure which provokes a pain or a discomfort [7]. A reported increase of PPT values on subjects after a treatment would suggest an hypoalgesic action of the SM, whereas a reported decrease of PPT values would suggest hyperalgesia.

Spinal manipulation and its regional effect on the pressure pain threshold

To be able to establish whether SM truly has a hypoalgesic effect, we performed a systematic review in which we separated out the sham-controlled studies, as reported elsewhere [8]. A description of these studies is found in Additional file 2.

Thus, we found eight randomized controlled trials of good and medium quality. They investigated the regional effect of SM, compared to a sham procedure in asymptomatic subjects. As previously reported (Additional file 2), five

out of these eight studies found that SM had a statistically significant effect on the PPT in these asymptomatic subjects.

However, the effect size and the duration of this effect need also to be investigated, to conclude whether this reaction is also clinically relevant.

The research objectives

To the best of our knowledge, the i) effect size and (ii) this effect size over time, for the PPT in asymptomatic subjects after a spinal manipulation, compared to a sham procedure, have never been reported in a systematic review. Therefore, we returned to the articles in our previous review [8] to report on these values.

Method

Design

This work consists of a secondary analysis of data from our previous systematic literature review, using data from eight randomized controlled trials that reported the regional effect of spinal manipulation on PPT in asymptomatic subjects compared to a sham procedure [8].

Search strategy and extraction of data

The search strategy and extraction of data for the original review have been extensively reported (Additional file 3). The flow chart for the screening process presented in the previous review has been included in this report for information. (Please, see Additional file 4).

For the present review, a descriptive and a quality checklist were created (Tables 1-2) to fit our new objectives. The quality score for the research method in general as reported in the previous article was included in the descriptive checklist for information (Table 1).

The present quality checklist (Table 2) is based on the various recommendations from the creator of the original effect size index [9] and its coeval authors [10], supported by more recent texts on the same subject ([2]; [11]). This consists of information on:

- whether the between-group effect size was provided [11],
- whether the formula for calculation was provided [10] or if, at least, an exact reference was provided (document and page, not just the name of a textbook), the reporting of the number of study participants, the exact mean values and standard deviations necessary to calculate the effect size [12], and the reporting of 95% confidence intervals (95% CI) [9]. If all this information was available, it would be possible to calculate the effect size.

Where effect size had not been calculated, it was our intention to do so, with the formulae provided in the Additional file 1 and verifying all calculations by a

Table 1 Descriptive checklist of the reported 'effect sizes' in eight randomized sham-controlled studies included in a previous systematic review on pressure pain threshold changes after spinal manipulation

First author Year	Quality score as reported in previous review (Honoré and al, 2018)	- Area of spinal manipulation - Regional testing site/s	Number of follow-ups and time of follow-ups	-Is there a reported effect size? (Yes/No) - Which type of "effect size" was reported (between or within-group comparison)?
Ruiz Saez 2007	8/9	- Cervical - Upper trapezius	3 follow-ups: 1) Immediately after 2) 5 min after 3) 10 min after	-Yes -Within-group comparison
Srbely2013	7.5/9	-Cervical (bilateral) - Infraspinatus muscle	4 follow-ups: 1) 1 min after 2) 5 min after 3)10 min after 4) 15 min after	-No - NA
Fernandez de la Penas 2008	7/9	- Cervical - C5-C6 level	1 follow-up: 1) 5 min after	-Yes - Within-group comparison
Fernandez de la Penas 2007	7/9	- Cervical - Ipsilateral and contralateral epicondyle	1 follow up: 1) 5 min after	- Yes - Within-group comparison
Hamilton 2007	7/9	- Cervical - Between C0 and C2	2 follow-ups: 1) 5 min after 2) 30 min after	- Yes - Within-group comparison
Yu 2012	8/9	- Lumbar - L5-S1 over apophyseal joints - L5 dermatome	1 follow-up: 1) Immediately after	- No - NA
Thomson 2009	6/9	- Lumbar -Spinous process of L3	1 follow-up: 1) Immediately after	- Yes -Within-group comparison
Fryer 2004	5/9	-Thoracic -Thoracic spinous process between T1 and T4	1 follow-up: 1) Immediately after	- Yes - Within-group comparison

NA: not applicable;

blinded third person. The information on the effect size at each time of measurement (provided by the authors or calculated by us) was collected in a table (Table 3) and illustrated in Fig. 1. We chose to report, when needed, the data concerning what happened on the "dominant side" [13], as we cared only for the regional effect.

Data analysis

Effect sizes were calculated using Eqs. 1 to 7 (as described in Additional file 1). The effect sizes and their 95% CI were calculated with Microsoft® Excel, version 16.17 (180909). Statistical significance of the effect size was defined as when the 95% CI does not include 'zero' [14]. The effect size was defined as small ($d < 0.5$), medium ($0.5 < d < 0.8$) or large ($d > 0.8$) [9].

Results

General description of the studies and their reported effect size

These studies have been extensively described in our previous review [8], with a general description available in Additional file 2. Briefly, the eight studies included in our new analyses provided information on the PPT at different follow-up times; four studies immediately after,

one study one minute after, five studies five minutes after, two studies ten minutes after, one study fifteen and thirty minutes after the interventions. The quality of the eight studies was established in the previous review to range from 'medium' to 'good' (Table 1).

In the present review, no additional quality score for the effect size was given, as no definitive consensus can be found on this subject. However, we noted that no study reported a between-group effect size. Instead, they reported 'effect sizes' of intra-group differences, i.e. in fact, the 'outcome sizes'. Further, two studies failed to report any effect size at all (Table 1). In addition, no study reported the exact formula they used, and only one provided a 'precise' reference (Table 2). No additional descriptive information on the 'effect size' was given (95% CI or SD (d)). In sum, the reported 'effect sizes' were not real effect sizes, not transparent and possibly not comparable.

Fortunately, all studies had exploitable information, with reported numbers of study participants in each group, exact mean values and exact standard deviations, and only one study provided values only in a figure, which made it possible to retrieve information although it, for this reason, lacked precision. Thus, all authors had provided sufficient information to make it possible for us to calculate their between-group effect sizes (Table 3).

Table 2 Quality checklist of the reported 'effect sizes' in eight randomized sham-controlled studies included in a previous review on pressure pain threshold changes after spinal manipulation

First author Year	Did the authors report the between-group effect size? (Yes/No)	1) Did the authors report the 'exact' formula they used? (Yes/No/NA) 2) Or, at least: - Did they provide a reference? (Yes/No/NA) If so, - Was this an "exact" reference?	Did they report: 1) Number of study participants in each group 2) Exact mean values 3) Exact standard deviations	Did they report the 95% CI of their effect size, or of their within group 'effect' size? (Yes/No)	Was it possible to calculate between-group effect size based on data provided in the articles?
Ruiz Saez 2007	No, only the within-group comparison	1) No 2) -Yes -Yes	1) Yes 2) Yes 3) Yes	No	Yes
Srbely 2013	No, not even the within-group comparison	1) NA	1) Yes 2) Yes 3) Yes	NA	Yes
Fernandez de la Penas 2008	No, only the within-group comparison	1) No 2) -Yes -Yes - No	1) Yes 2) Yes 3) Yes	No	Yes
Fernandez de la Penas 2007	No, only the within-group comparison	1) No 2) -Yes -Yes -No	1) Yes 2) Yes 3) Yes	No	Yes
Hamilton 2007	No, only the within-group comparison	1) No 2) -Yes -Yes - No	1) Yes 2) Yes 3) Yes	No	Yes
Yu 2012	No, not even the within-group comparison	1) NA	1) Yes 2) Yes 3) Yes	NA	Yes
Thomson 2009	No, only the within-group comparison	1) No 2) - No - No	1) Yes 2) Shown in figures, so lack of precision. -3) Yes	No	Yes
Fryer 2004	No, only the within-group comparison	1) No 2) - No - No	1) Yes 2) Yes 3) Yes	No	Yes

NA: Not applicable

Table 3 Calculation of between-group effect sizes, based on information provided in eight randomized sham-controlled studies included in a previous review on pressure pain threshold changes after spinal manipulation

First author Year	What is the number of participants of the experimental group (N _E) and the control group (N _C) and are they equal? - N _E = N _C - N _E ≠ N _C	What are the reported mean PPT values for the experimental group (M _E) and for the control group (M _C) with their standard deviation (+/- SD), at each follow-up time (units)?	At each follow-up time, what are the: - Effect size (d/g), - Its standard deviation (SD(d)) - Its confidence interval (95% CI) - p value between groups	Effect sizes of clinical significant findings at each follow-up: 0.2 to 0.49 (small) - 0.5 to 0.79 (medium) - 0.8 to 1.00 (large)
Ruiz Saez 2007	<ol style="list-style-type: none"> 1) N_E = N_C = 36 2) SD_E ≠ SD_C 3) Cohen's d coefficient 4) $-d = \frac{M_E - M_C}{SD}$ - SD* = $\sqrt{\frac{SD_E^2 + SD_C^2}{2}}$ - SD(d) = $\sqrt{\frac{N_E + N_C}{2N_E N_C} + \frac{d^2}{2(N_E + N_C)}}$ - 95% CI: [d - 1.96 × SD(d); d + 1.96 × SD(d)] 	<p>-T0: M_E = + 1.35 +/- 0.5 Kg/cm2 M_C = + 1.27 +/- 0.4 Kg/cm2</p> <p>-T + 5: M_E = + 1.38 +/- 0.5 Kg/cm2 M_C = + 1.15 +/- 0.4 Kg/cm2</p> <p>-T + 10: M_E = + 1.39 +/- 0.5 Kg/cm2 M_C = + 1.1 +/- 0.5 Kg/cm2</p>	<p>-T0: -d = 0.17 -SD(d) = 0.24 - 95% CI: [- 0.29; + 0.63]</p> <p>-T + 5: -d = 0.51 -SD(d) = 0.24 - 95% CI: [+ 0.04; + 0.98] - p < 0.01</p> <p>-T + 10: -d = 0.58 -SD(d) = 0.24 - 95% CI: [+ 0.11; + 1.05] - p < 0.01</p>	<p>T0: small T + 5: medium T + 10: medium</p>
Srbely 2013	<ol style="list-style-type: none"> 1) N_E = N_C = 18 2) SD_E ≠ SD_C 3) Cohen's d coefficient 4) $-d = \frac{M_E - M_C}{SD}$ - SD* = $\sqrt{\frac{SD_E^2 + SD_C^2}{2}}$ - SD(d) = $\sqrt{\frac{N_E + N_C}{2N_E N_C} + \frac{d^2}{2(N_E + N_C)}}$ - 95% CI: [d - 1.96 × SD(d); d + 1.96 × SD(d)] 	<p>-T + 1: M_E = + 34.4 +/- 9.6 N M_C = + 30.7 +/- 7.5 N</p> <p>-T + 5: M_E = + 37.5 +/- 11.9 N M_C = + 28.7 +/- 6.0 N</p> <p>-T + 10: M_E = + 37.9 +/- 14.4 N M_C = + 28.9 +/- 6.3 N</p> <p>-T + 15: M_E = + 34.3 +/- 11.5 N M_C = + 28.6 +/- 7.0 N</p>	<p>-T + 1: -d = 0.42 -SD(d) = 0.34 - 95% CI: [- 0.24; + 1.08] - p < 0.01</p> <p>-T + 5: -d = 0.93 -SD(d) = 0.35 - 95% CI: [+ 0.24; + 1.62] - p < 0.01</p> <p>-T + 10: -d = 0.80 -SD(d) = 0.35 - 95% CI: [+ 0.12; + 1.48] - p < 0.01</p> <p>-T + 15: -d = 0.59 -SD(d) = 0.34</p>	<p>T + 1: small T + 5: large T + 10: large T + 15: medium</p>

Table 3 Calculation of between-group effect sizes, based on information provided in eight randomized sham-controlled studies included in a previous review on pressure pain threshold changes after spinal manipulation (Continued)

First author Year	1) What is the number of participants of the experimental group (N _E) and the control group (N _C) and are they equal? - N _E = N _C - N _E ≠ N _C	2) Are the standard deviations of the experimental group (SD _E) and the control group (SD _C) equal? - SD _E = SD _C - SD _E ≠ SD _C	3) Which type of effect size coefficient should be used? - Cohen's d coefficient (if N _E = N _C and SD _E = SD _C or SD _E ≠ SD _C) - Hedges' g coefficient (if N _E ≠ N _C and SD _E ≠ SD _C)	4) Give the equations that would be used: - Effect size (d/g) - Standard deviation of PPT values used to calculate the effect size (SD* or SD _{pool}) - Standard deviation of the effect size (SD(d)) - Confidence interval of the effect size (95% CI)	What are the reported mean PPT values for the experimental group (M _E) and for the control group (M _C) with their standard deviation (+/- SD), at each follow-up time (units)?	At each follow-up time, what are the: - Effect size (d/g) - Its standard deviation (SD(d)) - Its confidence interval (95% CI) - p value between groups	Effect sizes of clinical significant findings at each follow-up: 0.2 to 0.49 (small) - 0.5 to 0.79 (medium) - 0.8 to 1.00 (large)	
Yu 2012	$g = \frac{M_E - M_C}{SD_{pooled}}$ $-SD(g) = \sqrt{\frac{N_E + N_C}{N_E \times N_C} + \frac{d^2}{2(N_E + N_C)}}$ $-95\% \text{ CI: } [d - 1.96 \times SD(d); d + 1.96 \times SD(d)]$	1) N _E = N _C = 30 2) SD _E ≠ SD _C 3) Cohen's d coefficient $-d = \frac{M_E - M_C}{SD^*}$ $-SD^* = \sqrt{\frac{SD_E^2 + SD_C^2}{2}}$ $-SD(d) = \sqrt{\frac{N_E + N_C}{N_E \times N_C} + \frac{d^2}{2(N_E + N_C)}}$ $-95\% \text{ CI: } [d - 1.96 \times SD(d); d + 1.96 \times SD(d)]$	-L5-S1 PD side T0: M _E = + 5.64 +/- 1.13 Kg/cm2 M _C = + 4.85 +/- 1.12 Kg/cm2 -L5-S1 OPD side T0: M _E = + 5.56 +/- 1.17 Kg/cm2 M _C = + 4.91 +/- 1.13 Kg/cm2 -L5 dermatome PD side T0: M _E = + 4.77 +/- 0.96 Kg/cm2 M _C = + 4.14 +/- 1.13 Kg/cm2 -L5 dermatome OPD side T0: M _E = + 4.63 +/- 0.95 Kg/cm2 M _C = + 4.09 +/- 0.82 Kg/cm2	-SD(g) = 0.26 - 95% CI: [- 0.48; + 0.54] - p value: NS	-L5-S1 PD side T0: medium -L5-S1 OPD side T0: medium -L5 dermatome PD side T0: medium -L5 dermatome OPD side T0: medium	-L5-S1 PD side T0: M _E = + 5.64 +/- 1.13 Kg/cm2 M _C = + 4.85 +/- 1.12 Kg/cm2 -L5-S1 OPD side T0: M _E = + 5.56 +/- 1.17 Kg/cm2 M _C = + 4.91 +/- 1.13 Kg/cm2 -L5-S1 OPD side T0: M _E = + 4.77 +/- 0.96 Kg/cm2 M _C = + 4.14 +/- 1.13 Kg/cm2 -L5 dermatome PD side T0: M _E = + 4.63 +/- 0.95 Kg/cm2 M _C = + 4.09 +/- 0.82 Kg/cm2 -L5 dermatome OPD side T0: M _E = + 4.63 +/- 0.95 Kg/cm2 M _C = + 4.09 +/- 0.82 Kg/cm2	-d = 0.60 -SD(d) = 0.26 - 95% CI: [- 0.08; + 1.12] -p < 0.05 -L5 dermatome OPD side T0: M _E = + 4.63 +/- 0.95 Kg/cm2 M _C = + 4.09 +/- 0.82 Kg/cm2 -d = 0.60 -SD(d) = 0.26 - 95% CI: [- 0.08; + 1.12]	-L5 dermatome OPD side T0: M _E = + 4.63 +/- 0.95 Kg/cm2 M _C = + 4.09 +/- 0.82 Kg/cm2 -d = 0.60 -SD(d) = 0.26 - 95% CI: [- 0.08; + 1.12]

Table 3 Calculation of between-group effect sizes, based on information provided in eight randomized sham-controlled studies included in a previous review on pressure pain threshold changes after spinal manipulation (*Continued*)

First author Year	1) What is the number of participants of the experimental group (N _E) and the control group (N _C) and are they equal? - N _E = N _C - N _E ≠ N _C	2) Are the standard deviations of the experimental group (SD _E) and the control group (SD _C) equal? - SD _E = SD _C - SD _E ≠ SD _C	3) Which type of effect size coefficient should be used? - Cohen's d coefficient (if N _E = N _C and SD _E = SD _C or SD _E ≠ SD _C) - Hedge's g coefficient (if N _E ≠ N _C and SD _E = SD _C or SD _E ≠ SD _C)	4) Give the equations that would be used: - Effect size (d/g) - Standard deviation of PPT values used to calculate the effect size (SD or SD _{pooled}) - Standard deviation of the effect size (SD(d)) - Confidence interval of the effect size (95% CI)	What are the reported mean PPT values for the experimental group (M _E) and for the control group (M _C) with their standard deviation (+/- SD), at each follow-up time (units)?	At each follow-up time, what are the: - Effect size (d/g) - Its standard deviation (SD(d)) - Its confidence interval (95% CI) - p value between groups	Effect sizes of clinical significant findings at each follow-up: - 0.2 to 0.49 (small) - 0.5 to 0.79 (medium) - 0.8 to 1.00 (large)
Fernandez de la Penas 2008	1) N _E = N _C = 10 2) SD _E ≠ SD _C 3) Cohen's d coefficient			4) $d = \frac{M_E - M_C}{SD_C}$ $- SD^* = \sqrt{\frac{SD_E^2 + SD_C^2}{2}}$ $- SD(d) = \sqrt{\frac{N_E + N_C}{N_E \times N_C} + \frac{d^2}{2(N_E + N_C)}}$ - 95% CI: [d - 1.96 × SD (d); d + 1.96 × SD(d)]	-T + 5: (dominant side/dominant side) M _E = + 387.6 +/- 70.9 kPa/s M _C = + 312.3 +/- 47.7 kPa/s	- 95% CI: [- 0.08; + 1.26] -p < 0.01	T + 5: large
Fernandez de la Penas 2007	1) N _E = N _C = 15 2) SD _E ≠ SD _C 3) Cohen's d coefficient			4) $d = \frac{M_E - M_C}{SD_C}$ $- SD^* = \sqrt{\frac{SD_E^2 + SD_C^2}{2}}$ $- SD(d) = \sqrt{\frac{N_E + N_C}{N_E \times N_C} + \frac{d^2}{2(N_E + N_C)}}$ - 95% CI: [d - 1.96 × SD (d); d + 1.96 × SD(d)]	-T + 5: M _E = + 2.9 +/- 0.6 Kg/cm2 M _C = + 2.3 +/- 0.5 Kg/cm2	-d = 1.08 -SD(d) = 0.48 -95% CI: [+ 0.14; + 2.02] -p < 0.01	T + 5: large
Hamilton 2007	1) N _E ≠ N _C - N _E = 35 - N _C = 25 2) SD _E ≠ SD _C 3) Hedge's g coefficient			4) $d = \frac{M_E - M_C}{SD_C}$ $- SD^* = \sqrt{\frac{SD_E^2 + SD_C^2}{2}}$ $- SD(d) = \sqrt{\frac{N_E + N_C}{N_E \times N_C} + \frac{d^2}{2(N_E + N_C)}}$ - 95% CI: [d - 1.96 × SD (d); d + 1.96 × SD(d)]	-T + 5: M _E = + 398.06 +/- 133.51 kPa/s M _C = + 368.44 +/- 208.16 kPa/s -T + 30: M _E = + 374.58 +/- 127.50 kPa/s M _C = + 368.68 +/- 192.62 kPa/s	-g = 0.17 -SD(g) = 0.26 -95% CI: [- 0.34; + 0.68] -p < 0.01 -T + 30: -g = 0.03	T + 5: small T + 30: small

Table 3 Calculation of between-group effect sizes, based on information provided in eight randomized sham-controlled studies included in a previous review on pressure pain threshold changes after spinal manipulation (Continued)

First author Year	1) What is the number of participants of the experimental group (N _E) and the control group (N _C) and are they equal? - N _E = N _C - N _E ≠ N _C	2) Are the standard deviations of the experimental group (SD _E) and the control group (SD _C) equal? - SD _E = SD _C - SD _E ≠ SD _C	3) Which type of effect size coefficient should be used? - Cohen's d coefficient (if N _E = N _C and SD _E = SD _C or SD _E ≠ SD _C) - Hedges' g coefficient (if N _E ≠ N _C and SD _E ≠ SD _C)	4) Give the equations that would be used: - Effect size (d/g) - Standard deviation of PPT values used to calculate the effect size (SD* or SD _{pool}) - Standard deviation of the effect size (SD(d)) - Confidence interval of the effect size (95% CI)	What are the reported mean PPT values for the experimental group (M _E) and for the control group (M _C) with their standard deviation (+/- SD), at each follow-up time (units)?	At each follow-up time, what are the: - Effect size (d/g) - Its standard deviation (SD(d)) - Its confidence interval (95% CI) - p value between groups	Effect sizes of clinical significant findings at each follow-up: 0.2 to 0.49 (small) - 0.5 to 0.79 (medium) - 0.8 to 1.00 (large)
Yu 2012	$g = \frac{M_E - M_C}{SD_{pooled}}$ $-SD(g) = \sqrt{\frac{N_E + N_C}{N_E \times N_C} + \frac{d^2}{2(N_E + N_C)}}$ $-95\% \text{ CI: } [d - 1.96 \times SD(d); d + 1.96 \times SD(d)]$	1) N _E = N _C = 30 2) SD _E ≠ SD _C 3) Cohen's d coefficient $-d = \frac{M_E - M_C}{SD^*}$ $-SD^* = \sqrt{\frac{SD_E^2 + SD_C^2}{2}}$ $-SD(d) = \sqrt{\frac{N_E + N_C}{N_E \times N_C} + \frac{d^2}{2(N_E + N_C)}}$ $-95\% \text{ CI: } [d - 1.96 \times SD(d); d + 1.96 \times SD(d)]$	-L5-S1 PD side T0: medium M _E = + 5.64 +/- 1.13 Kg/cm2 M _C = + 4.85 +/- 1.12 Kg/cm2 -L5-S1 OPD side T0: medium M _E = + 5.56 +/- 1.17 Kg/cm2 M _C = + 4.91 +/- 1.13 Kg/cm2 -L5 dermatome PD side T0: medium M _E = + 4.77 +/- 0.96 Kg/cm2 M _C = + 4.14 +/- 1.13 Kg/cm2 -L5 dermatome OPD side T0: medium M _E = + 4.63 +/- 0.95 Kg/cm2 M _C = + 4.09 +/- 0.82 Kg/cm2	-L5-S1 PD side T0: medium -L5-S1 OPD side T0: medium -L5 dermatome PD side T0: medium -L5 dermatome OPD side T0: medium	-SD(g) = 0.26 - 95% CI: [- 0.48; + 0.54] - p value: NS	-L5-S1 PD side T0: medium -L5-S1 OPD side T0: medium -L5 dermatome PD side T0: medium -L5 dermatome OPD side T0: medium	-d = 0.60 -SD(d) = 0.26 - 95% CI: [- 0.08; + 1.12] -p < 0.05 -L5 dermatome OPD side T0: medium -d = 0.60 -SD(d) = 0.26 - 95% CI: [- 0.08; + 1.12]

Table 3 Calculation of between-group effect sizes, based on information provided in eight randomized sham-controlled studies included in a previous review on pressure pain threshold changes after spinal manipulation (Continued)

First author Year	1) What is the number of participants of the experimental group (N _E) and the control group (N _C) and are they equal? - N _E = N _C - N _E ≠ N _C	2) Are the standard deviations of the experimental group (SD _E) and the control group (SD _C) equal? - SD _E = SD _C - SD _E ≠ SD _C	3) Which type of effect size coefficient should be used? - Cohen's d coefficient (if N _E = N _C and SD _E = SD _C or SD _E ≠ SD _C) - Hedges' g coefficient (if N _E ≠ N _C and SD _E ≠ SD _C)	4) Give the equations that would be used: - Effect size (d/g) - Standard deviation of PPT values used to calculate the effect size (SD or SD _{pooled}) - Standard deviation of the effect size (SD(d)) - Confidence interval of the effect size (95% CI)	What are the reported mean PPT values for the experimental group (M _E) and for the control group (M _C) with their standard deviation (+/- SD), at each follow-up time (units)?	At each follow-up time, what are the: - Effect size (d/g), - Its standard deviation (SD(d)) - Its confidence interval (95% CI) - p value between groups	Effect sizes of clinical significant findings at each follow-up: 0.2 to 0.49 (small) - 0.5 to 0.79 (medium) - 0.8 to 1.00 (large)
Thomson 2009	1) N _E ≠ N _C - N _E = 19 - N _C = 13	2) SD _E ≠ SD _C	3) Hedge's g coefficient	4) $g = \frac{M_E - M_C}{SD_{pooled}}$ $SD_{pooled} = \sqrt{\frac{(N_E - 1)SD_E^2 + (N_C - 1)SD_C^2}{N_E + N_C - 2}}$ $-SD(g) = \sqrt{\frac{M_E + M_C}{N_E \times N_C} + \frac{g^2}{2(N_E + N_C)}}$ - 95% CI: [d - 1.96 × SD (d), d + 1.96 × SD (d)]	(Approximate data) -T0: M _E = + 2.2 +/- 1.1 Kg/cm2 M _C = + 2.1 +/- 0.8 Kg/cm2	-p < 0.05 -T0: -g = 0.10 -SD(g) = 0.36 - 95% CI: [- 0.61; + 0.81] -p value: NS	T0: small
Fryer 2004	1) N _E = N _C = 32 2) SD _E ≠ SD _C	3) Cohen's d coefficient	4) $d = \frac{M_E - M_C}{SD_{pooled}}$ $-SD^*(g) = \sqrt{\frac{SD_E^2 + SD_C^2}{2}}$ $-SD(g) = \sqrt{\frac{M_E + M_C}{N_E \times N_C} + \frac{d^2}{2(N_E + N_C)}}$ - 95% CI: [d - 1.96 × SD (d), d + 1.96 × SD(d)]	-T0: M _E = + 216.51 +/- 90.50 kPa M _C = + 244.64 +/- 91.59 kPa	-T0: -d = 0.30 -SD(d) = 0.25 - 95% CI: [- 0.19; + 0.79] -p value: NS	T0: medium	

NS: not significant; T0: Values at baseline; T + 1: Values after one minute; T + 5: Values after five minutes; T + 10: Values after ten minutes; T + 15: Values after fifteen minutes; T + 30: Values after thirty minutes; PD: Pelvic Deficiency; OPD: Opposite Pelvic Deficiency

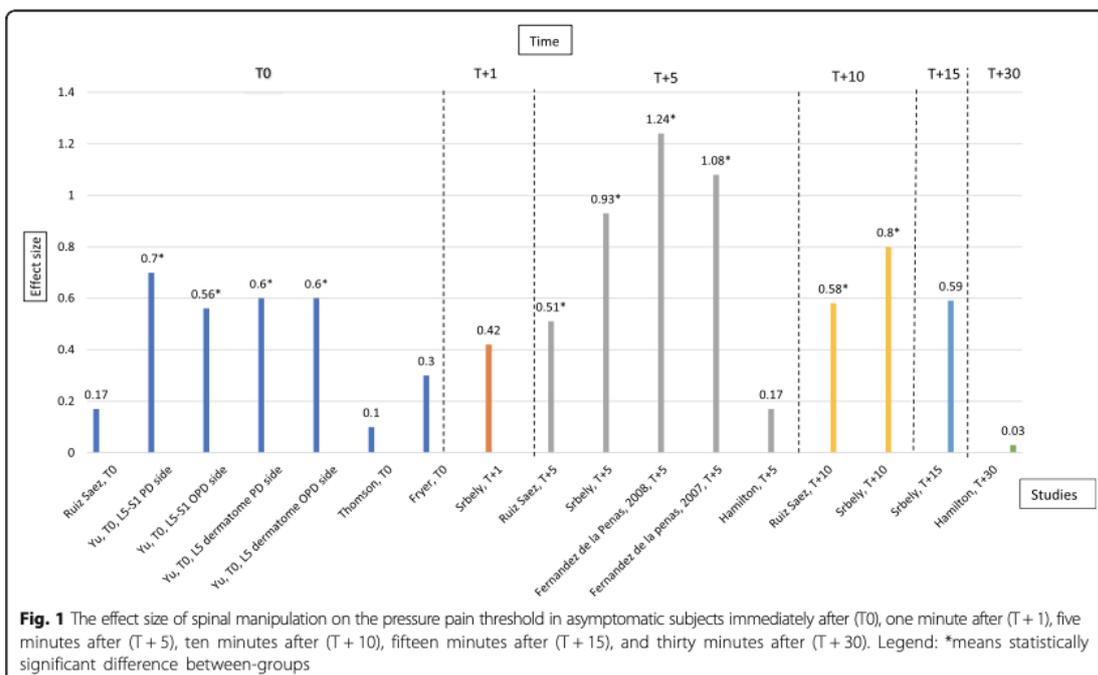


Fig. 1 The effect size of spinal manipulation on the pressure pain threshold in asymptomatic subjects immediately after (T0), one minute after (T + 1), five minutes after (T + 5), ten minutes after (T + 10), fifteen minutes after (T + 15), and thirty minutes after (T + 30). Legend: *means statistically significant difference between-groups

Our calculations of effect sizes at each follow-up time

Effect size immediately after spinal manipulation

Four studies had effect sizes immediately after SM, ranging from small [15–17] to medium [18] but only one study (with four different measurements) found these to be statistically significant [18], ranging from $d = 0.56$ (95% CI: 0.04–1.08) to $d = 0.70$ (95% CI: 0.18–1.22). In sum, the immediate effect would be considered as of medium size.

Effect size one minute after spinal manipulation

One study [19] was found to have a non-significant and small effect size one minute after SM ($d = 0.42$, 95% CI: -0.24–1.08) We drew no conclusion for this time interval.

Effect size five minutes after spinal manipulation

Five studies provided information on effect size five minutes after SM. One study [20] had a small non-significant effect size ($g = 0.17$, 95% CI: -0.34–0.68) whereas one [15] was classified as medium ($d = 0.51$, 95% CI: 0.04–0.98) and three as large [13, 19, 21] (from $d = 0.93$, 95% CI: 0.24–1.08 to $d = 1.24$, 95% CI: 0.28–2.20) and all statistically significant. In general, the effect at this time can therefore be considered mainly large.

Effect size ten minutes after spinal manipulation

Two studies had data that could be transformed into ten minutes effect sizes, [15] defined as medium ($d = 0.58$,

95% CI: 0.11–1.05) and the other [19] as borderline large ($d = 0.80$, 95% CI: 0.12–1.48), both statistically significant. This effect at ten minutes is therefore considered medium.

Effect size fifteen minutes after spinal manipulation

One study [19] found a non-significant, medium effect size fifteen minutes after SM ($d = 0.59$, 95% CI: -0.08–1.26). No conclusion was drawn on this result.

Effect size thirty minutes after spinal manipulation

One study [20] had a non-significant, small effect size thirty minutes after SM ($g = 0.03$; 95% CI: -0.48–0.54). No conclusion was drawn on this, but it is likely that the effect is no more present.

The results are illustrated in Fig. 1.

Discussion

Summary

In this additional analysis of data from a previous systematic review, we were confused by the reported effect sizes. A systematic approach revealed that no study reported between-group size differences, instead using the within-group differences, when reported at all. Further, none provided details on how this ‘effect size’ had been calculated. Therefore, we used information provided in the reviewed articles to produce our own estimates.

According to our own calculations obtained from data available in the eight reviewed studies, the estimated effect size of spinal manipulation on the PPT in asymptomatic subjects is 'medium' immediately after the intervention (T0), 'mainly large' five minutes after (T + 5) and 'mainly medium' ten minutes after the intervention (T + 10). No certain estimation of the effect size can be reported beyond T + 10, but it may be small after 30 min.

Using the examples provided in the introduction [1, 2] to explain the clinical importance of the different effect sizes, the 'medium' effect size immediately after SM would thus correspond to a difference in height between 14 and 18 years old girls. The 'large' effect size five minutes after SM would correspond to the difference in IQ between holders of a PhD degree and a 'typical college freshman'. The 'medium' effect size ten minutes after the intervention would, again, correspond to a difference in height between 14 and 18 years old girls.

The effect of SM on the PPT in asymptomatic subjects is therefore reported to be a reasonably large but probably short-lasting phenomenon. Whether these changes can also be 'appreciated' by study subjects, in such a way that they can differentiate between a small, medium and large effect size, is not known. Nevertheless, it serves as a comparator with other interventions in the same domain. For example, it could be used to compare the effect over time or effects of different types of interventions.

Methodological considerations of our own review

A description of the studies is found in the Table 1. Our quality checklist was established according to the various recommendations in the literature, including those provided by the creator of the Cohen's d coefficient. There is no definitive consensus on the calculation of the effect size nor on how to assess its quality, so we did not judge the quality of work in the reviewed articles but used our systematic approach to obtain a general understanding of the various effect size values (Table 2). This can be done online to obtain the effect size with its SD (d) and 95% CI, with A Practical Meta-Analysis Effect Size Calculator [22]. A blinded third researcher verified the calculations. Obviously, this approach assumes that the groups that are being compared are fairly similar at base-line. We did not investigate if this was the case.

Other methods of reporting the treatment effect

Depending on the type of data (continuous or categorical), treatment effect can be reported in other ways than with Cohen's d. Relative Risk, Odds Ratio, Number Needed to Treat (NNT) and Area Under the Curve are other possibilities [23].

Recommendations regarding effect size reporting

This additional analysis of data from our previous review on the effect of spinal manipulation on the pressure pain threshold in asymptomatic subjects revealed that all reviewed studies that reported an effect size used the within-group rather than the between-group differences. However, the within-group effect size is a purely descriptive outcome, interesting perhaps to understand the full picture of an effect, but it should never be provided alone. Therefore, the between-group calculations need to be calculated properly and in a transparent manner, to ensure that they are correct and comparable to other reports. We provide some information on how to do this in our Additional file 1, and we also provide references for these calculations.

Conclusion

The effect of spinal manipulation on the pressure pain threshold in asymptomatic subjects, as calculated by us, is 'medium' immediately after the intervention, has increased to mainly 'large' five minutes after and descended to mainly 'medium' ten minutes after intervention. The potential effect should be investigated over a longer period of time, and for other comparable interventions, to confirm if this effect is indeed only short lasting and to put it into a clinical perspective.

Additional files

Additional file 1: Calculation of the effect size [24–27]. (DOCX 70 kb)

Additional file 2: General description of data extracted from the abstracts of eight randomized controlled trials on the regional effect of spinal manipulation on the pressure pain threshold in asymptomatic subjects. (DOCX 20 kb)

Additional file 3: Search equation, inclusion and exclusion criterion of the previous review. (DOCX 14 kb)

Additional file 4: PRISMA flow-chart of the previous review. (DOCX 88 kb)

Abbreviations

HVLA: High Velocity Low Amplitude; PPT: Pressure Pain Threshold; SM: Spinal manipulation

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Availability of data and materials

The articles used for the current study are available from the corresponding author on reasonable request.

Authors' contributions

MH, CLY, OG and NW helped to plan the review and contributed in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors report that they have no competing interests.

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References

- Aron. Statistics for psychology. 2nd ed: Prentice Hall; 1999. p. 229–30.
- Coe Robert. It's the effect size, stupid. What effect size is and why it is important. Annual conference of the British Research Association, University of Exeter England, 12–14. September 2002.
- Malmqvist S, Leboeuf-Yde C, Ahola T, Andersson O, Ekstrom K, Pekkarinen H, Turpeinen M, Wedderkopp N. The Nordic back pain subpopulation program: predicting outcome among chiropractic patients in Finland. *Chiropractic & osteopathy*. 2008;16:13.
- Millan M, Leboeuf-Yde C, Budgell B, Amorim MA. The effect of spinal manipulative therapy on experimentally induced pain: a systematic literature review. *Chiropractic & manual therapies*. 2012;20(1):26.
- Hübscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshaug KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain—a systematic review and meta-analysis. *Pain*. 2013; 154(9):1497–504.
- Waller R, Smith AJ, O'Sullivan PB, Slater H, Sterling M, McVeigh JA, Straker LM. Pressure and cold pain threshold reference values in a large, young adult, pain-free population. *Scand J Pain*. 2016 Oct;13:114–22.
- Laura Frank PM, Vaughan B. The repeatability of pressure algometry in asymptomatic individuals over consecutive days. *International Journal of Osteopathic Medicine*. 2013;16(3):143–52.
- Honoré M, Leboeuf-Yde C, Gagey O. The regional effect of spinal manipulation on the pressure pain threshold in asymptomatic subjects: a systematic literature review. *Chiropractic & Manual Therapies*. 2018;26(1). <https://doi.org/10.1186/s12998-018-0181-3>.
- Cohen J. The earth is round ($p < .05$). *Am Psychol*. 1994;49(12):997–1003.
- Ray JW, Shadish WR. How interchangeable are different estimators of effect size? *J Consult Clin Psychol*. 1996;64(6):1316–25. <https://doi.org/10.1037/0022-006x.64.6.1316>.
- Cuijpers P, Weitz E, Cristea IA, Twisk J. Pre-post effect sizes should be avoided in meta-analyses. *Epidemiology and Psychiatric Sciences*. 2016; 26(04):364–8. <https://doi.org/10.1017/s2045796016000809>.
- Baguley T. Standardized or simple effect size: what should be reported? *Br J Psychol*. 2009;100(3):603–17. <https://doi.org/10.1348/000712608x377117>.
- Fernandez-de-Las-Penas C, Alonso-Blanco C, Cleland JA, Rodriguez-Blanco C, Alburquerque-Sendin F. Changes in pressure pain thresholds over C5-C6 zygapophysial joint after a cervicothoracic junction manipulation in healthy subjects. *J Manip Physiol Ther*. 2008;31(5):332–7.
- Dong Kyu Lee, 2016 Alternatives to p value : confidence interval and effect size. *Korean Journal of Anesthesiology* 2016;69(6):555–562. Published online: October 25, 2016 DOI: <https://doi.org/10.4097/kjae.2016.69.6.555>
- Ruiz-Saez M, Fernandez-de-las-Penas C, Blanco CR, Martínez-Segura R, García-León R. Changes in pressure pain sensitivity in latent myofascial trigger points in the upper trapezius muscle after a cervical spine manipulation in pain-free subjects. *J Manip Physiol Ther*. 2007;30(8):578–83.
- Thomson O, Haig L, Mansfield H. The effects of high-velocity low-amplitude thrust manipulation and mobilisation techniques on pressure pain threshold in the lumbar spine. *Int J Osteopath Med*. 2009;12(2):56–62. <https://doi.org/10.1016/j.ijosm.2008.07.003>.
- Fryer G, McIver JCS. The effect of manipulation and mobilisation on pressure pain thresholds in the thoracic spine. *Journal of Osteopathic Medicine*. 2004.
- Yu X, Wang X, Zhang J, Wang Y. Changes in pressure pain thresholds and basal electromyographic activity after instrument-assisted spinal manipulative therapy in asymptomatic participants: a randomized, controlled trial. *J Manip Physiol Ther*. 2012;35(6):437–45.
- Srbely JZ, Vernon H, Lee D, Polgar M. Immediate effects of spinal manipulative therapy on regional antinociceptive effects in myofascial tissues in healthy young adults. *J Manip Physiol Ther*. 2013;36(6):333–41.
- Luke Hamilton CB, Fryer G. The effects of high-velocity, low-amplitude manipulation and muscle energy technique on suboccipital tenderness. *International Journal of Osteopathic Medicine*. 2007.
- Fernandez-de-las-Penas C, Perez-de-Heredia M, Brea-Rivero M, Miangolarra-Page JC. Immediate effects on pressure pain threshold following a single cervical spine manipulation in healthy subjects. *The Journal of orthopaedic and sports physical therapy*. 2007;37(6):325–9.
- David B. Wilson, Ph.D., George Mason University. Practical Meta-Analysis Effect Size Calculator <http://www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-SMD1.php> Accessed on Sept 2018.
- McGough JJ, Faraone SV. Estimating the size of treatment effects: moving beyond p values. *Psychiatry (Edgmont)*. 2009 Oct;6(10):21–9.
- Ellis, P.D. (2009). "Effect size equations," website: [http://www.polyu.edu.hk/mnm/EffectSizeFAQs/Effect_size_equations2.html] accessed on [September 2018].
- Cohen. Statistical power analysis for the behavioral sciences. 2nd edition. 1988. Page 43.
- Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. *Journal of Educational Statistics*. 1981;6(2):106–28 Page 110.
- Hedge LV, Olkin. Statistical methods for meta-analysis. Orlando: Academic Press Inc; 2014. p. 86.

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ANNEXE 4 – Essai expérimental randomisé et contrôlé : L'effet régional de la manipulation vertébrale sur le seuil de la douleur à la pression chez des sujets jeunes et asymptomatiques, comparé à un placebo.

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RESEARCH

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What is the effect of spinal manipulation on the pressure pain threshold in young, asymptomatic subjects? A randomized placebo-controlled trial, with a cross-over design



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Abstract

Background: Spinal manipulation (SM) has been shown to have an effect on the pressure pain threshold (PPT) in asymptomatic subjects, but SM has never been compared in studies on this topic to a validated sham procedure. We investigated the effect of SM on the PPT when measured i) in the area of intervention and ii) in an area remote from the intervention. In addition, we measured the size and duration of the effect.

Method: In a randomized cross-over trial, 50 asymptomatic chiropractic students had their PPT measured at baseline, immediately after and every 12 min after intervention, over a period of 45 min, comparing values after SM and a previously validated sham. The trial was conducted during two sessions, separated by 48 h. PPT was measured both regionally and remotely from the 'treated' thoracic segment. Blinding of study subjects was tested with a post-intervention questionnaire. We used mixed linear regression with the baseline value and time as co-variables. If a significant difference were found between groups, then an effect size would be calculated using Cohen's d or Hedge's h coefficient. Statistical significance was set at $p < 0.05$.

Results: Study subjects had been successfully blinded. No statistically significant differences were found between SM and sham estimates, at any time or anatomical location.

Conclusion: When compared to a valid sham procedure and with successfully blinded subjects, there is no regional or remote effect of spinal manipulation of the thoracic spine on the pressure pain threshold in a young pain-free population.

Keywords: Spinal manipulation, Pressure pain threshold, Asymptomatic subjects, Randomized controlled trial, Sham, Effect, Duration, Effect size

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Resume

Contexte: La manipulation vertébrale (MV) a montré un effet sur le seuil de douleur à la pression (SDP) chez les sujets asymptomatiques, mais la MV n'a jamais été comparée dans les études sur le sujet à une procédure placebo validée. Nous avons étudié l'effet de la MV sur le SDP lorsque mesuré i) dans la zone d'intervention, ii) dans une zone éloignée de l'intervention. De plus, la grandeur et la durée de l'effet ont été évaluées.

Méthode: Un essai randomisé croisé portant sur cinquante jeunes étudiants en chiropratique asymptomatiques. Le SDP a été mesuré au départ, immédiatement après et toutes les douze minutes après l'intervention, sur une période de 45 min, en comparant les valeurs après MV et un placebo valide. L'essai a été conduit en deux sessions, séparées de 48 h. Le SDP a été mesuré à la fois régionalement et à distance du segment thoracique "traité", sur une période de 45 min. L'aveuglement était testé avec un questionnaire post-intervention. Nous avons utilisé une régression linéaire mixte avec la mesure de référence et la durée comme co-variables. La taille de l'effet a été calculée, à l'aide du coefficient *d* de Cohen ou *h* de Hedge, après constat d'une différence significative entre les groupes. La signification statistique a été fixée à $p < 0,05$.

Résultats: Les sujets de l'étude ont été aveuglés avec succès. Aucune différence statistiquement significative n'a été constatée entre les estimations MV et le placebo, à aucun moment, ni à aucune zone du rachis.

Conclusion: Comparé à une procédure placebo valide et à des sujets aveuglés avec succès, il n'existe aucun effet régional ou à distance de la manipulation vertébrale de la colonne thoracique sur le seuil de douleur à la pression chez une population jeune et indolore.

Mots clés: Manipulation vertébrale, Seuil de douleur de pression, Sujets asymptomatiques, Essai contrôlé randomisé, Placebo, Effet, Durée, Taille de l'effet

Introduction

Background

Spinal manipulation (SM) can be defined as a high velocity low amplitude forced manoeuvre applied to spinal joints outside the range of motion but within the normal range of anatomical joints, sometimes accompanied by a characteristic cracking sound [1]. It can be compared to a mobilisation, which also is defined as a type of manual therapy with a comparable execution and similar clinical results, but applied slower and/or repetitively over the joints within the range of motion and within the patient's control [2, 3] SM has been shown, sometimes, to have a clinical impact in the treatment of musculoskeletal pain [4], although the mechanisms underlying the reduction of pain are not yet well defined. Such mechanisms can be studied by the means of experimentally induced pain.

Spinal manipulation and experimentally induced pain

Asymptomatic subjects Experimentally induced pain can be used both in clinical and pain-free populations. The advantage of using study subjects from the asymptomatic population is that it makes it possible to deal with the 'normal' situation, as they are likely to have a normally functioning pain management system; as opposed to people with chronic pain, who are likely to have a dysfunction of the descending pain inhibitory mechanisms [5]. Therefore, studies of asymptomatic and symptomatic subjects may provide different insights on the treatment for pain. Also,

changes in pain perception arise late in life [6] with a decrease of pain sensitivity, so purely experimental studies are often performed on young asymptomatic people.

Pressure pain Pain can be induced in many ways in laboratory-controlled conditions, one of the most common being pain induced by pressure. The pressure pain threshold (PPT) is defined as the minimal pressure that provokes pain or discomfort [7]. PPT is commonly used in pain research. As everybody has a pain threshold, regardless pain status, PPT can be used also on pain-free subjects. It is tested using an algometer, which measures the exact pressure applied in a specific location, making it possible to determine the precise threshold.

Regional and remote effect of spinal manipulation on the pressure pain threshold A previous systematic review on studies including asymptomatic subjects [8] showed that SM could significantly and more consistently reduce pain induced by pressure, as opposed to other kinds of induced pain, at least when testing the pain sensation in the same area as the manipulated zone or along the same dermatome ('regionally'). More precisely, 12/20 studies included in the review showed a positive effect on the PPT when measured regionally, and 5/9 studies reported a remote effect (i.e. outside the manipulated area or its dermatome) on experimentally induced pain [8]. Unfortunately, none had a blind assessor, making it impossible to completely trust the results.

More knowledge is thus needed concerning both the regional and remote effect of spinal manipulation.

Spinal manipulation compared to a sham procedure

“Credible” sham procedure In research on the effect of manual therapy, the question of a “credible” sham procedure is challenging, as study subjects can easily deduce if they are treated or not. A recent systematic review [9] on the effect of SM on the PPT in the area corresponding to the SM (i.e. ‘regionally’) included an assessment of the credibility of the sham procedures in eight randomized controlled trials, by taking into account the psychological part of the placebo (i.e. can the subjects spot the difference between the “real” intervention or the placebo?) but also the physiological part of it (i.e. do the physical aspects of the sham procedure resemble the “real” intervention?). A completely “credible” placebo would fulfil both criteria. It was found that, in these studies when compared with a reasonably “credible” placebo procedure, a positive regional effect of SM was found as measured on the PPT. Surprisingly, no significant regional effect was reported when the placebo procedure was not considered credible at all. The credibility of the sham could be an important factor to consider when dealing with manual therapies studies, because the credibility of the placebo seems to affect the results.

Another factor to consider with sham interventions is the need to use a “thrust” to mimic the “real” intervention as much as possible, which means that it must be delivered outside the range of spinal joints. A recent study assessed the credibility of such a sham with a lateral and light “thrust” on the scapulae rather than on the thoracic joints. It was validated immediately after each of 12 treatment sessions over 3 months by post-treatment questionnaires with more than 80% of success (i.e. more than 80% of the subjects did not spot the difference between a “real” intervention and the sham intervention) [10]. Previously, it has been unusual that researchers check whether the sham intervention was recognized as such, or whether study subjects were ‘fooled’ by the procedure. Therefore, the effect of SM on PPT in asymptomatic subjects should be challenged by a validated sham procedure.

Size and duration of the effect of spinal manipulation

Previous analyses of eight randomized controlled trials that had investigated the regional effect of SM on the PPT in asymptomatic subjects showed the effect size to be ‘medium’ (Cohen’s d : 0.2–0.5) immediately after the intervention. Five minutes after intervention, the effect size was ‘mainly large’ (Cohen’s $d \geq 0.8$), and it was ‘mainly medium’ 10 min after intervention [11]. Therefore, it was concluded that the effect was probably rather short-lasting but should be investigated for a longer

period, as the included studies did not continue their measurements further than 30 min. Clearly, more information is needed on the element of time.

In conclusion, more knowledge is needed concerning the regional and remote effects of spinal manipulation, when compared to a valid sham procedure, as well as we need to know more about its duration and size, starting with asymptomatic subjects. For these reasons, we conducted a study on asymptomatic subjects to obtain answers to the following questions:

What is the effect of spinal manipulation on the pressure pain threshold when being compared with a valid sham procedure when measured i) in the area of intervention and ii) in an area remote from the intervention? If there is an effect, what is its i) size and ii) duration?

Method

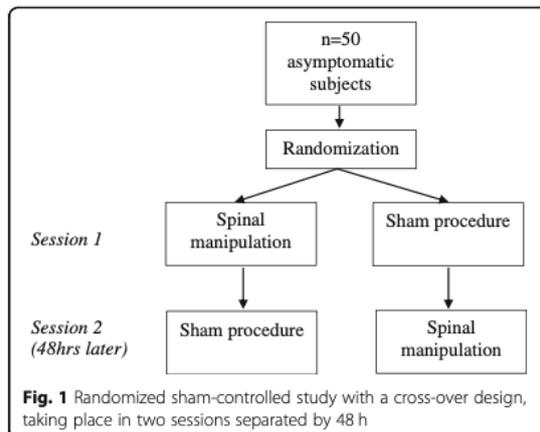
Design, ethics committee and registration

This study is a randomized sham-controlled trial with a cross-over design. The experiment took place in a research laboratory at the Institut Franco-Européen de Chiropraxie in Ivry sur Seine, France, from September 2017 to October 2018, with breaks over the school holidays. This report deals with the second part of a larger study, in which data were collected to investigate the effect of SM on both i) the autonomic system and ii) pain perception in asymptomatic individuals. Thus, the present report deals only with information relevant to the pain perception study. For more details, please see Picchiottino et al., 2019 [12]. The study was approved by the ethics committee EA 4532 of the University Paris Sud UFR STAPS, Orsay, France (October, 2016), registered as a clinical trial at <https://clinicaltrials.gov> (Registration NCT03776708), and, as required by French law, insured by HDI global assurance (N°01012787–14,009).

Study protocol

The experiments were carried out during two separate sessions. In the first session, subjects were randomly divided in two groups to receive either SM or a placebo procedure (‘sham’) by choosing a sealed and non-transparent envelope in an opaque box. They would thus choose the order of interventions at the first visit. The second session took place 48 h later, when the subjects received the second type of intervention, SM or placebo, the opposite to what they received the first time (Fig. 1). The second session was scheduled at the same time of the day as the first session, the duration of each being about an hour.

Each session started with a short period of rest. This was followed by the PPT measurements recordings before any intervention, both in the thoracic and in the lumbar spine, after which either SM or a sham intervention took place. These PPT measurements were repeated every 12 min, i.e. in total four times after each intervention over a period of 45 min (Fig. 2).



The experiment took place in a room with a stable and comfortable temperature with subjects lying prone on a treatment table. A ‘fake’ measurement of the PPT was done on the subjects with an algometer before the beginning of the study to initiate them to the procedure and to prevent anxiety.

A licensed chiropractor performed the interventions. The PPT assessor was trained for more than an hour in the use of the algometer, as previously recommended [13]. This person was blinded to the group allocation of study subjects. The study subjects could not see their own PPT readings, to prevent them from consciously affecting their values. They were instructed not to communicate with the investigator about the intervention they received.

The collected data were used to see if the PPT increased more after SM than after a sham intervention.

Study subjects consisted of first-year chiropractic students, who theoretically could be biased, as they were not naïve to SM. This required careful considerations. The procedures relating to them will therefore be explained in detail below.

Recruitment

With the permission of the College, posters and presentations were distributed at the beginning of the academic

year to spark an interest in the students for research projects. Students potentially interested in the study were invited to come to the research laboratory, where an information letter was given to them, including the informed consent sheet they would have to sign to participate. They were explained the potential risks of the interventions and their rights to withdraw at any moment. All information linking the study subjects to their data was protected during the experiment and destroyed at the end of the study. No individual student could therefore be identified in the data file after the experiment nor in the final report.

Inclusion and non-inclusion criteria

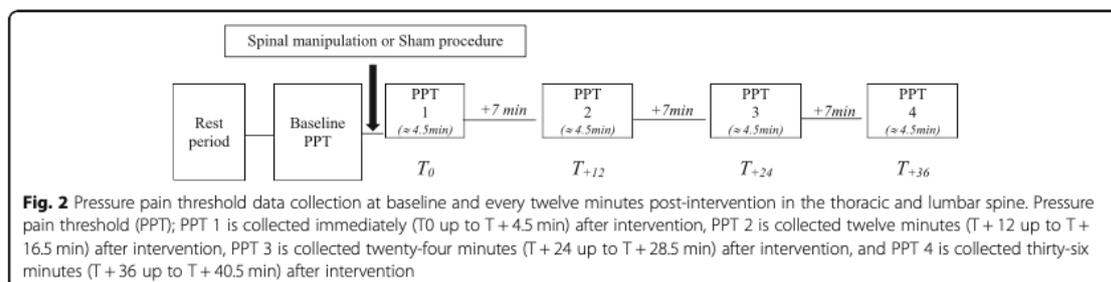
Included in the study were consenting, asymptomatic students between 18 and 40 years old. ‘Asymptomatic’ was defined as having no pain in the tested area. Further, they should not report having had any spinal pain lasting more than a month, having taken painkillers 24 h prior to the study, or having received manual treatment during the previous 48 h. There should be no contra-indications to spinal manipulation, such as instability (fracture, malformation), bony or ligamentous fragility, or local inflammation. Informed consent was obtained from potential study subjects by the treating chiropractor.

The data collection also included autonomic nervous system variables [12], so the students were informed not to ingest food, caffeine, alcohol, or tobacco in the hour prior to the sessions, as well as not to perform intense physical activity the day of the experimentation.

Spinal manipulation and sham procedure

The SM was performed on all participants at the level of the fifth thoracic vertebra (with a margin of palpatory error), making sure this was a pain free area on light palpation. The maneuver was of high velocity with low amplitude, oriented posterior to anterior, with the contact hand placed over the transvers process area of the c vertebra.

In order to imitate the SM to a maximum, the sham procedure consisted of a manual contact on the right medial angle of the scapula with both hands. After putting the tissues briefly under tension, a slight movement with a



thrust was performed, respecting the scapula-thoracic sliding planes laterally without influencing the spine. It was considered by us to be a “credible” sham procedure, as it resembles an actual act of thoracic manipulation being performed over the back and included manual contacts and movements used in manual therapy but lacked the precise action over a spinal joint. We selected this method to confuse the study subjects, who had been told that they would be subjected to different manipulative techniques. An almost identical version of this method has been previously validated with good results [10].

Blinding

The study subjects were first year chiropractic students. Throughout their undergraduate studies, these students will be exposed to several types of spinal manipulations. However, in their first year of study they would be unlikely to have enough knowledge and experience of manipulation to know about the various types that exist and, therefore, unlikely to discover a well performed sham intervention, if it was not directly contrasted to manipulation (i.e. manipulation vs. sham).

These subjects were therefore told that the aim of the study was to assess the outcomes of different efficacious techniques used in manual therapies, and that they would receive the same type of intervention during both sessions. During the random allocation procedure, they had the choice between six envelopes (to reinforce the idea that there were many intervention possibilities). They were also not informed of their treatment allocation throughout the study.

With this procedure, we made sure they were naïve to the exact objectives of our study with the intent to blind them to the type of intervention.

Further, the study subjects responded to a questionnaire at the end of each session to see what their beliefs regarding the effectiveness of each intervention was (see Additional file 1). A completely blinded subject would have the same beliefs for both interventions, and might even suppose the sham more effective than the real SM. As reported later, the results showed that they had been successfully blinded.

Algometer

An algometer type 2 (*SOMEDIC Electronics, Sweden*) was used to take these measurements. This algometer has a circular metal tip of 1cm², which is to be applied perpendicularly to the skin with a normalized speed (the pressure exerted is 50 kPa/s). Subjects were instructed to press a switch, when they felt the gradual pressure turning into pain. The reading was then frozen at this level, as indicated on the screen of the algometer, then transferred manually onto paper and then entered in Excel software. Data were entered separately and blindly by

two people and then checked for accuracy. These data were stored, unchangeable and confidential.

Measurements

The algometer is reported to have good reliability [14, 15], sensitivity [15] and specificity [15], which makes it a simple and efficient tool to use, after training the assessor [15]. It was calibrated frequently during data collection to ensure precise values of the PPT. We performed three PPT readings at 30 s interval, at each time of recording, as recommended [16] and at each site. The brief pause between readings is necessary to avoid sensitization of the skin. A cut-off pressure value of 1000 kPa was set for safety purposes [17].

Statistical analysis

Preliminary analyses

Data were analyzed with Stata (version 15.1) software. We ensured the blindness of the statistician by de-identifying the intervention groups (called A and B). Sample size calculation was performed using a repeated measures approach. We found that we would need 43 subjects in each group to show at least a difference of 15% of change between groups (‘supposed’ percentage of clinical significance [18]), with the mean pressure pain threshold of 500 kg/cm² at baseline. However, as this minimum clinical difference of the PPT is not clearly defined [18], the basis for this power calculation was purely speculative.

Descriptive data were presented as means and standard deviation for each group, at baseline and at the subsequent follow-up times. The distribution of the data was assessed visually with histograms and boxplots. A secondary analysis, where sex was included as covariate, was performed using mixed regression, and we tested for period-group interaction, with $p = 0.1$.

Subcutaneous fat could affect pain produced by pressure but there were no obese people in this study (Additional file 2). Therefore, BMI was not included in the analysis, although it might well be relevant in other study populations.

Age could influence pain perception, but the range in our study subjects was too narrow to be of any importance. We did not include any psychological variables such as fear avoidance, as we did not think this likely to have an influence on purely experimental pain without any previous suffering or secondary effect on life-style and psychological profile.

Testing the effect

We used linear mixed models with random intercept to estimate the adjusted difference in PPT between SMT and sham at each follow-up time point. A separate repeated-measures model was created for the regional

and remote PPT outcomes. The dependent variable was the mean of three PPT measurements taken at each time point, the independent variable was intervention (SMT/sham), and the covariates were the session baseline and time. If a significant difference were found between groups, then an effect size would be calculated using Cohen’s d or Hedge’s h coefficient [11]. Statistical significance was set at $p < 0.05$.

Results

Descriptive analysis of data

Fifty-one study subjects (male $n = 23$ and females $n = 28$; mean age 20 (+/- 3); range 18–37, (with one subject aged 37) were recruited and randomly assigned into a spinal manipulation group ($n = 26$ in the first session, i.e. equal allocation) or a sham procedure group for the first session. Thus, study subjects served as their own controls, switching to the other type of intervention at the second session.

Data were removed from the final analysis for one study subject because of malfunction of the algometer, resulting in 50 participants for the analyses of the regional PPT tests. For the remote PPT testing, another four subjects were excluded: one, because the lumbar region was painful at the second session and three because they had PPT values over 1000 kPa.

The post-trial questionnaires showed that 78% of the subjects had the same beliefs for both interventions or (although rarely) thought the sham superior to SM, suggesting a successful blinding (Table 1, rows A, B, C). The distributions were found to be within the ‘normal’ ranges both for the regional and remote values. No period-group interaction was found ($p > 0.25$).

1/ Is there a regional effect of spinal manipulation on the pressure pain threshold when compared to a valid sham in asymptomatic subjects over time?

The adjusted differences in PPT readings between SM and the sham procedure at regional and remote sites over time are shown in Table 2. The estimates were similar between groups and no statistically significant differences were found between groups at any of the follow-up times ($p > 0.05$).

2/ Is there a remote effect of spinal manipulation on the pressure pain threshold when compared to a valid sham in asymptomatic subjects over time?

The adjusted differences in PPT readings between SM and sham procedure at regional and remote sites over time are shown in Table 3. There were somewhat larger differences than for the regional estimates, but no statistically significant differences were found between groups at any of the follow-up times ($p > 0.05$).

The changes over time in the pressure pain threshold after the interventions in both regional and remote testing have been visualized in Fig. 3.

3/ If there is an effect, what is the duration of the regional and remote effect of spinal manipulation on the pressure pain threshold in asymptomatic subjects?

No statistically significant differences were found between the interventions over time at any of the testing sites. Hence, no duration of effect can be reported.

4/ If there is an effect, what is the effect size of spinal manipulation on the pressure pain threshold in asymptomatic subjects over time at both regional and remote testing sites?

As there are no regional or remote effects reported, the effect size is irrelevant.

Table 1 Expectation questionnaire of the subjects between both sessions of the experiment

Beliefs regarding SM or sham	Total of subjects (n/50)	Percentage (%)	Are the subjects considered completely blinded? (Yes/No)
A Subjects had same beliefs for SM and sham	32/50	64%	Yes (78%)
B Subjects thought that both interventions were effective and Sham > SM	1/50	2%	
C Subjects did not know if SM was effective but thought that the Sham was effective	6/50	12%	
D Subjects thought that both interventions were effective and SM > Sham	2/50	4%	No (22%)
E Subjects did not know if the sham was effective but thought that SM was effective	3/50	6%	
F Subjects did not know if the SM was effective but thought that the Sham was ineffective	3/50	6%	
G Subjects thought that SM was effective and Sham ineffective	3/50	6%	

-Sham > SM means stronger certainty for the Sham
 -SM > Sham means stronger certainty for the SM
 SM spinal manipulation

Table 2 Adjusted differences in pressure pain threshold (PPT) readings in kPa at regional testing site at four different times after the interventions

Time measurements	SPINAL MANIPULATION			SHAM procedure			Differences between groups (95% CI)	P value
	Means (SD)	Min-Max Values	95% CI	Means (SD)	Min-Max values	95% CI		
Baseline	406 (158)	118–873	361–451	416 (162)	143–877	370–462	–10 (–73;53)	0.76
PPT 1	446 (169)	125–1048	395–487	447 (154)	173–768	389–482	–1 (–64;63)	0.98
PPT 2	450 (168)	137–903	401–494	438 (159)	145–807	386–478	12(–53;77)	0.72
PPT 3	443 (158)	125–853	394–487	438 (180)	151–962	387–480	4(–50;58)	0.90
PPT 4	444 (161)	146–823	395–487	432 (167)	136–859	378–470	12(–51;75)	0.71

SD standard deviation, SE standard error, PPT pressure pain threshold, PPT 1 follow-up time 1 immediately after intervention, PPT2 follow-up time 2 at T + 12 min after intervention, PPT 3 follow-up time 3 at T + 24 min after intervention, PPT 4 follow-up time 4 at T + 36 min after intervention

Discussion

Summary of findings

Although several studies have been conducted on the subject, this is the first experimental study testing the effect of spinal manipulation on pressure pain threshold in asymptomatic subjects using a sham, which was shown to be valid with a post-intervention questionnaire. No effect was found for the pressure pain threshold in the area of the intervention (thoracic spine), nor in an area further away (lumbar spine) immediately after SM. Additional measurements were taken over 45 min, which did not change the results.

Comparison with literature

Our findings are in contradiction with a recent review on the same subject (the effect of SM in asymptomatic regions), which identified 19 studies measuring the PPT [8]. Only 13 of these compared SM with a sham procedure, of which 11 reported a positive effect. Two studies, similarly to us, tested thoracic SM; one with a positive effect. Although the authors of this review examined the general quality of the studies, they did not investigate the validity of the sham.

A second review, also with a positive conclusion in relation to SM in pain free study subjects, further investigated the quality of the sham [9] and found a positive effect in 5

of 8 sham-controlled studies. None of these sham interventions were validated after intervention. A major difference with other studies was, therefore, that our trial used a previously validated sham procedure that imitated a proper SM in all aspects expect in the area and direction of the thrust, as it was performed over the scapula in the plane of the thoracic cage [10]. Very importantly, we also confirmed with a post-intervention questionnaire, if study subjects had identified the ‘effective’ intervention from the ‘ineffective’ intervention, which they had not. These results are strengthened by similar findings in the literature but on study subjects *with* musculoskeletal problems. Thus a recent systematic review concluded that there was no effect of SM on the pressure pain threshold in people with musculoskeletal problems [18] A recent subsequent study, using the same sham as us with verification of blinding afterwards, also failed to identify an effect of SM on PPT in people *with* musculoskeletal problems [19].

However, there are other methodological issues than the sham that have to be taken into account in a successfully randomized controlled clinical trial.

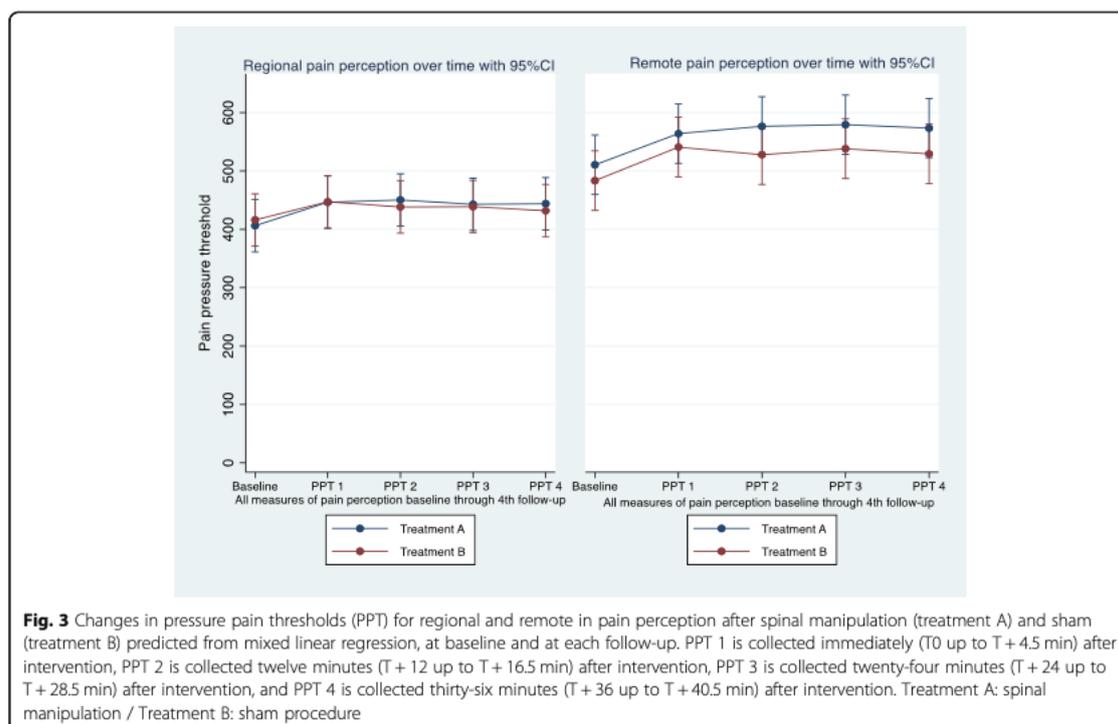
Methodological considerations concerning our study

Our previous systematic review [9] revealed that the most common methodological problems in this type of literature were the lack of blindness of statistician/

Table 3 Adjusted differences in pressure pain threshold (PPT) readings in kPa at remote testing site at four different times after the interventions

Time measurements	SPINAL MANIPULATION			SHAM procedure			Differences between groups (95% CI)	P value
	Means (SD)	Min-Max values	95% CI	Means (SD)	Min-Max values	95% CI		
Baseline	511 (166)	221–894	462–568	479 (154)	187–831	432–525	32(– 33;97)	0.34
PPT 1	564 (192)	248–1027	517–623	536 (172)	203–916	485–588	27(– 12;66)	0.47
PPT 2	576 (199)	205–1128	529–635	523 (176)	190–950	471–576	53(– 10;96)	0.18
PPT 3	579 (204)	190–1097	533–639	533 (177)	170–910	486–581	38(–48;124)	0.23
PPT 4	573 (203)	207–1195	527–633	524 (160)	197–817	480–570	49(– 53;151)	0.19

SD standard deviation, SE standard error, PPT pressure pain threshold, PPT 1 follow-up time 1 immediately after intervention, PPT2 follow-up time 2 at T + 12 min after intervention, PPT 3 follow-up time 3 at T + 24 min after intervention, PPT 4 follow-up time 4 at T + 36 min after intervention



statistical analysis, the failure to report losses and exclusions, and, importantly, the absence of blindness of the subjects. Our study avoided these errors. We ensured the blindness of the statistician by de-identifying the intervention groups (called A and B). Missing values and exclusion of data were reported and explained, but too few to change the results. Concerning the blindness of the subjects, a particular potential problem of our study was that our subjects consisted of chiropractic students (potential recruitment bias). They were likely to have previous knowledge of SM and to have a desire to show 'positive' results in favor of SM. To counteract this, we included only first year students. Apart from the use of post-study questionnaires, as explained above, we made sure that they were blind to i) the real purpose of the study, ii) to the interventions, iii) to the allocation of the groups, and iv) to the PPT readings.

Because the study subjects were all chiropractic students, even if this did not affect their ability to differentiate between intervention and sham, it is still possible that these results cannot be transposable to the general population. However, it could be argued that as the results were *not* in favor of SM, this recruitment factor would not have been significant in this study.

Other potential sources of error were also avoided by ensuring that the assessor was blinded to the type of intervention and that clinician and assessor were both

experienced. Further, our PPT readings in the lumbar spine were found to be within the 'normal' range of values [20], whereas we could find no literature on 'normal' values in the thoracic spine.

Other potential issues specific to the sham procedure

The validated sham procedure consisted of a pre-load tension with both hands on the medial part of the right scapula, followed by a 'thrust' to resemble as much as possible the real intervention. It could be argued that the 'thrust' movement on the scapula resembles too much a mobilization, with an active component capable of changing the pain perception in the subjects. However, the 'thrust' part was done on the scapula, i.e. outside the thoracic spine, and therefore could not be considered a form of spinal mobilization.

In our previous review [9] we theorized that a credible sham procedure should be acceptable both from a psychological point of view (*subjects found naïve, and blind*) and physiologically (*the sham resembling the active intervention*). Interestingly, we found in our previous review [9] that when the sham procedure was considered by us to be completely credible, the studies found positive results, with moderate general quality. In retrospect, this criterion may not have been sufficient, as it did not include an actual *validation* of the sham. In the light of our results, this previous definition seems not to have been sufficient.

Other methodological considerations

Other experimental pain variables than PPT would perhaps have reacted differently to SM, such as pain induced by cold and heat, temporal summation (i.e. pain induced by repetitive irritations) and pain induced by irritating substances. However, a recent RCT on symptomatic subjects, testing lumbar SM using a validated sham included also temporal summation, with no effect [19]. This indicates that the lack of effect of SM is not primarily related to the type of test for pain.

Interpretation of our findings

According to our study, SM has no specific effect on pain perception by pressure in the asymptomatic population. Recent literature indicates that this is also the case in the symptomatic population. The mechanisms of action of the SM on pain are therefore probably similar to those involved in a placebo maneuver, or at least the interpretation that the brain makes of these two interventions.

Perspectives

- The validity of the sham intervention is essential in the study of the effects of manual therapies. It is necessary that the active intervention and the sham are as similar as possible in order to ensure the blindness of the subjects. In the same way, it is fundamental to always check the blindness of the subjects by the means of questionnaires.
- As suggested by one of the reviewers, in future studies the remote site should perhaps not only be non-dermatomal but also removed from the truncus, such as the elbow, wrist, knee or ankle.
- An important issue in relation to experimental studies of this type is to establish what level of improvement would be necessary before it corresponds to a clinically noticeable difference. This change should be above 'the minimum change that would be greater than measurement error or chance', calculated as between about 0.5 and 3.4 kg/cm² (20–50% change) for PPT [13, 21–23].
- Obviously, the effect size should be reported as well, but, as we have previously observed [11], this is often done in several and non-transparent ways, making real comparisons difficult.
- Another approach to grasp the 'clinical' validity of studies like this is to calculate the 'Number Needed to Treat' (NNT) [11]. For example, in our study we calculated how many subjects the study would need to obtain a statistically significant difference and found that more than 5000 subjects would be needed in each intervention group, assuming that the estimates remained unchanged.

Conclusion

In conclusion, when compared to a valid sham procedure and with successfully blinded subjects, there is no regional or remote effect of spinal manipulation of the thoracic spine on the pressure pain threshold in a young pain-free population. Since our study was carefully designed and carried out and the results showed no relevant changes, we conclude that bigger and better studies are not to be recommended, at least not on asymptomatic people, manipulated in the thoracic spine measuring effect on the pressure pain threshold.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12998-020-0296-1>.

Additional file 1. Post-study questionnaire

Additional file 2 Descriptive data of the participants in the study (*n* = 50)

Abbreviations

NNT: Number needed to treat; PPT: Pressure pain threshold; RCT: Randomized controlled trial; SM: Spinal manipulation

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Authors' contributions

MH, MP, CLY, NW and OG contributed in planning the study and in writing the manuscript. MP performed the treatments, MH measured the PPT and both of them were responsible for all practical aspects. NW did the statistical analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The data used in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee EA 4532 of the University Paris Sud UFR STAPS, Orsay, France (October, 2016), registered as a clinical trial at www.clinicaltrials.gov (Registration NCT03776708), and insured by HDI global assurance (N°01012787–14009). The subjects are young healthy volunteers, who all signed a consent sheet to participate.

Consent for publication

All authors consented to publication. Written informed consent was obtained from the participants for publication of their individual details in this manuscript. The consent form is held by the authors and is available for review by the Editor-in-Chief.

Competing interests

All authors declare that they have no competing interests. CLY is a consultant of the Journal but had not input into the review process.

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References

- Bergmann TF. High-velocity low-amplitude manipulative techniques. In: Haldeman S, editor. Principles and practice of chiropractic. 3rd ed. USA: McGraw-Hill; 2005. p. 755–66.
- Pickar JG. Neurophysiological effects of spinal manipulation. *Spine J*. 2002; 2(5):357–71. [https://doi.org/10.1016/s1529-9430\(02\)00400-x](https://doi.org/10.1016/s1529-9430(02)00400-x).
- Gross A, Langevin P, Burnie SJ, Bédard-Brochu MS, Empey B, Dugas E, Faber-Dobrescu M, Andres C, Graham N, Goldsmith CH, Brønfort G, Hoving JL, LeBlanc F. Manipulation and mobilisation for neck pain contrasted against an inactive control or another active treatment. *Cochrane Database of Systematic Reviews* 2015, Issue 9. Art. No.: CD004249. doi: <https://doi.org/10.1002/14651858.CD004249.pub4>
- Bialosky JE, Beneick JM, Bishop MD, Coronado RA, Penza CW, Simon CB, George SZ. Unraveling the mechanisms of manual therapy: modeling an approach. *J Orthop Sports Phys Ther*. 2018;48(1):8–18. <https://doi.org/10.2519/jospt.2018.7476>.
- Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Rev Neurother*. 2012;12(5):577–85. <https://doi.org/10.1586/ern.12.41>.
- Lautenbacher S, Peters JH, Heesen M, Scheel J, Kunz M. Age changes in pain perception: a systematic-review and meta-analysis of age effects on pain and tolerance thresholds. *Neurosci Biobehav Rev*. 2017;75:104–13. <https://doi.org/10.1016/j.neubiorev.2017.01.039>.
- Laura Frank PM, Vaughan B. The repeatability of pressure algometry in asymptomatic individuals over consecutive days. *Int J Osteopathic Med*. 2013;16(3):143–52.
- Millan M, Leboeuf-Yde C, Budgell B, Amorim MA. The effect of spinal manipulative therapy on experimentally induced pain: a systematic literature review. *Chir Manual Ther*. 2012;20(1):26.
- Honoré M, Leboeuf-Yde C, Gagey O. The regional effect of spinal manipulation on the pressure pain threshold in asymptomatic subjects: a systematic literature review. *Chiropr Man Ther*. 2018;26(1). <https://doi.org/10.1186/s12998-018-0181-3>.
- Chaibi A, Šaltytė Benth J, Bjørn RM. Validation of placebo in manual therapy randomized controlled trial. *Nature Sci Rep*. 2015;5:11774. <https://doi.org/10.1038/srep11774>.
- Honoré M, Leboeuf-Yde C, Gagey O, Wedderkopp N. How big is the effect of spinal manipulation on the pressure pain threshold and for how long does it last? – secondary analysis of data from a systematic review. *Chiropr Man Ther*. 2019;27:22. <https://doi.org/10.1186/s12998-019-0240-4>.
- Mathieu P, Margaux H, Olivier G, François C, David H. The effect of a single spinal manipulation on cardiovascular autonomic activity and the relationship to pressure pain threshold: a randomized, cross over, sham-controlled trial. *Chiropractic & Manual Therapies*. 2019. <https://doi.org/10.1186/s12998-019-0293-4>.
- Walton D, MacDermid J, Nielson W, Teasell R, Chiasson M, Brown L. Reliability, standard error, and minimum detectable change of clinical pressure pain threshold testing in people with and without acute neck pain. *J Orthop Sports Phys Ther*. 2011;41(9):644–50.
- Chesterton LS, Sim J, Wright CC, Foster NE. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. *Clin J Pain*. 2007;23(9):760–6. <https://doi.org/10.1097/ajp.0b013e318154b6ae>.
- Kinser AM, Sands WA, Stone MH. Reliability and validity of a pressure Algometer. *J Strength Conditioning Res*. 2009;23(1):312–4. <https://doi.org/10.1519/jsc.0b013e31818f051c>.
- Lacourt TE, Houtveen JH, LJP v D. Experimental pressure-pain assessments: test-retest reliability, convergence and dimensionality. *Scand J Pain*. 2012; 3(1):31–7.
- Chien A, Sterling M. Sensory hypoesthesia is a feature of chronic whiplash but not chronic idiopathic neck pain. *Man Ther*. 2010;15:48–53.
- Aspinall SL, Leboeuf-Yde C, Etherington SJ, Walker BF. Manipulation-induced hypoalgesia in musculoskeletal pain populations: a systematic critical review and meta-analysis. *Chiropr Man Ther*. 2019;27(1). <https://doi.org/10.1186/s12998-018-0226-7>.
- Aspinall SL, Jacques A, Leboeuf-Yde C, Etherington SJ, Walker BF. No difference in pressure pain threshold and temporal summation after lumbar spinal manipulation compared to sham: a randomised controlled trial in adults with low back pain. *Musculoskelet Sci Pract*. 2019. <https://doi.org/10.1016/j.msksp.2019.05.011>.
- Waller R, Smith AJ, O'Sullivan PB, Slater H, Sterling M, Alexandra McVeigh J, Straker LM. Pressure and cold pain threshold reference values in a large, young adult, pain-free population. *Scand J Pain*. 2016;13(1):114–22. <https://doi.org/10.1016/j.sjpain.2016.08.003>.
- Walton DM, Levesque L, Payne M, Schick J. Clinical pressure pain threshold testing in neck pain: comparing protocols, responsiveness, and association with psychological variables. *Phys Ther*. 2014;94(6):827–37.
- Potter L, McCarthy C, Oldham J. Algometer reliability in measuring pain pressure threshold over normal spinal muscles to allow quantification of anti-nociceptive treatment effects. *Int J Osteopath Med*. 2006;9(4):113–9.
- Bisset LM, Evans K, Tittle N. Reliability of 2 protocols for assessing pressure pain threshold in healthy young adults. *J Manip Physiol Ther*. 2015;38(4): 282–7.

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ANNEXE 5 – Autorisation par le comité éthique EA 4532 de l'Université Paris Sud UFR STAPS Orsay de l'essai expérimental.

AUTORISATION DU COMITÉ D'ÉTHIQUE

Tenant compte des réponses et spécifications fournies par le(s) chercheur(s) cidessous (avec confirmation par un des éventuels directeurs de recherche) :

Nous confirmons par la présente que ce projet de recherche est approuvé par le Comité d'Éthique EA 4532.

Nicole El Massioui *Nicole El Massioui* 14/10/2016

Membre Comité 1 – Nom et signature

Date

Membre Comité 2 – Nom et signature Pierre PORTERO

Date 17/10/2016



ANNEXE 6 – Assurance HDI GLOBAL pour l'essai expérimental.

HDI Global SE
Tour Opus 12 – Défense 9
77 Esplanade du Général de Gaulle
92914 PARIS LA DEFENSE CEDEX
478 913 882 RCS Nanterre
N° SIRET : 478 913 882 000 54



Contrat d'Assurance

Nom et adresse du Souscripteur	N° de Contrat HDI global SE	N° 01012787-14009		
IFEC 24 BLD PAUL VAILLANT COUTURIER 94200 IVRY SUR SEINE	Affaire Nouvelle			
	Date d'Effet	Durée		
	01/06/2017	DUREE FERME		
	Intermédiaire	GRAS SAVOYE PUTEAUX		
	Branche	R. C. RECHERCHES IMPLIQUANT LA PERSONNE HUMAINE		
Échéance Principale	Fractionnement			
DUREE FERME	UNIQUE			
Période de la Cotisation	Cotizat. Nette HT	Frais	Taxes	Cotizat. Totale
Du 01/06/2017 au 31/12/2018	4 950,00 EUR	0,00 EUR	445,50 EUR	5 395,50 EUR
Cotisation au Comptant	Nouvelle Cotisation Annuelle hors taxes			
5 395,50 EUR	NON RENOUELABLE			

Le présent contrat est régi par la loi française, notamment par les dispositions du Code des Assurances, ainsi que par les Dispositions particulières, les Conventions spéciales et les Conditions générales qu'il comporte ou dont il est accompagné.

Protocole PICCHIOTTINO

LE PRESENT CONTRAT SE COMPOSE DES DOCUMENTS SUIVANTS DONT LE SOUSCRIPTEUR RECONNAIT AVOIR RECU UN EXEMPLAIRE :

- Conditions Générales imprimé Edition 2017
- Dispositions Particulières et Conventions Spéciales Edition 2017 ci-annexées (5 pages y compris la présente).

L'assurance prend effet le lendemain à midi du paiement de la première cotisation et au plus tôt à la date d'exigibilité fixée ci-dessus à midi.

Pour la Société

HDI GLOBAL SE

Fait en 2 exemplaire(s) à Paris
Le 08/06/2017 – CDS/NT

Le présent contrat est souscrit pour la durée

DUREE FERME
DU 01/06/2017 A ZERO HEURES (0H00)
AU 31/12/2018 A VINGT QUATRE HEURES (24H00)

HDI Global SE
RCS Nanterre 478 913 882
TOUR OPUS 12 - LA DEFENSE 9
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Le Souscripteur
(Cachet commercial et Signature)



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ANNEXE 7 – Questionnaire donné à la fin de chaque session de l’expérimentation pour connaître leurs convictions quant à l’efficacité des deux interventions.

Additional file 1. Post-study questionnaire

Subject ID:

Session ID:

Post session questionnaire

I am definitely of the opinion that the intervention that I have received can modify the measured parameters

I am rather of the opinion that the intervention that I have received can modify the measured parameters

I do not know

I am rather of the opinion that the intervention that I have received cannot modify the measured parameters

I am definitely of the opinion that the intervention that I have received cannot modify the measured parameters

Titre : L 'effet hypoalgésique de la manipulation vertébrale

Mots clés : Manipulation vertébrale, seuil de douleur à la pression, sujets asymptomatiques, placebo

Résumé : La manipulation vertébrale est connue pour son effet clinique sur les douleurs musculo squelettiques. Or, ses mécanismes d'action sur la douleur sont encore peu connus. C'est pourquoi ce projet doctoral a cherché à déterminer l'existence d'un effet spécifique sur le seuil de la douleur à la pression, chez des sujets asymptomatiques, et s'il existe, d'en préciser sa taille et sa durée.

Nos deux revues systématiques et critiques de la littérature ont mis en évidence la présence d'un effet régional spécifique de la manipulation vertébrale sur cette perception douloureuse dans la population asymptomatique, avec une taille de l'effet moyenne et de courte durée.

Cependant, ces résultats sont en contradiction avec notre essai expérimental sur l'effet d'une manipulation vertébrale thoracique contrôlé par placebo dans cette population.

Cette différence s'explique par la qualité de la manoeuvre placebo, avec la vérification de l'aveuglement réussi durant l'expérimentation par un questionnaire.

En conclusion, nos travaux n'ont pas réussi à reproduire un effet spécifique de la manipulation vertébrale sur le seuil de la perception douloureuse à la pression, suggérant que les mécanismes d'action de la manipulation sont similaires à ceux impliqués dans une manoeuvre placebo. Par conséquent, l'importance principale de ce travail est d'avoir montré l'importance de l'effet placebo et comment les résultats d'un essai peuvent dépendre de la manière dont l'intervention placebo est réalisée et évaluée.

Title: Hypoalgesic effect of spinal manipulation

Keywords: Spinal manipulation, pressure pain threshold, asymptomatic subjects, placebo

Abstract : Spinal manipulation is known for its clinical effect on musculoskeletal pain. Or, its mechanisms of action on pain are still little known. This is why this doctoral project sought to determine the existence of a specific effect on the threshold of pressure pain, in asymptomatic subjects, and if it exists, to specify its size and its duration.

Our two systematic and critical reviews of the literature have highlighted the presence of a specific regional effect of vertebral manipulation on this painful perception in the asymptomatic population, with a medium effect size and short duration. However, these results contradict our experimental trial on the effect of placebo-controlled thoracic spinal manipulation in this population.

This difference can be explained by the quality of the placebo maneuver, with the verification of successful blindness during the experiment by a questionnaire. In conclusion, our work has not succeeded in reproducing a specific effect of vertebral manipulation on the threshold of pain perception at pressure, suggesting that the mechanisms of action of manipulation are similar to those in a placebo maneuver. . Therefore, the main importance of the work is to have shown the importance of the placebo effect and commenting on the results of a trial may depend on the way the placebo intervention is performed and indicated.