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Le rôle du stade 2 du sommeil non-paradoxal et des fuseaux de sommeil dans la consolidation de la mémoire motrice séquentielle

par

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Résumé

De l'enfance au vieil âge, l'apprentissage moteur fait partie intégrale de notre vie de tous les jours. Suite à l'acquisition d'une nouvelle habileté motrice, notre cerveau continue d'en renforcer sa trace mnésique. Ce processus est mieux connu sous le nom de « consolidation de la mémoire », dans lequel le sommeil jouerait un rôle clé. Bien qu'il n'existe pas encore de consensus quant à savoir durant quel stade de sommeil ce processus à lieu, de plus en plus d'indices tendent à démontrer que les fuseaux de sommeil (FS) du stade 2 du sommeil non-paradoxal (SNP2) sont impliqués dans la consolidation. Néanmoins, ces résultats sont tous de nature corrélationnelle, seulement. Ainsi, le but de cette thèse est d'identifier le stade de sommeil durant lequel la consolidation d'une nouvelle mémoire motrice séquentielle à lieu et de définir le rôle des FS dans ce processus. Afin d'aborder ces objectifs, nous avons pairé une tâche d'apprentissage moteur séquentiel (AMS) à un paradigme olfactif de réactivation ciblée de la mémoire (RCM). Les participants ont été entrainés à la tâche d'AMS tout en étant exposé à une odeur. Cette même odeur leur a été présenté durant le sommeil afin de servir d'indice contextuel et ainsi réactiver la trace mnésique de la tâche nouvellement apprise. Enfin, au matin, leur niveau de consolidation a été mesuré à l'aide d'une session de retest à la même tâche. La première étude s'est intéressée au rôle des stades de sommeil principalement par la comparaison entre les gains en performance motrice entre les groupes indicés durant le stade de SNP2 ou de sommeil paradoxal (SP), ainsi que sur l'effet de l'indiçage sur les FS. Les résultats ont démontré que les participants conditionnés et indicés en stade de SNP2 avaient des gains en performance significativement plus élevés au retest que ceux indicés en SP ou ceux qui n'avaient pas été conditionnés à l'odeur. De plus, nous avons observé que l'indiçage entrainait des augmentations plus importantes en fréquence et amplitude des FS pariétaux chez le groupe indicé durant le SNP2. Finalement, nos résultats ont démontré que ces changements en fréquence prédisaient le degré des gains en performance des sujets. Au cours de la seconde étude nous avons exploré comment les FS pariétaux du SNP2 interagissaient avec différentes bandes de fréquence voisines localement et entre diverses régions corticales (connectivité). Les résultats ont démontré que la stimulation RCM avait instigué des augmentations d'activité concomitante dans des bandes de basse fréquence (delta [1-4 Hz], theta [4-8 Hz]) précédant et suivant les FS, et

des augmentations dans la bande haut-bêta (25-30 Hz) pendant les FS. Ces changements ont été identifiés particulièrement au-dessus de régions corticales motrices et associatives. Nous avons aussi rapporté des hausses de la connectivité entre régions associées à l'apprentissage d'une tâche d'AMS, ainsi que des augmentations globales dans les bandes delta et thêta. Ensemble, ces deux études ont souligné l'importance du sommeil et de certains de ces constituants, c'est-à-dire le stade de SNP2 et les FS, dans la consolidation de mémoires motrices séquentielles. En effet, elles ont fait la démonstration qu'une nouvelle trace mnésique pouvait être réactivée et consolidée durant le SNP2 à l'aide d'un stimulus olfactif conditionné, menant ultimement à une performance motrice améliorée au-delà de ce qui est normalement observé, alors que le même effet est absent en SP. Cette thèse a établi que les FS sont instrumentaux au processus de consolidation bien que leur effet soit dépendant d'interrelations complexes locales et interrégionales avec d'autres bandes de fréquence, incluant le delta, thêta et haut-bêta. Ainsi, elle met les fondations pour une étude efficace du rôle des FS dans la consolidation de la mémoire au sein de leurs contextes temporal, topographique et fréquentiel.

Mots-clés : consolidation, mémoire motrice séquentielle, sommeil, sommeil non-paradoxal, sommeil paradoxal, fuseau de sommeil, delta, thêta, haut-beta

Abstract

From infancy to old age, motor learning is part of our everyday life. After learning a new motor skill, our brain continues to reinforce its memory trace. This process is known as "memory consolidation", in which sleep is thought to be a key period. However, there is still no consensus concerning the sleep stage when consolidation of a motor sequence memory trace takes place, although there is increasing evidence pointing towards stage-2 non-rapid eye movement (NREM2) sleep. Some of this evidence suggests that sleep spindles, hallmark features of NREM sleep, are associated with improvement in consolidation. Yet, these reports are only correlational in nature. Hence, the aim of this thesis is to identify the sleep stage during which motor sequence consolidation occurs and define the involvement of sleep spindles in this process. To tackle these objectives, we used a finger tapping task paired to an olfactory targeted memory reactivation (TMR) paradigm. Participants were trained to a motor sequence learning (MSL) task while being exposed to an odor. The same olfactory stimulus was used during sleep as a cue to reactivate the memory trace of the newly learned motor task. In the morning, consolidation was assessed through a retest session of the same task. The first study probed the role of sleep stages by comparing motor performance gains between groups cued in NREM2 and rapid eye movements (REM) sleep. It also assessed the effect of cuing on sleep spindles characteristics. Results showed that participants cued during NREM2 sleep showed greater gains in performance at retest than those cued during REM sleep or those not conditioned but exposed during NREM2 sleep. Furthermore, they demonstrated that cuing led to increases in frequency and amplitude of parietal sleep spindles only. Finally, we found that cue-related changes in specific spindle frequency bands predicted the overnight gains in performance. In the second study, building on our previous findings, we investigated how parietal NREM2 sleep spindles interact with other frequency bands locally and between cortical regions (connectivity). Results showed that TMR stimulation instigated increases of concomitant activity in lower frequency bands (delta [1-4 Hz], theta [4-8 Hz]) preceding and following spindles, and increases within the high-beta (25-30 Hz) band during spindles. These changes were found particularly over motor and associative areas. We also reported enhanced connectivity between task-related regions in the sigma band as well as widespread increases in the delta and theta bands. Together, both studies demonstrated the importance of sleep and its constituents, namely NREM2 sleep

and spindles, in the consolidation of motor sequence memories. Indeed, they showed that the newly learned memory trace can be reinforced during NREM2 by the use of an olfactory stimulus leading ultimately to an enhanced motor performance in the morning over and above normal behaviour, while the same effect does not appear to occur with REM sleep. They also demonstrated that sleep spindles are instrumental to the consolidation process although its effect relies on a complex interaction between multiple frequency bands, including delta, theta and high-beta, both locally and inter-regionally. Overall, this thesis underlines the significance of NREM2 sleep spindles' contribution to motor sequence consolidation. Importantly, building on decades of work, it lays the groundwork for studying the role of sleep spindles in memory consolidation within their temporal, topographical and frequential context.

Keywords : consolidation, sequential motor memory, sleep, non-rem sleep, rem sleep, sleep spindle, delta, theta, haut-beta

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Liste des abréviations

En français

AM : adaptation motrice

AMS : apprentissage moteur séquentiel

AOL : activité à onde lente

EEG : électroencéphalographique

FS : Fuseau de sommeil

nRT : noyau réticulaire thalamique

OL : oscillation lente

RCM : réactivation ciblée de la mémoire

SNP : sommeil non-paradoxal

SNP1 : stade 1 du sommeil non-paradoxal

SNP2 : stade 2 du sommeil non-paradoxal

SNP3 : stade 3 du sommeil non-paradoxal

SOL : sommeil à ondes lentes

SP : sommeil paradoxal

SWR : *sharp waves/ripple*

TC : thalamo-corticaux

(*Liste des abréviations, suite*)

En anglais

Δ%: percent of change

BMI: body mass index

Cond: experimental group conditioned to the olfactory stimulus and cued during NREM2 sleep

Cond-NREM2: experimental group conditioned to the olfactory stimulus and cued during NREM2 sleep

Cond-REM: experimental group conditioned to the olfactory stimulus and cued during REM sleep

EEG: electroencephalography

EMG: electromyography

EOG: electrooculography

ERSP: Event-related signal perturbations

ESD: extreme studentized deviate (statistical method)

fMRI/EEG: imaging technique combining functional magnetic resonance imaging and electroencephalography

GPI: global performance index

iCoh: imaginary part of coherency

MSL: motor sequence learning

NoCond: experimental group not previously conditioned to the olfactory stimulus but exposed to the odor during NREM2 sleep

NREM: non rapid eye movement sleep This sleep stage is comprised of four different sub-stages (1 to 4) However, the American Academy of Sleep Medicine now regroup stage 3 and 4 into a single stage : NREM3

PEA: phenyl ethyl alcohol

PSG: polysomnographic

REM: rapid eye movement sleep

SRTT: serial reaction-task

SO: slow oscillation

SWA: slow wave activity

SSS: Standford Sleepiness Scale questionnaire

SWS: slow wave sleep (stage 3 and 4 sleep, also known as NREM3)

TMR: targeted memory reactivation

TST: total sleep time

TSP: total sleep period

SE: sleep efficiency

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Do not go gentle into that good night,
Old age should burn and rave at close of day;
Rage, rage against the dying of the light.

Though wise men at their end know dark is right,
Because their words had forked no lightning they
Do not go gentle into that good night.

(Dylan Thomas, 1952)

Chapitre I : Contexte théorique

1. Introduction générale

Porter un verre d'eau à nos lèvres nous apparait autant être un geste vital que simple et automatique. Pourtant, cette action consiste en une série de mouvements distincts et stéréotypés que nous avons appris, pratiqués et perfectionnés au fil des années. Ce type d'acquisition procédurale est connu sous le nom d'apprentissage moteur séquentiel. Il est maintenant reconnu que le sommeil joue un rôle important dans la consolidation de nouvelles mémoires motrices séquentielles — c'est-à-dire qu'il favorise le passage de ce type d'habileté, d'un stockage temporaire et labile, à une représentation à long terme et stable. Bien qu'il n'y ait pas encore de consensus définissant l'importance de chaque stade du sommeil dans ce processus de consolidation, il appert que les fuseaux de sommeil (FS) que l'on retrouve principalement durant le stade 2 du sommeil non-paradoxal (SNP2), constituent une composante cruciale de ce mécanisme. Leur rôle serait associé aux réactivations spontanées de nouvelles traces mnésiques qui se produisent pendant le sommeil. De plus, les connaissances actuelles suggèrent que les FS interagissent avec d'autres types d'oscillations afin de favoriser la consolidation de la mémoire. Cependant, à ce jour, aucune étude n'a encore démontré que la modulation des caractéristiques des fuseaux de sommeil a une influence sur le degré de consolidation de la trace mnésique d'une tâche nouvellement apprise. De plus, l'interaction entre les FS et d'autres types de fréquences dans le cadre de la réactivation d'une trace mnésique motrice reste à être étudiée. Ainsi, le premier volet de cette thèse vise à confirmer l'implication du sommeil non-paradoxal, et plus spécifiquement des FS, dans la consolidation de la mémoire motrice séquentielle. Le deuxième volet vise plutôt à observer les FS dans leur contexte topographique, fréquentiel et temporel, ainsi qu'à identifier les changements reliés à la réactivation de la trace mnésique motrice durant le sommeil.

2. Processus mnésiques moteurs

2.1 La mémoire procédurale

Il est généralement accepté de distinguer en deux grandes catégories les processus mnésiques : d'une part, la mémoire déclarative permettant de comprendre le monde qui nous entoure et de se souvenir du fils des événements vécus (Milner, 1968; Squire & Zola, 1998); d'autre part, la mémoire non-déclarative incluant l'apprentissage procédural (habiletés et habitudes motrices), le conditionnement classique, l'amorçage et l'apprentissage non-associatif. Tandis que la mémoire déclarative renvoie au "quoi", la mémoire procédurale détermine le "comment". Elle sous-tend non seulement le développement et l'apprentissage de mouvements volontaires ciblés, mais aussi la rétention et le perfectionnement de ces acquis, ainsi que les multiples facettes des troubles moteurs dus à des lésions ou au vieillissement normal.

La littérature scientifique utilise plusieurs classifications pour définir l'apprentissage moteur dépendant de ce qu'elle désire mesurer. L'une d'entre elles distingue deux types spécifiques, mais complémentaires d'apprentissages moteurs: l'adaptation motrice (AM) reflétant la compensation motrice face à des changements environnementaux, et l'apprentissage moteur séquentiel (AMS) définissant l'acquisition de mouvements séquentiels simples et stéréotypés en un mouvement complexe fluide et précis (Doyon, Bellec, et al., 2009). Dans le cadre de cette thèse, nous nous attarderons particulièrement à cette dernière forme d'apprentissage moteur.

2.2 L'apprentissage moteur séquentiel

Afin de refléter une certaine réalité écologique, l'étude des mécanismes qui sous-tendent l'AMS nécessite la production d'une séquence de mouvements soit implicitement ou explicitement connue du sujet. Lorsque la tâche utilisée est dite "implicite", le sujet apprend la séquence de façon non-consciente à travers la répétition de mouvements dirigés par des indices visuels ou sonores (Doyon, Owen, Petrides, Sziklas, & Evans, 1996; Grafton, Hazeltine, & Ivry, 1998; E M Robertson, Pascual-Leone, & Press, 2004). Au contraire, lors de l'administration

d'une tâche explicite, le sujet connaît la séquence à effectuer avant même de débuter l'entrainement (Doyon et al., 2002, 1996, Karni et al., 1995, 1998). Comme il le sera décrit plus loin, la nature implicite ou explicite de la tâche expérimentale définira en partie les réseaux neuronaux et structures cérébrales impliqués lors de la production et l'apprentissage de la séquence.

Le but d'un AMS étant de minimiser les contraintes cognitives dans l'exécution des mouvements (ex., analyse de la distance, rythmes, compensation physique), la production de séquences se fait à l'aide de tâches impliquant des mouvements simples avec un minimum de charge cognitive – telles la rétention d'information, l'exploration spatiale, l'adaptation motrice. Ainsi, ces tâches expérimentales peuvent comprendre l'exécution de mouvements doigts-à-pouce opposés (pincements) (Gabitov, Manor, & Karni, 2014; Karni et al., 1995, 1998), du bras (Doyon et al., 1996; Grafton et al., 1998), oculomoteurs (Albouy et al., 2006, 2008) ou des doigts en appuyant les boutons d'une boite de réponse (Doyon et al., 2002; Grafton, Hazeltine, & Ivry, 1995).

La progression de la performance à ces tâches est établie par l'identification des changements dans le temps requis pour compléter une séquence (vitesse), le nombre d'erreurs commis (précision) et/ou, la synergie et cinématique des mouvements (voir Doyon, 1997; Maquet, 2001 pour revue de littérature). Les changements dans la performance sont habituellement identifiés en comparant la valeur de ces mesures entre deux segments d'entrainement, soit durant la même session ou lors de deux sessions différentes. Ces changements sont reconnus comme étant de nature implicite et durable.

Il a été démontré que l'acquisition d'une habileté motrice se produit par le biais d'une série de phases d'apprentissage incrémentielles (Karni et al., 1998). Premièrement, se produisant durant l'entrainement initial, on retrouve une phase d'apprentissage rapide pendant laquelle sont observés des progrès importants sur toutes les mesures de performance. Cette phase rapide est généralement atteinte lors de la première séance d'entrainement d'une nouvelle tâche motrice séquentielle. Deuxièmement, la performance des sujets atteint une phase lente de l'apprentissage, durant laquelle le sujet continue de s'améliorer au cours de nombreuses sessions de pratique, par une constante et lente progression – en comparaison à celle de la phase rapide. Ces deux phases représentent des processus mnésiques dits *en ligne*, c'est-à-dire, se produisant

durant l'exécution de la tâche. Il existe une troisième phase, dite *hors-ligne*, se produisant après une session d'apprentissage représentant une fenêtre temporelle où ont lieu plusieurs processus neuronaux reliés à la consolidation des traces mnésiques en lien avec l'exécution de la tâche d'AMS (Karni & Sagi, 1993; Walker, 2005).

2.3 Consolidation de la mémoire

Le principe de *consolidation de la mémoire* a été avancé pour la première fois par Müller et Pilzecker (1900), et ce suite à leurs observations concernant les processus d'interférences dans la rétention de listes de syllabes. Depuis, cette hypothèse a été largement acceptée et démontrée par des études psychologiques, pharmacologiques, comportementales et électrophysiologiques chez l'animal et l'humain (voir revues Cahill & McGaugh, 1996; Chorover, 1976; McGaugh, 2000; Squire, Genzel, Wixted, & Morris, 2015; Wixted, 2004). Pour qu'un apprentissage soit dit "consolidé", certains critères doivent être rencontrés. D'une part, la performance à cette tâche ne doit pas être influencée négativement par l'apprentissage d'une nouvelle séquence de mouvements différente. On appelle ceci la résistance à l'interférence (Balas, Netser, Giladi, & Karni, 2007; Herszage & Censor, 2017; E M Robertson, 2012). D'autre part, pour que la consolidation d'un apprentissage moteur séquentiel soit complète, il doit aussi y avoir un transfert des habiletés acquises, d'une séance à l'autre, et ce malgré le passage du temps. Ainsi, la performance d'un sujet normal accomplissant une tâche AMS devrait être similaire lorsque l'on compare les derniers blocs d'un entrainement aux premiers d'une séance qui lui succède. Finalement, lorsqu'un apprentissage est consolidé, la production des mouvements est dite automatisée, puisqu'elle requiert très peu d'effort et de ressources attentionnelles (Doyon, Bellec, et al., 2009).

Ce processus de consolidation sous-tend des changements synaptiques structurels et physiologiques se produisant peu après le début de l'apprentissage d'une nouvelle tâche et se poursuivant immédiatement après celui-ci (Dudai, 2004, 2006). Après l'apprentissage, et ce durant plusieurs heures, voire jours, les nouvelles traces mnésiques sont créées par des altérations dans la transmission synaptique excitatrice qui est associée au glutamate. Cette activité électrique réverbérante à travers le réseau soutenant une nouvelle trace mnésique

entraîne les processus de deux mécanismes de consolidation dits synaptique et systémique (Dudai, 2004). Dans un premier lieu, la consolidation synaptique transforme les connexions synaptiques et dendritiques des neurones participant à la représentation mnémonique de la trace (voir revues Hofer, 2010; Kandel, 2001). De plus, l'activité neuronale produite lors de ces changements synaptiques soutenant la représentation de la nouvelle trace mnésique permet son stockage à long-terme à travers divers systèmes interconnectés; ce processus de plus au niveau est ce que l'on nomme la consolidation systémique (Frey & Morris, 1998). Ultimement, ce processus de consolidation mènera à l'automatisation de l'habileté motrice.

2.4 Un modèle de l'apprentissage moteur séquentiel

En se basant principalement sur les résultats d'études d'imagerie fonctionnelle, Doyon et collègues (2009; 2005; 2003) ont proposé un modèle théorique décrivant les systèmes et structures actifs lors des différentes étapes de consolidation tout en tenant compte de la nature de la tâche d'apprentissage moteur (AM ou AMS). Ce modèle suggère qu'au début de l'entrainement, soit durant la phase rapide d'encodage, l'AMS recrute le striatum, le cervelet, l'hippocampe, les régions corticales motrices ainsi que les cortex préfrontal et pariétal (Albouy et al., 2015; Albouy, King, Maquet, & Doyon, 2013; Doyon et al., 2002; Floyer-Lea & Matthews, 2004; Lehéricy et al., 2005; Schendan, Searl, Melrose, & Stern, 2003). Durant ce stade initial, ces régions interagissent dynamiquement entre elles afin d'établir la base nécessaire à la production, l'amélioration et l'apprentissage de la tâche. Lorsque la trace mnésique est consolidée, la représentation motrice de la séquence est alors distribuée dans un réseau cortico-striatal, comprenant le striatum et les régions corticales associées (Albouy, King, et al., 2013). Enfin, lorsque la trace mnésique est rappelée, même après un longue période sans pratique, le modèle propose que c'est ce même réseau cortico-striatal qui sera réactivé (Doyon, Bellec, et al., 2009; Doyon et al., 2003).

3. Le sommeil et la mémoire motrice séquentielle

3.1 Le sommeil

Le sommeil représente l'un des deux états, avec l'éveil, que l'on expérimente lors d'une journée normale. Il se définit comme étant un état naturel et réversible, d'inactivité et de baisse de sensibilité aux stimuli externes, que l'on retrouve chez pratiquement toutes les espèces animales (Cirelli & Tononi, 2008). Il apparait en intervalles réguliers régulés de façon homéostatique – c'est-à-dire qu'un manque ou un délai dans son initiation produira un effet de rebond, entrainant un sommeil prolongé durant le cycle suivant (Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981). Chez l'humain, on distingue plusieurs phases de sommeil, dont deux principales, soit le sommeil paradoxal (SP) et le sommeil non-paradoxal (SNP). Le SNP se décompose lui-même en trois stades se distinguant chacun par le type d'activité cérébrale que l'on peut observer à l'aide de tracés électroencéphalographiques (EEG) (Iber, Ancoli-Israel, Chesson Jr., & Quan, 2007). Le passage de l'éveil au sommeil se fait habituellement via une phase plus ou moins courte de sommeil non-paradoxal 1 (SNP1). Au fur et à mesure que l'état de sommeil devient plus profond, l'activité corticale change et le SNP1 fait place au stade de sommeil non-paradoxal 2 (SNP2). Chez l'humain, ce dernier constitue la majorité du sommeil durant une nuit normale et se distingue par la présence d'événements EEG particuliers appelés, fuseaux de sommeil (voir section 4.1) et complexes K (ondes rapides de grande amplitude). Succédant au SNP2, le sommeil non-paradoxal 3 (SNP3) ou sommeil à ondes lentes (SOL) est caractérisé par l'abondante présence d'ondes lentes de grande amplitude et est particulièrement présent au début de la nuit lorsque la pression de sommeil est élevée. Finalement, le stade de SP est une période particulière du sommeil où l'on retrouve une activité globale désynchronisée et plusieurs changements physiologiques, dont la présence d'atonie et de mouvements des yeux rapides. Contrairement au SOL la durée des intervalles de SP s'accroit au fil de la nuit.

3.2 Sommeil et consolidation de la mémoire

Le concept du sommeil, agissant comme agent facilitateur dans la consolidation des apprentissages, date du début du 20^{e} siècle (Jenkins & Dallenbach, 1924). Depuis, de

nombreuses études ont démontré les effets bénéfiques du sommeil sur la rétention et la consolidation des mémoires déclaratives, non-déclaratives et même, émotionnelles (voir revues Diekelmann & Born, 2010; Rasch & Born, 2013). Cette attention particulière au rôle du sommeil dans la consolidation a engendré un débat quant à savoir si ces effets sur l'apprentissage étaient causés par une influence passive (protection contre les interférences) ou active (réactivation et renforcement menant à des gains mnésiques) (Ellenbogen, Payne, & Stickgold, 2006; Rickard, Cai, Rieth, Jones, & Ard, 2008). Ce débat n'est toujours pas clos, cependant, il appert que pour certains types de tâches, comme l'AMS par exemple, le sommeil jouerait un rôle actif dans la consolidation de l'apprentissage (Albouy et al., 2015; Albouy, Fogel, et al., 2013; Backhaus & Junghanns, 2006; Brown & Robertson, 2007; Cai & Rickard, 2009; Djonlagic, Saboisky, Carusona, Stickgold, & Malhotra, 2012; Doyon, Korman, et al., 2009; Fenn & Hambrick, 2012; Fischer, Hallschmid, Elsner, & Born, 2002; Gais, Rasch, Wagner, & Born, 2008; King et al., 2016; Korman et al., 2007; Kuriyama, Stickgold, & Walker, 2004; Plihal & Born, 1997; E M Robertson, Pascual-Leone, & Press, 2004; Walker et al., 2003; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002; Witt, Margraf, Bieber, Born, & Deuschl, 2010).

Une fois qu'a été établi l'effet bénéfique du sommeil dans la rétention et consolidation de plusieurs types d'apprentissages, les chercheurs ont tenté d'identifier si le processus de consolidation se produisait pendant un stade de sommeil spécifique. Bien que certaines des premières études utilisant des tâches motrices implicites (Cajochen et al., 2004; Robertson, Pascual-Leone, & Press, 2004) et explicites (Fischer et al., 2002; Plihal & Born, 1997) suggéraient que le SP supportait la consolidation, il y a maintenant de plus en plus d'évidences identifiant plutôt le SNP comme moteur principal dans ce processus (Doyon, 2008; Doyon, Korman, et al., 2009; Korman et al., 2007; Maquet, 2001; Walker, 2005; Walker et al., 2002). Il semble en effet que dans les cas où la séquence motrice est explicitement connue des sujets, des gains différés de performance apparaissent lorsqu'une période de sommeil entrecoupe l'entrainement initial et le retest. C'est-à-dire, qu'en comparaison avec la performance à la fin de l'entrainement, les sujets sont plus rapides à faire la séquence au début du retest. En outre, ces gains différés ont été associés à des modifications au niveau d'un des événements caractéristiques du SNP: le fuseau de sommeil (Barakat et al., 2011, 2012; Morin et al., 2008; Nishida & Walker, 2007). Ainsi, malgré l'accumulation d'indices supportant le rôle marqué du

SNP dans la consolidation de la mémoire motrice séquentielle, il n'existe pas encore, à ce jour, de consensus quant au stade de sommeil sous-tendant ce processus.

4. Les fuseaux de sommeil et la mémoire motrice séquentielle

4.1. Les fuseaux de sommeil

Le FS est une caractéristique électroencéphalographique distinctive du SNP. Il a été décrit pour la première fois en 1929 par Dr Berger (1929), mais ce n'est que des années plus tard qu'on lui donna le nom de "fuseau de sommeil", décrivant ainsi sa forme particulière rappelant un fuseau de couture (Loomis, Harvey, & Hobart, 1935). Un FS consiste en un regroupement d'oscillations ayant une progression d'amplitude caractérisée par une "inflation suivie d'une déflation", et a été tout d'abord décrit chez l'humain comme étant d'une durée de 0.5 à 2 secondes et ayant une fréquence d'oscillation de 12 à 14 Hz (Rechtschaffen & Kales, 1968). L'apparition de détecteurs automatiques, beaucoup plus sensibles que l'œil humain, a cependant modifié les paramètres de durée et fréquence permettant d'identifier les FS. Malgré le fait qu'il n'existe pas encore de standardisation des valeurs à utiliser, il est maintenant généralement accepté que, chez l'humain, les fuseaux peuvent avoir une durée entre 0.2 à 3 secondes et une fréquence moyenne entre 11 et 18 Hz (Andrillon et al., 2011; Astori, Wimmer, & Lüthi, 2013; Clawson, Durkin, & Aton, 2016; Fogel et al., 2012; Siapas & Wilson, 1998; Ulrich & Daniel, 2016). On retrouve des FS exclusivement durant le SNP bien qu'ils soient particulièrement plus nombreux durant le SNP2 (Luigi De Gennaro & Ferrara, 2003). D'ailleurs, les SP consistent en un des événements clés dans l'identification du SNP2 lors de l'identification des stades de sommeil. La densité moins élevée des FS durant les périodes de stade 3 de sommeil (SNP3) peut être expliquée par la plus grande quantité d'ondes lentes durant ce stade, d'où provient la dénomination de ce stade "sommeil à ondes lentes" (SOL). En effet, la densité (événements/minutes) des FS est inversement corrélée à celle des ondes lentes.

4.2 Neuro-dynamique des fuseaux de sommeil

Les mécanismes neuronaux qui sous-tendent la génération et le maintien des fuseaux de sommeil ont fait objet d'études *in vitro*, *in vivo* et *in computo*, et sont maintenant clairement identifiés (Andrillon et al., 2011; Beenhakker & Huguenard, 2009; Bonjean et al., 2011; Fuentealba, Timofeev, Bazhenov, Sejnowski, & Steriade, 2005; M Steriade, 2005). La génération d'un fuseau se produit à travers l'interaction de neurones thalamo-corticaux (TC) et du noyau réticulaire thalamique (nRT). Le nRT consiste en une mince couche de neurones GABAergique entourant la partie dorsale du thalamus. Cet ensemble de neurones a la capacité de générer semi-indépendamment des décharges hautement synchrones et ce, sur plusieurs cycles successifs, déclenchants par le fait même un FS. Le SNP est une période propice à l'apparition de ces décharges due à l'hyperpolarisation relative du potentiel membranaire des neurones nRT (Destexhe, Contreras, Sejnowski, & Steriade, 1994; Destexhe & Sejnowski, 2001). Bien que les neurones du nRT aient la capacité de produire des rythmes semblables à des fuseaux de façon indépendante, la génération et le maintien des FS sont le produit d'interactions coordonnées à l'intérieur d'un réseau bien défini. Ainsi, les décharges provenant du nRT provoquent une hyperpolarisation transitoire des neurones TC, entrainant une série d'événements post-synaptiques dans ces derniers. Tout d'abord, une inhibition induite par des récepteurs GABA bloque la génération de nouveaux influx nerveux. Ceci produit alors une hyperpolarisation de la membrane, entrainant à la fois, une activation du courant rectifiant entrant cationique et une désinhibition du courant calcique de type T. Ce courant "pacemaker" engendre une dépolarisation rapide déclenchant ainsi des décharges de potentiels d'action (Clawson et al., 2016; McCormick & Bal, 1997). Finalement, ces décharges mènent à une salve d'inputs excitatrices atteignant les cibles des neurones du TC dans le nRT et le cortex, conduisant à une nouvelle décharge d'influx nerveux des neurones du nRT et amorçant ainsi un nouveau cycle, et par le fait même créant l'oscillation typique du FS.

Bien que la génération des FS découle de la circuiterie intra-thalamique, ses déclencheurs peuvent provenir de sources externes. En effet, dès leur découverte, il était reconnu que des stimuli auditifs induits durant le sommeil pouvaient engendrer des FS (Berger, 1929). Plus récemment, se basant sur le modèle de Destexhe et collègues (2001) et investiguant l'existence de déclencheurs neuronaux externes, plusieurs études ont démontré que des cellules

pyramidales cortico-thalamiques de la couche 6 du cortex formaient une importante partie des inputs excitateurs du nRT (Fuentealba & Steriade, 2005; Fuentealba et al., 2005). Bonjean et collègues (2011) ont par la suite confirmé cette hypothèse à l'aide de modèles *in computo* et *in vivo*. Ils conclurent que des pointes d'activités provenant de neurones TC produisaient des salves d'activité dans le nRT lors de l'amorçage d'un fuseau. De plus, leurs résultats ont démontré que sans une excitation cortico-thalamique continue, le réseau thalamique est incapable de soutenir une activité continue de fréquence sigma (11-16 Hz) de part lui-même.

4.3 Fuseaux de sommeil et apprentissage moteur

Dans la foulée des études investiguant l'impact du sommeil sur l'apprentissage, plusieurs d'entre elles, utilisant des tâches déclaratives, ont conclu que les FS avaient un rôle à jouer dans la consolidation de ce type de mémoire (Maquet, 2001; Sejnowski & Destexhe, 2000; R Stickgold, Hobson, Fosse, & Fosse, 2001). Pour sa part, la relation entre apprentissage moteur et FS a tout d'abord été rapportée à l'aide de tâches d'AM. En effet, ces études ont montré que suite à un entrainement à 4 différentes tâches d'adaptation motrices, la densité (Fogel & Smith, 2006) ainsi que la durée (Fogel, Smith, & Cote, 2007) des FS augmentaient, et que la progression observée de la performance à ces tâches expliquait les changements mesurés dans les fuseaux. Ce n'est que par la suite que Nishida et Walker (2007) ont démontré que les gains moteurs *hors lignes,* mesurés après l'apprentissage d'une tâche d'AMS, précédant une sieste d'environ 90 minutes, corrélaient avec la densité latéralisée des FS centraux-droits, contra-latéraux à la main qui avait effectué la tâche. Succédant à ces études, plusieurs autres ont observé des augmentations dans la durée et la densité des fuseaux suivant l'entrainement à une nouvelle tâche d'AMS, certains rapportant que ces mêmes changements prédisaient la performance à la tâche après le sommeil (Albouy, Fogel, et al., 2013; Barakat et al., 2011, 2012, Fogel et al., 2014, 2017; Genzel et al., 2012; Morin et al., 2008; Saletin, Coon, & Carskadon, 2017). Ensemble, ces données suggèrent que les FS jouent un rôle important dans la consolidation de la mémoire motrice séquentielle.

5. Interaction entre les fuseaux de sommeil et autres oscillations dans le contexte de la consolidation de la mémoire

L'étude des oscillations détectées par les potentiels de champs en EEG a défini au moins deux autres types d'événements apparaissant régulièrement de façon synchrone avec les FS: l'activité à ondes lentes (AOL) et les « *sharp waves/ripples* (SWRs) ».

5.1 L'activité à ondes lentes

Dans l'étude du sommeil chez l'humain, deux types d'oscillations définissent l'AOL. D'abord, les oscillations lentes (< 1 Hz), générées à même le néocortex, représentent l'événement EEG principal du stade de SOL, bien que l'on en retrouve aussi en SNP2 (Achermann & Borbély, 1997). Les OL synchronisent l'activité corticale suivant deux phases distinctes (M Steriade, 2006). En premier lieu, une phase d'inactivité neuronale due à une hyperpolarisation généralisée (*down-state*). Cette phase de silence neuronale est suivie d'une dépolarisation globale et simultanée de grands ensembles de neurones (*up-state*). L'amplitude et la pente de l'AOL, telles que définies par les tracés EEG, sont associées au nombre de neurones entrant un *up-state* ou *down-state* simultanément. Par ailleurs, la synchronie de l'AOL est directement reliée à la qualité (i.e., nombre, robustesse, distribution) des connections synaptiques entres ces neurones (Esser, Hill, & Tononi, 2007; Olcese, Esser, & Tononi, 2010; Tononi & Cirelli, 2014).

Il existe un autre type d'activité lente que l'on retrouve durant le SNP et appelé onde delta (1-4 Hz). Au lieu d'une origine corticale, ces oscillations seraient générées par l'hyperpolarisation des neurones thalamo-corticaux (TC), partageant avec les FS, le même générateur(Steriade, 2006; Steriade, McCormick, & Sejnowski, 1993). Le critère définissant le type d'onde généré par l'activité des neurones TC serait relié au niveau de potentialisation de la membrane : autour de -60 mV, les neurones TC oscilleraient dans la bande sigma alors qu'en dessous de -65 mV ils produiraient des ondes dans la bande delta (Steriade & McCarley, 1990). Ainsi, la génération des ondes delta et FS ne se produirait pas de façon simultanée, mais plutôt

en séquence (Mölle, Marshall, Gais, & Born, 2002), telle l'apparition de FS suivant ou précédant les complexes-K — un type d'onde delta caractéristique du SNP2.

5.2 Les sharp waves/ripples

Les SWRs proviennent de la combinaison de deux événements d'origine hippocampique. D'une part, les *sharp waves* générées dans la région hippocampique CA3 résultent d'une dépolarisation subite et de grande amplitude. Simultanément, celles-ci sont superposées à des oscillations de hautes-fréquences (100-300 Hz), nommées *ripples*, engendrées par l'interaction entre des interneurones inhibiteurs et cellules pyramidales de la région CA1. Ces SWRs sont présentes aussi bien en éveil qu'en SNP; depuis plusieurs années nous savons que, pendant le sommeil, leurs apparitions coïncident avec la réactivation d'ensembles de neurones actifs durant les apprentissages faits à l'éveil (Buzsáki, 1989; Karlsson & Frank, 2009; Nádasdy, Hirase, Czurkó, Csicsvari, & Buzsáki, 1999; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009; Wilson & McNaughton, 1994a). Par ailleurs, il a été démontré chez l'animal que les neurones corticaux déchargeant dans la bande gamma pouvaient moduler leur fréquence à la bande bêta en un très court laps de temps, grâce à de faibles dépolarisations (Steriade, Amzica, & Contreras, 1996). Chez l'humain, des études ont aussi rapporté qu'il n'y avait pas de séparation définie entre bêta et gamma lors de différents types de tâche de mnésique (Palva, Palva, & Kaila, 2005; Slotnick, Moo, Kraut, Lesser, & Hart, 2002).

5.3 Interactions entre fuseaux du sommeil, activité à ondes lentes et sharp waves/ripples

Les SWRs seraient temporellement reliées aux FS puisqu'on les retrouve aux creux des oscillations des FS (Siapas & Wilson, 1998). Il a été proposé que cette interaction, entre FS et SWRs, serait cruciale pour le transfert d'information de l'hippocampe au cortex, la réactivation d'une trace mnésique hippocampique ayant lieu exactement durant les périodes excitatrices des FS (Buzsàki, 1998; Marshall & Born, 2007; Sirota, Csicsvari, Buhl, & Buzsáki, 2003). De plus,

autant chez l'animal que chez l'humain, il a été démontré que le nombre d'ondes delta, de FS et SWRs augmente durant les *up-states* des OL alors qu'il diminue durant les *down-state* (Clemens et al., 2007; Klinzing et al., 2016; Mölle et al., 2002; Mölle, Yeshenko, Marshall, Sara, & Born, 2006; Sirota et al., 2003; Steriade, 2006). Étant caractérisée par une dépolarisation généralisée, la période de *up-state* représente un moment opportun à l'instigation de changements synaptiques. Ainsi, l'OL serviraient en quelque sorte de métronome cortical facilitant la génération d'ondes rapides synchrones, d'origines hippocampiques (SWRs) et thalamiques (FS et delta), et par le fait même, permettraient la consolidation en mémoire à long terme d'une nouvelle trace mnésique (Buzsáki, 2015; Diekelmann & Born, 2010; Genzel, Kroes, Dresler, & Battaglia, 2014; Maingret, Girardeau, Todorova, & Goutierre, 2016; Staresina et al., 2015).

Cette interaction entre FS, OL et SWRs est au cœur même de la théorie de la "consolidation systémique active" telle que proposée par Marshall et Born (2007). Celle-ci suggère qu'au lieu de jouer un rôle passif (protection contre l'interférence), le sommeil aurait un rôle actif dans la consolidation de la mémoire. Ainsi, les mémoires nouvellement créées, durant la période d'éveil précédent le sommeil, seraient réactivées durant le SNP afin de les faire passer à un stockage à long-terme. Cette théorie propose que la consolidation de la mémoire se produirait à travers l'activité neuronale simultanée (FS, AOL et SWRs) impliquant plusieurs régions (hippocampe, thalamus, cortex) associées dans l'apprentissage. Bien que plusieurs études semblent appuyer ce modèle (Buzsàki, 1998; Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009; Ji & Wilson, 2007; Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009; Mednick et al., 2013; Mölle & Born, 2009; Peyrache et al., 2009; Ramanathan, Gulati, & Ganguly, 2015; Rasch, Büchel, Gais, & Born, 2007), les interactions des FS avec d'autres types d'ondes fréquentielles, dans le cadre de la réactivation et la consolidation de la mémoire motrice séquentielle, sont encore peu comprises. De plus, ce modèle se base presqu'entièrement sur des études analysant seulement le sommeil profond (SNP3) et ignorant le SNP2, où l'interaction entre les différentes ondes décrites ci-haut est différente. En effet, alors que le SNP3 est composé d'une prédominance d'ondes lentes et delta (> 20%), celles-ci apparaissent en moins grand nombre durant le SNP2 (< 20%). Plutôt, ce sont les FS et les SWRs qui dominent durant ce stade, entrecoupés de volés éparses d'ondes delta (particulièrement les complexes-K). Ainsi, l'interaction entre ces différentes ondes, propre au SNP2, reste à être élucidé.

6. La réactivation ciblée de la mémoire durant le sommeil

L'une des principales critiques vis-à-vis le rôle du SNP et des fuseaux de sommeil dans la consolidation de la mémoire motrice est qu'à ce jour, les preuves accumulées sont de nature corrélationnelle, et non causale. En effet, outre une étude utilisant un design de suppression pharmacologique du SP (Rasch, Pommer, Diekelmann, & Born, 2009) et une autre de privation de SP (Genzel, Dresler, Wehrle, Grözinger, & Steiger, 2009), aucune n'a effectivement manipulé les caractéristiques des stades de sommeil ou des fuseaux suivant une tâche d'AMS. Afin de répondre en partie à cette lacune, des chercheurs ont utilisé un paradigme combinant un conditionnement entre un stimulus sensoriel (olfactif ou auditif) et un nouvel apprentissage, et une stimulation successive (indicée) durant le sommeil. Ce type de paradigme est appelé *réactivation ciblée de la mémoire* (RCM). Durant la période de stimulation pendant le sommeil, le stimulus joue le rôle d'indice contextuel afin de réactiver la trace mnésique de l'apprentissage associée à celui-ci. Initialement, ce type de protocole expérimental a été utilisé dans les années 80 par des chercheurs français (Guerrien, Dujardin, Mandal, Sockeel, & Leconte, 1989) et canadiens (Smith & Weeden, 1990) tentant d'améliorer la mémoire déclarative à l'aide de stimuli auditifs durant le SP.

Ce n'est que 17 ans plus tard que Rasch et collègues (2007), dans une étude innovatrice, ont réutilisé ce type de paradigme couplé à une tâche d'AMS. Ils ont premièrement exposé leurs participants à une odeur florale (rose) pendant que ceux-ci accomplissaient deux tâches successives (visuospatiale [déclarative] et AMS [procédurale]). Par la suite, pendant qu'ils dormaient, les sujets ont été réexposés à la même odeur en stade de SOL ou SP. Leur hypothèse concernant la tâche motrice était que la réexposition en SP, et non en SOL, allait avoir un impact sur la performance à l'AMS, au retest, le matin suivant. Contrairement à ce qu'ils avaient prédit, la stimulation en SP (et en SOL) n'a produit aucun gain différé à l'AMS. Cependant, des gains ont été observés pour la tâche déclarative indicée durant la période de SOL. Deux principales raisons peuvent expliquer l'absence de gains différés pour la tâche AMS dans cette étude. Premièrement, tous les participants avaient préalablement accompli de façon successive deux tâches de nature différente, dans le même ordre, tout en étant exposés à l'indice olfactif. Puisque

la présence d'une odeur produit une habituation physiologique au bout de seulement quelques minutes seulement d'exposition et que, dans tous les cas, la tâche déclarative était pratiquée avant la tâche motrice, il est possible que l'association entre la tâche et l'odeur n'a été réussi exclusivement que pour la tâche visuospatiale. De plus, comme il a été précisé dans une section précédente, bien que les FS soient présents aussi durant le stade de SOL, ils sont beaucoup plus nombreux en SNP2. Étant donné que l'on suspecte les FS de jouer un rôle important dans la consolidation de la mémoire motrice séquentielle, il est raisonnable de penser qu'une exposition en SOL, et non en SNP2, n'est pas suffisante pour générer des gains différés au retest.

La publication des résultats de cette étude raviva l'intérêt pour l'utilisation de paradigmes de type RCM. Ainsi, cela amena d'autres chercheurs à tenter de réactiver la trace mnésique d'apprentissages moteurs séquentiels, mais cette fois en utilisant des stimuli auditifs (Antony, Gobel, O'Hare, Reber, & Paller, 2012; Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2014; Schönauer, Geisler, & Gais, 2014). Leurs résultats ont démontré qu'il est possible de produire des gains différés en stimulant les sujets durant le sommeil sans distinction de stade (Schönauer et al., 2014) ou pendant le stade SOL (Antony et al., 2012; Cousins et al., 2014). Ces deux dernières études ont rapporté des corrélations entre les FS et les gains différés. Cependant, aucune de ces études n'a réussi à générer un changement au niveau des caractéristiques propres aux FS (amplitude, durée, fréquence, densité). De plus, tout comme lors de l'étude initiale de Rasch et collègues, la réexposition aux stimuli ne ciblait pas spécifiquement le stade SNP2.

7. Problématique

Le sommeil joue un rôle crucial dans la consolidation des apprentissages moteurs séquentiels (Diekelmann & Born, 2010; Walker et al., 2002), particulièrement lorsque la tâche est connue explicitement par le sujet. L'un des mécanismes sous-jacents impliquerait les FS via une interaction complexe et temporellement dépendante avec d'autres types d'oscillation (Albouy et al., 2015; Marshall & Born, 2007; Morin et al., 2008; Nishida & Walker, 2007).

À ce jour, aucune expérimentation utilisant un protocole olfactif de RMC et une tâche d'AMS n'a observé de gains différés chez le groupe indicé durant le sommeil. Aussi, bien que

les indices s'accumulent démontrant une ségrégation des rôles des stades de sommeil dans la consolidation de la mémoire motrice séquentielle, il n'existe pas encore de consensus afin de départager l'implication du SNP2 et du SP. Une partie des preuves existantes soutenant le rôle du sommeil dans ce type de consolidation s'appuient sur l'impact d'un AMS sur les FS pendant la période de sommeil succédant à l'entrainement initial. De plus, à ce jour, les résultats liant les FS à la consolidation sont uniquement de nature corrélationnelle. En effet, aucune étude n'a encore réussi à démontrer que la réactivation d'une trace mnésique durant le sommeil est à la fois associée à des gains de performance et des changements au niveau des caractéristiques des FS. En conjonction avec cette dernière lacune, nous ne savons pas s'il existe une région corticale spécifique où la modulation de l'activité provenant des FS est liée aux gains différés à une tâche d'AMS. En outre, aucune étude n'a déterminé s'il existe une interaction entre l'activité corticale générée par les FS et d'autres types d'ondes (ou bandes de fréquences) dans le contexte d'une réactivation d'une trace mnésique. Pareillement, il reste encore à déterminer l'effet de l'indiçage d'un stimulus conditionné sur l'activité corticale concomitante à un FS (FS-simultanée) autant localement qu'au niveau de la connectivité entre différentes régions.

8. Objectifs et hypothèses

L'objectif général de la thèse est de confirmer et déterminer le rôle du stade de SNP2 et des fuseaux dans la consolidation de la mémoire motrice séquentielle. Pour ce faire, nous avons utilisé un paradigme expérimental olfactif de RCM couplé à l'apprentissage d'une tâche motrice séquentielle, précédant une nuit de sommeil complète et un retest à cette même tâche au levé. Nous avons demandé à un premier groupe de pratiquer une tâche d'AMS de nature explicite tout en les exposant à une odeur florale. Suivant cet entrainement, pendant leur sommeil, nous les avons réexposés à cette odeur en stade de SNP2 (soit dans la deuxième partie de la nuit) afin de réactiver la trace mnésique reliée à la tâche. Enfin, au levé, ils ont pratiqué à nouveau la même tâche afin de nous permettre d'identifier les changements au niveau de la performance. Afin de pouvoir comparer l'implication des stades SNP2 et SP dans la consolidation, un deuxième groupe a été soumis au même protocole à la seule différence que l'odeur a été présentée durant le stade SP et en fin de nuit, soit dans le période de sommeil plus apte à générer ce type d’activité

corticale. Finalement, un dernier groupe a été exposé à l'odeur durant le stade SNP2 sans y avoir été préalablement exposé durant la tâche motrice. Ce groupe allait permettre de contrôler pour des changements possibles et indéfinis, au niveau de l'architecture du sommeil ou des caractéristiques des FS, causés par l'exposition à une odeur durant le sommeil. Surtout, il rendait possibles les comparaisons entre groupes au niveau de la performance et des caractéristiques des FS.

8.1 Étude 1 : rôle du stade 2 du sommeil non-paradoxal et des fuseaux de sommeil dans la consolidation de la mémoire motrice séquentielle

Deux objectifs interdépendants étaient au centre de la première étude. Tout d'abord, elle avait comme première et essentielle mission de déterminer si l'exposition durant le SNP2 à un stimulus olfactif, précédemment associé à une tâche d'AMS, avait un effet positif et significatif sur la performance motrice, comparativement à celle succédant à une stimulation durant le stade SP ou à un stimulus non-conditionné. Par la suite, elle visait à observer l'effet de la réactivation de la nouvelle trace mnésique, provenant de l'AMS, sur les FS. En accord avec la littérature, nous prévoyions observer des gains différés pour chacun des groupes expérimentaux, mesure indirecte du niveau de consolidation. En outre, nous faisions l'hypothèse que le groupe conditionné à l'odeur durant la tâche d'AMS et indicé durant le stade de SNP2 présenterait des gains différés de performance significativement plus élevés que ceux du groupe réexposé en SP, et celui qui n'avait pas été conditionné. Également, il était attendu que l'indiçage durant le SNP2 produirait des changements au niveau des caractéristiques des FS et que ces derniers prédiraient le niveau des gains différés.

8.2 Étude 2 : interactions entre fuseaux de sommeil et autres fréquences lors de la réactivation d'une trace mnésique motrice

Se basant sur les résultats de l'étude précédente démontrant l'importance des FS d'origine pariétale, la seconde étude avait pour but d'identifier les changements fréquentiels

associés à ces mêmes FS pariétaux du SNP2 pendant la réactivation de la trace mnésique indicée. Plus particulièrement, celle-ci s'intéressait aux changements locaux (spectraux) et inter-régionaux (connectivité) concomitants à l'occurrence des FS durant l'indiçage. Pour ce faire, les mêmes deux groupes de l'étude précédente, stimulés durant le SNP2, ont été utilisés – c'est-à-dire un groupe conditionné durant la tâche et l'autre non. En tenant compte de l'effet de regroupement des FS et ondes delta produit par les ondes lentes, nous prévoyions observer des augmentations en puissance spectrale dans la bande delta (1 à 4 Hz) précédant et suivant les FS indicés, ainsi qu'une hausse dans la bande fréquentielle des FS (sigma) durant les fuseaux indicés, en comparaison avec les FS du groupe non conditionné. Finalement, des changements de connectivité entre régions corticales étaient anticipés dans la bande de fréquence des FS seulement chez le groupe conditionné.

Chapitre II : Méthodologie et résultats

Article 1: NREM2 and Sleep Spindles are Instrumental to the Consolidation of Motor Sequence Memories

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Abstract

Although numerous studies have convincingly demonstrated that sleep plays a critical role in motor sequence learning (MSL) consolidation, the specific contribution of the different sleep stages in this type of memory consolidation is still contentious. To probe the role of stage 2 non-REM sleep (NREM2) in this process, we used a conditioning protocol in 3 different groups of participants who either received an odor during initial training on a motor sequence learning task and were re-exposed to this odor during different sleep stages of the post-training night (i.e., NREM2 sleep [Cond-NREM2]; REM sleep [Cond-REM], or were not conditioned during learning but exposed to the odor during NREM2 [NoCond]). Results show that the Cond-NREM2 group had significantly higher gains in performance at retest than both the Cond-REM and NoCond groups. Also, only the Cond-NREM2 group yielded significant changes in sleep spindles characteristics during cueing. Finally, we found that a change in frequency of sleep spindles during cued-memory reactivation mediated the relationship between the experimental groups and gains in performance the next day. These findings strongly suggest that cued-memory reactivation during NREM2 sleep triggers an increase in sleep spindle activity that is then related to the consolidation of motor sequence memories.

Keywords: sleep, non-rapid eye-movement sleep, sequential motor learning, sleep spindle, memory consolidation, targeted memory reactivation.

Abbreviations: Δ%: percent of change; BMI: body mass index; Cond-NREM2: experimental group conditioned to the olfactory stimulus and cued during NREM2 sleep; Cond-REM: experimental group conditioned to the olfactory stimulus and cued during REM sleep; EEG: electroencephalography; EMG: electromyography; EOG: electrooculography; ESD: extreme studentized deviate (statistical method); fMRI/EEG: imaging technique combining functional magnetic resonance imaging and electroencephalography; GPI: global performance index; MSL: motor sequence learning; NoCond: experimental group not previously conditioned to the olfactory stimulus but exposed to the odor during NREM2 sleep; NREM: non rapid eye movement sleep. This sleep stage is comprised of four different sub-stages (1 to 4). However,

the American Academy of Sleep Medicine now regroup stage 3 and 4 into a single stage : NREM3; PEA: phenyl ethyl alcohol; PSG: polysomnographic; REM: rapid eye movement sleep; SRTT: serial reaction-task; SSS: Standford Sleepiness Scale questionnaire; SWS: slow wave sleep (stage 3 and 4 sleep, also known as NREM3); TMR: targeted memory reactivation; TST: total sleep time; TSP: total sleep period; SE: sleep efficiency.

Introduction

From lacing up a shoe, to typing at a computer, motor skills are learned and become automatic through the repetitive practice of a precise series of movements. This type of procedural memory, known as motor sequence learning (MSL), depends initially on repeated practice but is also enhanced offline after initial training. During this latent post-learning phase, the memory trace of a given motor experience is thought to be transformed into an enduring state, a process called memory consolidation (Doyon, Bellec, et al., 2009; Maquet, 2001; E M Robertson, Pascual-Leone, & Miall, 2004; Robert Stickgold & Walker, 2013). A plethora of studies has shown that sleep is critical for consolidating the memory trace of newly acquired motor sequences, especially when the sequence of movements is known explicitly prior to the training phase (Doyon, 2008; Doyon, Korman, et al., 2009; Korman et al., 2007; Maquet, 2001; Walker, 2005).

While some authors investigating the existence of a relationship between sleep stages and the consolidation of motor memories using implicit (Cajochen et al., 2004; E M Robertson, Pascual-Leone, & Press, 2004) or explicit (Fischer et al., 2002) sequential tasks proposed that consolidation was linked to rapid eye movement (REM) sleep, there is now increasing evidence that the consolidation of sequential motor memories is associated with changes in non-REM (NREM) sleep (Doyon et al., 2011; Genzel et al., 2014; Korman et al., 2007; Rasch et al., 2009; Walker et al., 2002), and to alterations in characteristics of sleep spindles, in particular (Barakat et al., 2011, 2012; Fogel & Smith, 2011; Morin et al., 2008; Nishida & Walker, 2007). Sleep spindles are short (< 2 sec.) synchronous burst of activity between 11 and 17 Hz. They are found throughout NREM sleep, but are particularly numerous in NREM Stage 2 (NREM2) sleep. Importantly, animal studies have shown that neurons activated during a motor task are reactivated during subsequent NREM sleep (Yang et al., 2014) and that these task 'replays' during sleep coincide with slow-wave and spindle events (Ramanathan et al., 2015). Although a link between sleep spindles and consolidation of sequential motor learning has also been observed in many experiments in humans (for review see Ackermann & Rasch, 2014), most findings reported so far have been correlational in nature, hence precluding to determine whether their role in consolidation is causal or not.

To address this limitation, researchers have recently investigated the effects of manipulating sleep-specific brain oscillations (e.g., slow oscillations; Marshall, Helgadóttir, Mölle, & Born, 2006) or neurotransmitter systems (e.g., noradrenaline; Rasch et al., 2009) in order to probe the tenets of reactivation and consolidation mechanisms of memory, thereby getting closer to testing for causality (Ackermann & Rasch, 2014; Diekelmann, 2014; Rasch & Born, 2013). Others have employed conditioning experimental designs, also called targeted memory reactivation (TMR) paradigms, which are thought to target the processing of specific memory representations during sleep through reactivation with an external olfactory or auditory stimulus that was previously associated during training (Oudiette & Paller, 2013). The use of this innovative technique has demonstrated that it is possible to enhance performance on declarative (Guerrien et al., 1989; Rasch et al., 2007; Rihm, Diekelmann, Born, & Rasch, 2014; Rudoy, Voss, Westerberg, & Paller, 2009), complex/cognitive procedural (Smith & Weeden, 1990) and more recently, MSL tasks (Antony et al., 2012; Cousins et al., 2014; Schönauer et al., 2014) by cuing subjects during their sleep with either olfactory (Arzi et al., 2012; Rasch et al., 2007; Rihm et al., 2014) and/or auditory stimuli (Antony et al., 2012; Arzi et al., 2012; Cousins et al., 2014; Guerrien et al., 1989; Rudoy et al., 2009; Schönauer et al., 2014; Smith & Weeden, 1990; for review see, Diekelmann, 2014; Oudiette & Paller, 2013; Rasch & Born, 2013).

More specifically in the procedural memory domain, the TMR approach has been employed in four studies to investigate the contribution of specific sleep stages in the consolidation of MSL. First, in a seminal study, Rasch and colleagues (Rasch et al., 2007) used a rose-like odor as a context cue while participants performed two successive tasks (visuo-spatial and MSL), and re-exposed subjects to the olfactory cue either during SWS or REM sleep. They hypothesized that re-exposure to the olfactory stimulus in REM sleep would improve consolidation of this type of learning. Contrary to their prediction, however, subjects did not show any difference in motor memory consolidation after re-exposure to either sleep stages. Although conjectural, one reason for the lack of a significant effect may be that subjects were cued during SWS and REM, but not during NREM2 sleep. As sleep spindles are thought to be implicated in the consolidation of MSL, it is possible that an improvement in post-sleep performance on the motor task might be observed if the conditioned stimulus is presented

instead during NREM2, a sleep stage during which spindles occur most often (L De Gennaro, Ferrara, & Bertini, 2000; Guazzelli et al., 1986; Himanen, Virkkala, Huhtala, & Hasan, 2002). Since the same odor was used as stimulus for both types of task, it is also possible that the context-association of one task interfered with the other, hence reflecting the presence of improvements on the declarative, but not the MSL task.

Other investigators have used tones and melodies associated to the learned motor task as cue for memory reactivation during the post-learning night, and have demonstrated overnight improvement in performance on a MSL task the morning after (Antony et al., 2012; Cousins et al., 2014; Schönauer et al., 2014). In the latter three studies, procedural learning as well as enhanced motor sequence consolidation were assessed using versions of the serial reaction-time task (SRTT), and auditory cuing condition was administered either during slow-wave sleep (SWS) (Antony et al., 2012; Cousins et al., 2014) or during the night without distinction to the sleep stage (Schönauer et al., 2014). Overall, their results revealed that re-exposure to auditory cues associated with learning during sleep, and more precisely SWS, improved motor memory consolidation. This boosting in performance was also specific to cued-memory reactivation performed during sleep (Antony et al., 2012; Schönauer et al., 2014), and remarkably to the finger transitions that were cued (Schönauer et al., 2014), as no performance enhancement was observed when cued-memory reactivation occurred during a wake period (Cousins et al., 2014; Schönauer et al., 2014), when part of the sequence was not cued (Schönauer et al., 2014) or when subjects were tested in a no-cuing condition (Antony et al., 2012; Schönauer et al., 2014). Importantly, correlations were also found between sleep spindles (Antony et al., 2012; Cousins et al., 2014, but see Schönauer et al., 2014 for a different pattern of findings) and gains in performance on the sequence task, suggesting again that sleep spindles play a role in the reactivation of the motor memory trace. Yet despite the fact that these TMR studies provide correlational evidence of a link between sleep spindles and motor sequence consolidation, none have reported changes in spindle activity, which were then associated with better motor memory consolidation. Furthermore, in both studies that found correlations between sleep spindles and performance, cuing of the conditioned stimuli was carried out during SWS, and not NREM2 sleep. If sleep spindles are crucial in the consolidation process, one would expect that cuing during NREM2 sleep stage would be most effective in modulating spindles, irrespective of the

type of conditioned stimulus. Finally, only one of the previous studies using a TMR approach compared cuing conditions in two different sleep stages, hence limiting somewhat one's interpretations regarding the specificity of the sleep stage during which reactivation of the memory trace optimizes motor sequence consolidation.

In the present study, we thus investigated the contributing role of NREM2 sleep – in particular, via the action of sleep spindles - on MSL using an olfactory TMR paradigm design similar to the one used by Rasch et al. (Rasch et al., 2007). Following a MSL training session where we exposed participants to a rose-like odor, subjects were then re-exposed to the same olfactory stimulus during NREM2 or REM sleep occurring during the second half of the post-learning night (see Figure 1A). This approach did not only enable us to compare the effect of these two olfactory stimulation conditions during similar portions of the night, but also to compare sleep spindle activity before and after stimulation in order to test directly whether cuing resulted in an increase in sleep spindles and their characteristics (e.g. amplitude, duration, frequency and density), associated with performance gains. We also tested a third group that was not conditioned to any odor during training, but exposed for the first time to the odor during NREM2. The latter group allowed us to ensure that our results would not be biased due to changes in NREM2 sleep and spindle characteristics induced by mere exposure to the olfactory stimulation during sleep.

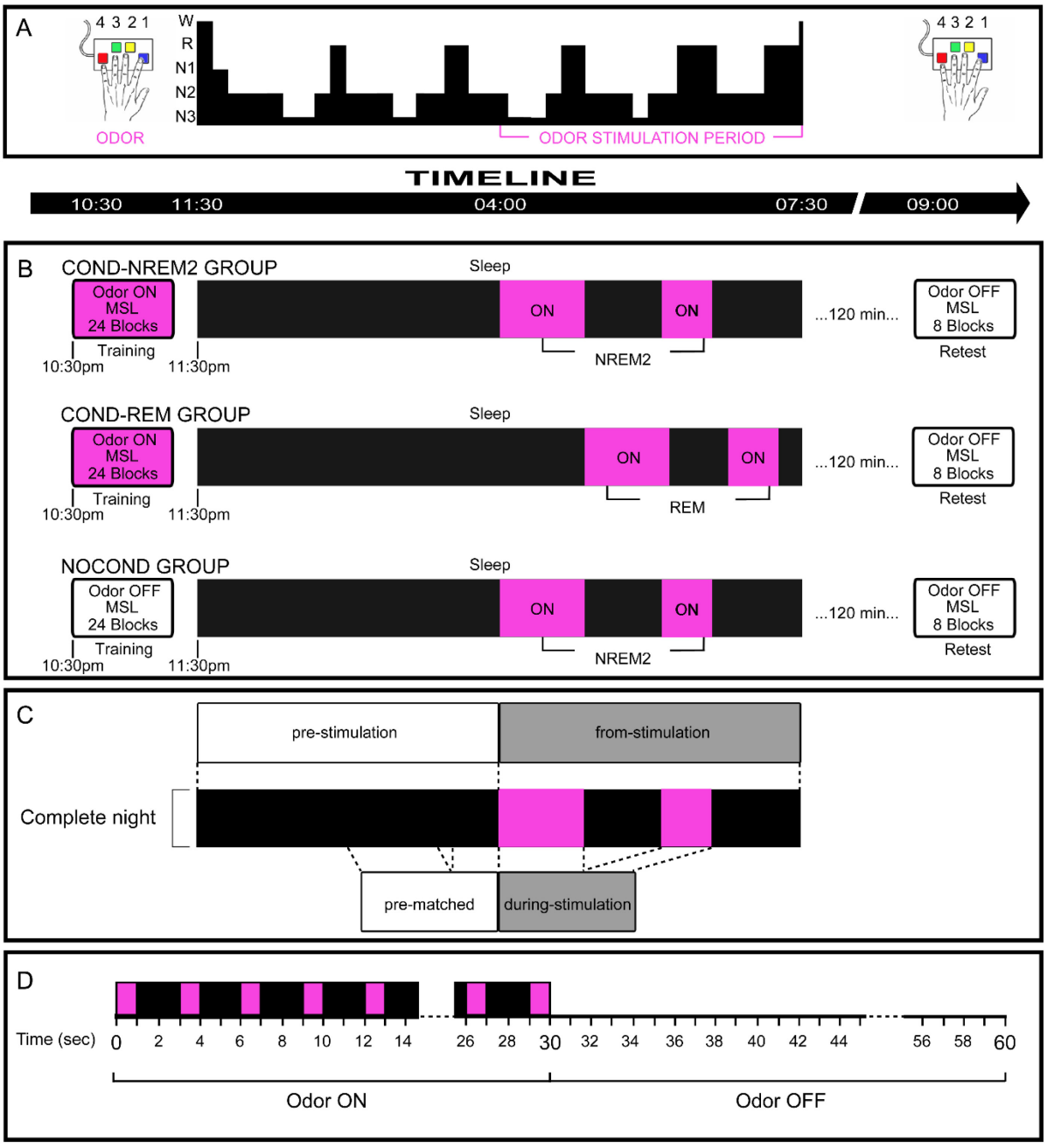


Figure 1. Experimental design.

(A) **Overview of the experimental design**. The odor was first presented while participants performed the MSL task. They were then re-exposed during sleep to the associated olfactory cue. This type of manipulation called *targeted memory reactivation* is thought to reactivate part of the memory trace previously associated to the cue. The effect of the manipulation was assessed by comparing performance between the evening training and morning

retest sessions. (B) **Experimental groups, exposure and cueing protocol**. Subjects were randomly assigned to one of three groups. Both Cond-NREM2 and Cond-REM groups were exposed to the odor during the evening training session and re-exposed to the same stimulus during their respective sleep stage. By contrast, the NoCond group wasn't exposed to the odor while training, but received olfactory stimulation during NREM2 sleep. All groups were exposed to the odor during the second half of the night and were retested the next morning. (C) **Description of the segmentation of sleep periods**. The *pre-stimulation* and *from-stimulation* periods were defined for each participant using the onset of exposure to the odor during sleep. The d*uring-stimulation* period represented the period during which the odor was presented to the participants while in their target sleep stage. The *pre-matched* period consisted of a period of sleep that corresponded to the exact same length as that of the *during-stimulation* period, and that occurred just before the onset of the olfactory cuing. (D) **Olfactory delivery method.** Odor delivery followed an ON/OFF block design. During ON blocks, the odor was sent during 1 s (in pink) every 3 s, while OFF blocks consisted of periods without odor delivery. For the MSL training session, the ON blocks consisted of the period during which subjects were practicing the sequence, while the OFF blocks corresponded to the periods of 30 s of rest in-between. During the targeted stage of sleep, the odor was delivered on a 30 s ON/ 30 s OFF block design for a maximum of 60 minutes.

Each group was retested in the morning to measure the subjects' level of consolidation as reflected through gains in performance. We conjectured that each group would consolidate the MSL task during sleep as shown by gains in performance during the retest session. In addition, we hypothesized that cuing in the post-training night to a conditioned olfactory stimulus during NREM2 sleep, as compared to re-exposure during REM or exposure during NREM2 with no prior conditioning, would produce greater gains in performance on the MSL task the next day, hence demonstrating that re-exposure to the conditioned stimulus associated with the motor memory trace during NREM2 enhanced the consolidation process. Finally, consistent with the literature showing that sleep spindles are involved in motor memory consolidation, we proposed that re-exposure to the conditioned olfactory stimulus during NREM2 sleep would significantly increase spindle activity for the group conditioned and re-exposed during NREM2 sleep only.

Results

MSL consolidation as a function of odor manipulation

Offline gains in performance in the MSL task were assessed in 76 participants using a global performance index (GPI) corresponding to a measure of performance that takes into account possible speed and accuracy trade-offs (Figure 2A; see S2 Figure for detailed information on separate measures of speed and accuracy).

A mixed repeated measures ANOVA of the GPI performed on the entire session of training (24 blocks – repeated measures), showed a significant effect of block ($F_{23, 1679} = 77.771$, $p < .00001$), with no significant block x group interaction ($F_{46, 1679} = .422$, $p = .99$) nor any main effect of group ($F_{2, 73} = .785$, $p = .46$). These results suggest that, while all participants showed improvement in performance across the training session, all groups had similar rates of learning and overall level of motor performance. Furthermore, a similar analysis performed on the last four blocks of the evening training session only, revealed no significant main effect of block ($F_{3, 219} = .423$, $p = .42$), block x group interaction ($F_{6, 219} = .623$, $p = .71$) nor between subjects effect of group ($F_{2, 73} = 1.338$, $p = .27$) showing that, at the end of the training session, all participants had reached an asymptotic performance and that the performance level in the MSL task was similar among the three groups.

Differences in level of consolidation were measured by comparing the mean GPI score of the first four blocks of retest to the last four blocks of training using a repeated measures ANOVA while controlling for individual cuing duration and olfactory threshold. The results yielded a main effect of session ($F_{1, 71} = 49.901$, $p < .00001$) and a session x group interaction ($F_{2, 71} = 5.794$, $p = .005$), hence demonstrating that while all participants revealed gains in performance between the 2 sessions, there was a difference in the level of motor skill consolidation between groups. As predicted, post-hoc univariate tests demonstrated that each group significantly increased their performance across sessions (Cond-NREM2: mean = .042 ±.012, $p < .00001$; Cond-REM: mean = .021 ±.013, $p = .001$; NoCond: mean = .012 ±.012, $p = .04$; see Table 1). Most importantly, however, planned contrasts analyses revealed that the Cond-NREM2 group exhibited significantly higher gains in performance than both the Cond-REM ($p = .03$) and NoCond ($p = .001$) groups, and that Cond-REM and NoCond groups did not differ

significantly (p = .27), demonstrating that cued-memory reactivation during NREM2 enhanced performance over-and-above the gains normally afforded by sleep.

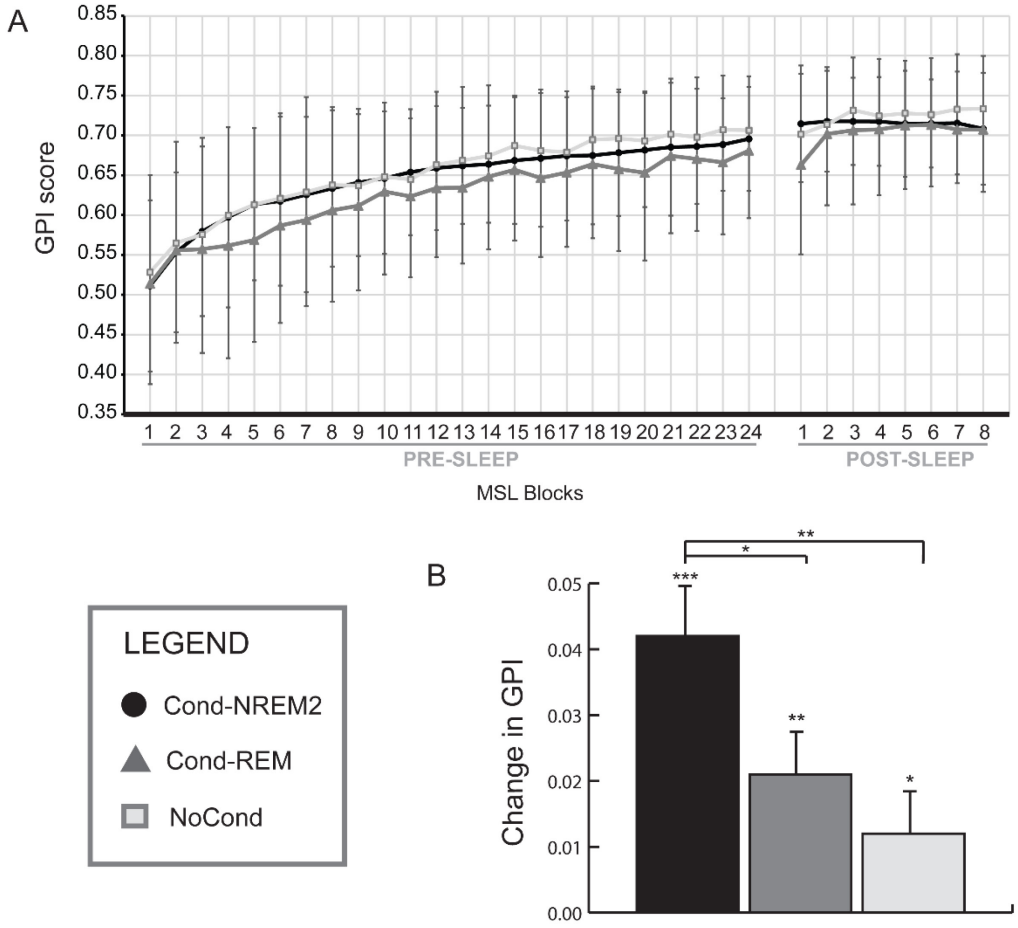


Figure 2. Behavioral results.

(A) **MSL learning curves**. Learning curves of all three groups during the evening and morning MSL sessions. Scores were calculated with the global performance index (GPI). Blocks used for the calculation of the change in GPI (i.e. offline gains) are indicated on the "x axis" in bold format. (B) **Offline gains in performance on the MSL task**. This graph illustrates the offline gains per group on the MSL task performance as measured by the mean GPI between the four first blocks of post-sleep retest and the four last blocks of pre-sleep training sessions. All groups showed increases in performance after a night of sleep. The Cond-NREM2 group had significantly higher gains

than both the Cond-REM and NoCond groups. No difference was found between the Cond-REM and NoCond groups (S Laventure, 2016). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

In order to relate more directly the subjects' level of motor sequence consolidation with their own polysomnographic (PSG) data, we then carried out additional behavioural analyses after discarding 12 participants in whom electroencephalography (EEG) recordings were of poor quality because of technical difficulties. The analyses based upon this smaller subset of subjects (i.e., n = 64) yielded a similar (albeit not identical) pattern of results. While the overall distribution of group means was similar, the overnight offline gains in performance differed slightly as changes in performance in the Cond-NREM2 (mean gain = +.041 ±.033, $p < .0001$) and Cond-REM (mean gain = +.019 ±.014, $p = .008$) groups remained significant, but those related to the NoCond group did not reach significance (mean gain = +.010 ±.014, $p = .17$). Because the NoCond group (from the *All Subjects* set) demonstrated the smallest overnight MSL consolidation effect ($p = 0.01$), it is not surprising that a subset of this group (i.e., the PSG subset) did not reach significance using the same measure. More importantly, however, when looking at both sets of subjects, the significant differences in offline gains between groups did not change, hence demonstrating that the cuing procedure was effective. Finally, it is important to note that the pattern of results described above could not be due to poor control of olfactory cuing because stimulation in targeted sleep stages was successful (see S1 Figure). Furthermore, the present findings cannot be due to the rejection of subjects with outlying performance (see Method below), as additional behavioral analyses including those individuals (n=4) revealed similar results (see S1 Text).

Table 1. Offline GPI gains on the MSL task.

	n	GPI	95% CI	p
All subjects (n = 76)				
Cond-NREM2	25	.042	.012	<.00001
Cond-REM	23	.021	.013	0.001
NoCond	28	.012	.012	0.04
PSG subset (n = 64)				
Cond-NREM2	21	.041	.033	<.0001
Cond-REM	21	.019	.014	0.008
NoCond	22	.010	.014	0.17

Legend: Results from the ANOVA for repeated measures assessing the level of offline gains in performance (consolidation) between the evening and morning MSL sessions as measured with the GPI for each of the experimental groups. Analyses from all subjects and the PSG subset are shown. These results demonstrate that all groups in the main set of participants (*all subjects*) showed a significant increase in performance after a night of sleep.

Olfactory threshold and stimulation during sleep analyses

A one-way ANOVA showed that there were no differences between groups in olfactory detection threshold ($F_{2, 73} = 2.324$, $p = .10$) as measured with the *Sniffin'sticks* test. The same analysis performed on the participants included in the PSG analyses also produced similar results.

Another series of analyses were conducted to ensure that the length of exposure to the rose-like odor during sleep did not differ between groups, and that targeted stages were successfully stimulated. First, a one-way ANOVA revealed that there was no difference in the total length of exposure to the odor cue during sleep between the three groups ($F_{2, 73} = 2.671$, $p = .08$; Cond-NREM2: 53.4 min ±3.3, Cond-REM: 48.4 min ±3.4, NoCond: 49.2 min ±3.1). Then, another one-way ANOVA, testing for differences during NREM2 was conducted ($F_{2, 73} = 73.127$, $p < .0001$), and post-hoc univariate tests demonstrated that there was no difference in the duration of exposure to the odor during NREM2; that is between the Cond-NREM2 (39 min

±4.4 min) and NoCond groups (32 min ±4.2 min) (see S1 Figure and S1 Table for detailed analyses).

Sleep architecture

Sleep architecture and spindles were analyzed using recordings throughout the night, which were separated into several distinct periods (see Methods for details): a) sleep occurring before onset of the olfactory stimulation (*pre-stimulation*), b) sleep following the start of olfactory stimulation (*from-stimulation)*, c) sleep during stimulation in the targeted sleep stage (*during stimulation)* and d) sleep of the same length as *during-stimulation*, but selected in the *pre-stimulation* period (*pre-matched)* (see Figure 1C).

One-way ANOVAs performed separately on *pre-* and *from-stimulation* periods did not reveal any significant difference between the three groups in any of the sleep stages with regards to the total sleep time (TST), total recording time (TRT), sleep efficiency (SE) or wake duration, demonstrating that our manipulation did not generate differential changes in sleep architecture between our groups (see S2 Table for more information).

Sleep spindle analyses

Spindles were extracted from Fz, Cz and Pz derivations with an automatic algorithm (Ray et al., 2014). Sleep spindle analyses focused on peak-amplitude, duration, peak-frequency and density. Spindle analyses were only conducted in the Cond-NREM2 and NoCond groups, as no spindle were generated during the Cond-REM targeted stage. All analyses were carried on NREM2 sleep spindles only.

A categorization algorithm was used to identify spindles originating from a single source (e.g. a unique channel/electrode – see Method section). Overall, the algorithm identified 29.8% of spindles at Fz, 36.2 % at Cz and 20.1% at Pz, as overlapping spindles. Filtering of these redundant spindle events had the effect of lowering the median spindle frequency value of the overall spindle distribution from 11.49 Hz to 11.37 Hz at Fz (t_{63} = -5.439, $p < .001$) and increasing the median frequency from 13.40 Hz to 13.60 Hz at Pz (t_{63} = 3.131, $p = .003$). Thus,

this categorization approach helped to reduce the overlap between frontal and parietal distribution of spindle frequencies, hence allowing for a better classification between these two midline sources. All analyses of sleep spindle characteristics reported below were thus carried out using these filtered events. Yet note that a similar pattern of results was observed when analyses included the entire set of spindles before applying the categorization algorithm (see S1 Text).

Fz and Cz derivations

There were no significant differences between the two groups in terms of peak amplitude, duration, peak frequency and density of sleep spindles in the *pre-matched* and *during-stimulation* or when looking at the difference between *during-stimulation* and *pre-matched* periods in both frontal (Fz) and central regions (Cz).

Pz derivation

A one-way ANOVA did not reveal any statistically significant differences between the two experimental groups with respect to spindles amplitude, duration, frequency and density, in the *pre-matched* suggesting that, before stimulation, spindles characteristics were similar between groups. No difference was also found in the *during-stimulation* period either (see S3 Table).

By contrast, when we compared changes in spindle characteristics between the *pre-matched* and *during-stimulation* sleep periods, the one-way ANOVA comparing percent change (Δ%) revealed a significant difference in peak amplitude ($F_{1, 41} = 5.257$, $p = .03$) and peak frequency ($F_{1, 41} = 4.842$, $p = .03$) between the Cond-NREM2 and NoCond groups (see Table 2 for details). A similar pattern of results was observed for spindles duration, although the effect did not reach significance ($F_{1, 41} = 3.523$, $p = .07$). Follow-up, one-sample t-tests revealed that only the Cond-NREM2 group had a significant increase in Δ% in peak frequency (Cond-NREM2: $t_{20} = 2.443$, $p = .02$; NoCond: $t_{21} = -.511$, $p = .62$), Δ% in peak amplitude (Cond-

NREM2: $t_{20} = 2.394$, p = .03; NoCond: $t_{21} = -.481$, p = .64) and Δ% in duration (Cond-NREM2: $t_{20} = 3.013$, p = .007; NoCond: $t_{21} = .881$, p = .39) (Figure 3A).

Table 2. Differences in spindle characteristics between *pre-matched* and *during-stimulation* sleep periods.

	Cond-NREM2 (n=21)			**NoCond (n=22)**				
	Δ%	$T_{(20)}$	p	Δ%	$T_{(21)}$	p	$F_{(1, 42)}$	p
Amplitude	**11.6%**	**2.394**	**.03**	-1.5%	-0.481	.64	**5.257**	**.03**
Frequency	**0.7%**	**2.443**	**.02**	-0.1%	-0.511	.61	**4.842**	**.03**
Density	0.6%	0.246	.81	2.3%	1.033	.31	0.261	.61
Duration	**10.1%**	**3.013**	**.007**	2.2%	0.881	.39	3.523	.07

Legend: One-sample t-tests were carried out on spindle characteristics Δ% in each group. The results revealed that the stimulation probed an increase in amplitude, duration and frequency of spindles in the Cond-NREM2 group, but not in the NoCond group. One-way ANOVAs tested for differences in the same characteristics between groups. Compared to NoCond, the Cond-NREM2 group spindles increased significantly in amplitude and frequency. Statistical significance is highlighted in bold.

Additionally, bootstrap analyses (with 5000 samples) performed on changes in sleep spindles characteristics between the *pre-matched* and *during-stimulation* sleep periods at Pz showed that amplitude (p = .0012), frequency (p = .0026) and duration (p = .0094) yielded significant changes while density (p = .7764) did not (see S3 and S4 Figs; see S1 Text). Bonferroni correction for 12 comparisons (3 electrodes x 4 characteristics; reference p-value = .0041) applied on these results confirm the effects reported above: spindle amplitude and frequency increased significantly, while duration and density did not, between these two sleep periods.

To determine the precise spindle frequencies that were enhanced through cueing when comparing the *pre-matched* and *during-stimulation* periods, further Chi^2 analyses were carried out on the change in number of spindles in each 0.5 Hz frequency bin from 11 to 17 Hz. Such analyses revealed that very narrow ranges in spindle frequencies were modulated by the olfactory manipulation during sleep. Indeed, the number of slow frequency spindles for the

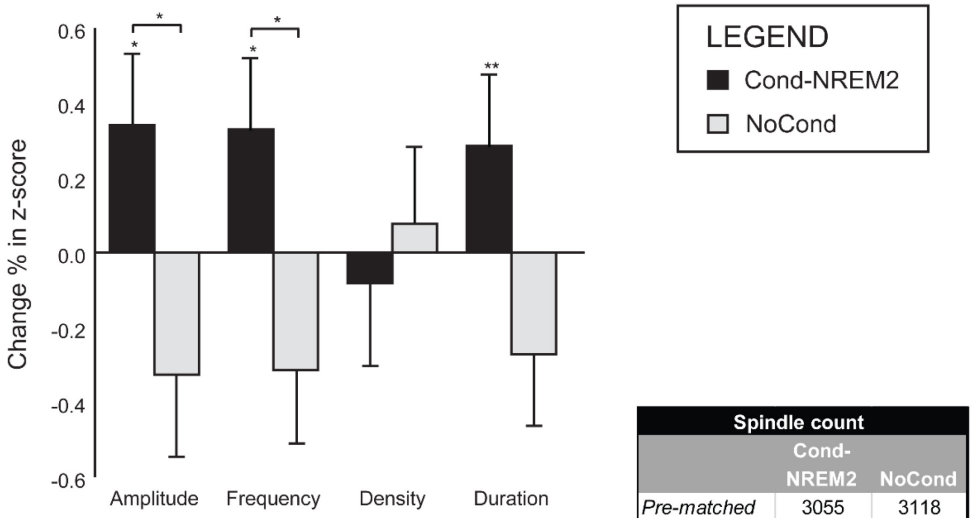
Cond-NREM2 group in the 11 Hz to 11.49 Hz bin decreased (X^2 [1, N = 1109] = 18.04, p = 0.0003, bonf.-corrected), while the number of higher frequency spindles in the 13.5 Hz to 13.99 Hz bin increased significantly (X^2 (1, N = 2463) = 18.04, p = 0.03, bonf.-corrected) compared to the NoCond group. Yet the total number of spindles (11-17 Hz) was similar between groups and periods of sleep (Figure 3B).

To ensure that the odor sent for a few minutes during SWS did not significantly influence the performance of the cued group, we tested if the duration of exposure to the odor in SWS at Pz, correlated with gains in performance. Neither the results of the Cond-NREM2 nor the NoCond groups showed any significant correlations between the duration of stimulation in SWS and gains in performance (Cond-NREM2: r = -.168, p = 0.47; NoCond: r = -.012, p = 0.96). Also, we found no correlation between spindle characteristics and gains in performance in the Cond-NREM2 group (amplitude: r = 0.06, p = 0.82; frequency: r = -0.09, p = 0.73; density: r = -0.07, p = 0.78; duration: r = -0.16, p = 0.53).

Mediation analyses

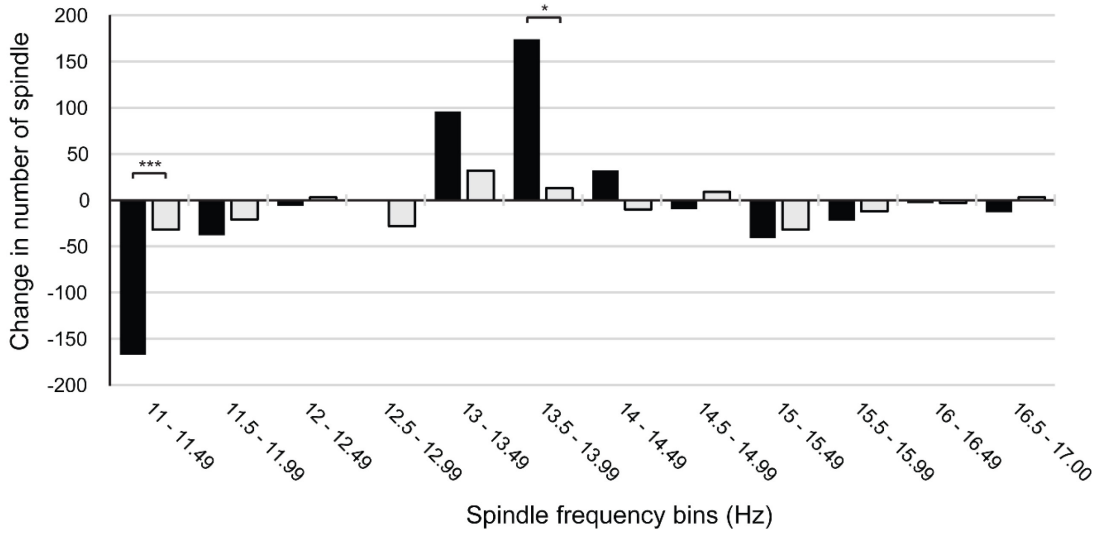
Using NREM2 Δ% peak frequency at Pz from *pre-matched* vs. *during-stimulation* as a mediator (see Figure 3C), we found a significant indirect effect of the experimental groups (Cond-NREM2 [1]; NoCond [0]) on gains in performance through Δ% peak frequency (b = 0.027 Bca CI [.004, .077]) with a medium effect size (k^2 = .106, 95% BCa CI [.018, .256]). Although differences were found between the Cond-NREM2 and NoCond groups in spindle amplitude, mediation analyses did not reveal a significant effect.

A

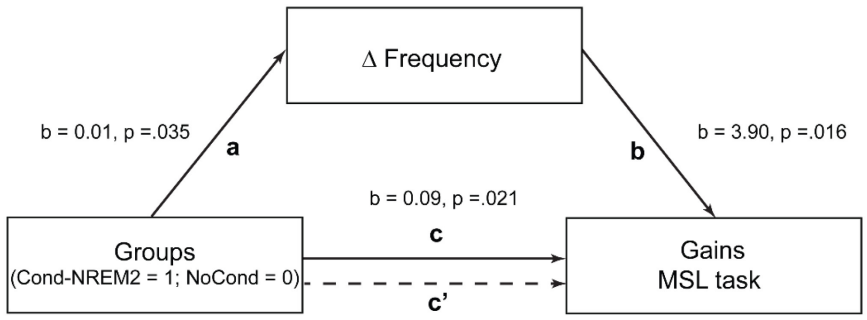


Spindle count		
	Cond-NREM2	NoCond
Pre-matched	3055	3118
During-	3056	3040

B



C



Direct effect, b = 0.06, p =.115

Indirect effect, b = 0.03, 95% CI [0.004, .077]

Figure 3. Sleep spindle results.

(A) **Changes in parietal sleep spindle characteristics**. Standardized (Z-score) differences in sleep spindle characteristics between the *pre-matched* and *during-stimulation* periods at Pz. Only the Cond-NREM2 group showed significant increase in spindle amplitude, frequency and duration. Amplitude and frequency were significantly different between the Cond-NREM2 and NoCond groups. (B) **Changes in the number of spindle at Pz in specific frequency ranges.** Differences at Pz in the number of spindles categorized by frequency range between the *pre-matched* and d*uring-stimulation* sleep periods. Significance was determined using a Chi^2 analysis with Bonferroni correction on the number of bins. The total number of spindles detected for each group and sleep period is shown in the "Spindle count" table. The results revealed a significant decrease of spindle in the 11-11.49 Hz range, but an increase in the 13.5-13.99 Hz range. (C) **Changes in frequency at Pz mediates the relationship between the TMR protocol and MSL offline gains**. The significant relation between the experimental protocol and the gains in performance on the MSL task (relation *c*) disappeared when the change in frequency in sleep spindles over the parietal cortex between the *pre-matched* and d*uring-stimulation* periods were included in the mediation model (direct effect: relation *c'*). The indirect effect composed of 1) the experimental protocol and the change in spindle frequency (relation *a*) and, 2) the change in spindle frequency and the MSL offline gains (relation *b*) was significant, as demonstrated by the bootstrap analysis (Cl .004, .077). This pattern of results strongly suggests that sleep spindles occurring in the parietal regions are crucial to motor memory consolidation through an increase of spindles of higher frequency (S Laventure, 2016). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Discussion

The present study investigated the contributing role of NREM2 and sleep spindles in motor sequence memory consolidation. As expected, all experimental groups showed offline improvements in their performance on the motor sequence task after a night of sleep, highlighting again the influence of sleep on the consolidation of this type of motor learning. More importantly, however, the TMR paradigm allowed us to demonstrate that post-training cuing during NREM2 sleep with a conditioned olfactory stimulus significantly increased sequential motor performance, while cuing during REM sleep or exposing participant to an unconditioned stimulus during NREM2 did not. Our results also show that cuing during NREM2 sleep produced an increase in a variety of spindle characteristics, and that such changes were found only over parietal areas. Finally, we demonstrate that the increase in sleep spindle frequency over parietal regions mediated the difference between the MSL performance of the

conditioned versus unconditioned group. Altogether, the results of the present study reveal that NREM2 sleep is crucial for sequential memory consolidation, and that part of this effect may be explained by a specific modulation of sleep spindles.

As expected, sleep had a positive impact on MSL consolidation in all three groups. The fact that the non-conditioned control group improved at retest is consistent with a large number of studies that have reported that a night of sleep is sufficient to trigger a consolidation process, which in turn produces gains in performance (Ackermann & Rasch, 2014; Doyon, Korman, et al., 2009; Rasch & Born, 2013; Walker et al., 2002). Furthermore, our pattern of results demonstrates that stimulation with the conditioned stimulus during REM sleep does not elicit greater behavioural improvement over and above the effect of sleep. This replicates the findings from Rasch et al. (Rasch et al., 2007) who did not report any significant changes in performance on a very similar TMR protocol using the motor sequence learning task after presentation of a conditioned olfactory stimulus during REM or SWS. Although findings from Rasch et al. (Rasch et al., 2007) and ours do not appear to support prior studies, which suggested that the process mediating motor sequence consolidation is dependent upon REM sleep (Fischer et al., 2002; Plihal & Born, 1997; Smith, 2001), we argue that it was likely because of cognitive demands associated to the task employed (i.e., probabilistic serial reaction time task, mirror tracing task) and that it underlines the possibility that REM sleep might be implicated in other aspects (i.e., more cognitively demanding processes) of motor memory consolidation. Yet our results and those from other recent investigations (Barakat et al., 2011, 2012; Fogel & Smith, 2011; Korman et al., 2007; Morin et al., 2008; Nishida & Walker, 2007; Rasch et al., 2009) indicate that the consolidation of a newly acquired explicit and cognitively simple motor sequential skill is particularly dependent on NREM sleep.

NREM2 sleep promotes motor memory consolidation

More importantly and as expected, our results show that participants conditioned to an olfactory stimulus during training to a novel MSL task, and re-exposed to that same stimulus during NREM2 sleep, experienced a significant enhancement in performance the next day compared to the two other groups. The latter finding is in accord with previous studies, which

found that performance at retest on a MSL task is correlated to the amount of NREM (E M Robertson, Pascual-Leone, & Press, 2004), and to NREM2 sleep more specifically (Nishida & Walker, 2007; Walker et al., 2002). It is also consistent with evidence that pre-sleep training on a motor task increases the time spent in NREM2 sleep (Fogel & Smith, 2006; Fogel et al., 2007), but that deprivation of post-training SWS or REM sleep do not produce any decrease in motor task performance at retest (Genzel et al., 2012, 2009; Rasch et al., 2009), hence supporting further the conclusion that NREM2 sleep plays an important role in the motor sequence memory consolidation process (see 23 for a review).

It is important to note that previous TMR studies that investigated the implication of sleep in MSL learning found greater gains in performance when subjects were cued during SWS (Antony et al., 2012; Cousins et al., 2014). The current study extends these findings and provides, to our knowledge, the first evidence that possible reactivation of the motor memory trace during NREM2 sleep does facilitate offline consolidation processes capable to produce increases in sequential motor performance when tested again the next day. Our results are also in line with a recent integrative model proposed by Genzel and colleagues (Genzel et al., 2014), which states that such memory trace reactivations occur particularly (but not exclusively) during the so-called light NREM sleep. Although still conjectural, this model put forward the notion that such an active memory consolidation process, possibly due to exchange of information between the striatum and motor related-cortical regions (Debas et al., 2014; Lansink et al., 2009) would take place during this light NREM phase because it offers the most optimal conditions for global brain interactions. Thus consistent with Genzel's model, our behavioral results strongly suggest that mnemonic processes occurring during NREM2 sleep are involved in sequential motor memory consolidation.

Changes in spindle characteristics associated with motor sequence consolidation

Over and above the changes in performance as a result of cueing during NREM2, the present olfactory TMR protocol induced changes in sleep spindle characteristics (i.e., amplitude, duration and frequency) only for the group conditioned and re-exposed during NREM2 sleep. Importantly, we demonstrate that these changes were not caused by differences in sleep

architecture or spindles present prior to the stimulation, but were prompted specifically through re-exposure to the conditioned odor during NREM2 sleep. Previous TMR studies investigating the role of SWS in motor memory consolidation have reported correlations between gains in performance and the number or density of sleep spindles, but no change in spindle characteristics *per se* (Antony et al., 2012; Cousins et al., 2014). The reasons for such differences with our own findings may be two-folds. First, it is possible that because sleep spindles are more numerous in the stage we targeted (NREM2) than in SWS, predominance of spindles between these two stages could account for the increases in several characteristics shown in our own study. Second and most importantly, however, the protocol employed here offered the unique opportunity to compare the effect of reactivation during cuing compared to a baseline period recorded during the same night prior to any re-exposure. Thus this enabled us to compare non-cued segments that were uncontaminated by previous cuing trials to cued segments of NREM sleep, hence allowing us, for the first time, to detect changes in sleep spindle characteristics in a TMR study on MSL consolidation.

Interestingly, the present study also revealed that re-exposure to the conditioned stimulus produced significantly greater increases in sleep spindle amplitude and frequency, and that this change was present at Pz for the group cued during NREM2, compared to the non-conditioned group. These results are in line with reports, as those from Schabus and colleagues (Schabus et al., 2004, 2006, 2008), suggesting that changes in spindle characteristics may be more important than an increase in spindle density for consolidating memories. They are also in accord with some known properties related to the underlying physiology of sleep spindle oscillations. Indeed, a recent study demonstrated that sleep spindles of higher frequency had higher amplitude and, interestingly, greater rate of cortical propagation (O'Reilly & Nielsen, 2014b). Since sleep and spindle burst activity are thought to provide favourable conditions for synaptic plasticity (see Astori et al., 2013 for review; Contreras, Destexhe, & Steriade, 1997; Rosanova & Ulrich, 2005; Sejnowski & Destexhe, 2000; Yang et al., 2014), it is thus possible that, without the need for a larger number of spindle events, the increases in frequency and amplitude found in the present study allowed for a more efficient potentiation of long-term synaptic changes and increased synchrony in the thalamo-cortical loop, hence facilitating consolidation of the memory trace.

Further analyses on spindle frequencies at Pz showed that, in the conditioned NREM2 group only, the number of spindles increased in a distinct range of frequency (13.5-13.99 Hz), while there was a decrease in a lower frequency range (11-11.49 Hz). This pattern of results is even more revealing that the NoCond group did not show any change in either of the frequency bins, but revealed instead an overall normal pattern of decrease in mean frequency (S3 Table) that is usually observed during an undisturbed night of sleep in normal subjects (Werth, Achermann, Dijk, & Borbély, 1997). In sum, since parietal spindles in the 13.5 to 13.99 Hz range are generally considered as fast spindles, our results in the Cond-NREM2 group are thus consistent with previous studies that have reported increases in fast spindle density (Barakat et al., 2011) and higher sigma band (13 Hz) activity (Morin et al., 2008) over parietal regions following MSL training.

The reason why changes in spindle characteristics were found in the parietal regions only is speculative at this point. Yet it is now known that the early stage of MSL is characterized by the acquisition of two different sequence representations (motor, spatial), which are associated with plastic changes in different motor related networks and that are depending differently on sleep for consolidation (Albouy, King, et al., 2013; Genzel et al., 2015). Learning the motor representation of the sequence relies, in part, on activation of the striatum, motor cortex and cerebellum (Dayan & Cohen, 2011; Doyon et al., 2011; see Doyon, Bellec, et al., 2009; Hikosaka, Nakamura, Sakai, & Nakahara, 2002 for review). By contrast, acquisition of the spatial representation depends mainly upon the hippocampus as well as the prefrontal and parietal regions (Albouy et al., 2015; Albouy, King, et al., 2013; Hikosaka et al., 2002). Results from studies in our laboratory have demonstrated that the consolidation of the latter type of memory trace is related to spindle activity during NREM sleep (Albouy, Fogel, et al., 2013). Furthermore, TMR studies investigating the effect of sleep on declarative memory using visuo-spatial memory tasks have previously shown that cuing during SWS with an olfactory stimulus produced increases in fast spindle density over parietal regions (Cox, Hofman, de Boer, & Talamini, 2014; Rihm et al., 2014). Thus, in light of past studies and our present results, it is possible that the olfactory cue reactivated preferentially the spatial representation of the motor sequence during sleep, which in turn was enhanced via spindle activity in parietal regions.

Spindle frequency as a mediator of the effect of olfactory cueing on performance improvements

In the present paper, we show that the change in sleep spindle frequency over parietal regions mediated the relationship between cueing and offline gains. These results indicate that the experimental manipulation (i.e. cuing the memory of a motor task with an odor, or not) can predict both the level of offline gains as measured at retest and the increase in parietal spindle frequency before vs. during stimulation. This mediation effect implies that, regardless of the presence of a conditioned stimulus or not, spindle frequency variations over the parietal region predict the level of gains in performance the next morning. Thus the present findings provide the first evidence of a mediator effect of sleep spindles on the relationship between a TMR protocol and MSL offline gains. Taken together, the combination of the TMR experimental design used here, the specific increase in spindle characteristics yielded by cuing, and the mediating effect of spindle frequency on offline gains, suggest that NREM2 sleep spindles are instrumental to sequential motor learning consolidation.

Again, it is difficult to explain why an increase in spindles of higher frequencies is particularly important for consolidating the memory trace associated with a newly acquired sequence of movements. As such changes were observed over Pz, the latter finding is in accord with the fact that sleep spindles detected over central and parietal regions are characterized by higher frequencies (called fast spindles) (Anderer et al., 2001; Andrillon et al., 2011), and that these events have often been found to be associated with motor memory consolidation (Barakat et al., 2011; Cousins et al., 2014; Rasch et al., 2009). Furthermore, our results are consistent with those of innovative studies using combined fMRI/EEG recordings during sleep by Tyvaert and collaborators (Tyvaert, Levan, Grova, Dubeau, & Gotman, 2008) who have shown a link between spindle activity and increased BOLD signal in the putamen, as well as others, who have reported that fast spindles are associated with increased activity in cortical motor regions and the hippocampus (Andrade et al., 2011; M Schabus et al., 2007); all structures that have been shown to play a significant role in motor learning.

Conclusion

Although it is important to note that the present TMR study does not prove causality as we did not manipulate directly the occurrence of sleep spindles, we believe that our results and the experimental design used here offer, to our knowledge, the first evidence toward an instrumental role of NREM2 sleep in the consolidation of motor sequence memory through the increased activity of sleep spindles over parietal regions. We show that cuing during NREM2 not only increases posterior spindle frequency, but also that these changes predict future performance on a motor sequence task. Based on the present findings, and those of other groups of investigators, we thus propose that NREM, and NREM2 sleep in particular, through the specific neuronal activity of sleep spindles, play a critical role in the consolidation process of a motor memory trace generated through practice of a new sequence of movements. More specifically, the increases in spindle amplitude, duration and especially frequency observed during the stimulation phase (hence possibly facilitating the reactivation process) lead to a better consolidation process, and ultimately to higher sequential motor performance the next day. Yet, further combined sleep/imaging studies are needed to investigate the neural correlates of the spindle-related reactivated memory trace from the enhancement through cuing of a conditioned stimulus.

Method

Participant recruitment and selection

Pre-selection

To be included in the study, eligible participants had to be right handed, between 20 and 35 years old, and had to have no previous formal training playing a musical instrument, nor any training as a professional typist in order to control for pre-existing experience in tasks requiring highly coordinated finger movements. Obese individuals (BMI > 30) and those using nicotine regularly or users of recreational drugs were excluded. Also they had to be free of any history of neurological, psychological, psychiatric disorders and sleep disorders. Furthermore, individuals who worked night shifts, were engaged in trans-meridian trips in the three months

prior to the study, or reported taking 3 or more servings of caffeinated beverages per day, were not included in the study. All eligible participants had to have a score lower than 10 on the Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988) and the short version of the Beck Depression Inventory (Beck, Rial, & Rickels, 1974). The quality of their sleep was assessed with the Pittsburgh Sleep Quality Index questionnaire (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

Screening session

A total of 135 participants met the initial eligibility criteria prior to engaging in an overnight PSG screening (the main eligibility criterion prior to enrollment into the experimental night) in the sleep laboratory according to American Academy of Sleep Medicine guidelines (Iber et al., 2007). PSG screening included EEG, electrooculography (EOG), leg and facial (submental) electromyography (EMG), thoracic and abdominal respiratory effort belts and airflow; all of these measures being employed to identify signs of sleep disorders (e.g., insomnia, apnea, parasomnias, etc.), which were used as exclusion criteria. In addition, the screening night allowed us to objectively quantify the subjects' sleep quality and to provide an opportunity for the participants to become acclimatized to the laboratory environment. The latter comprised sleep rooms that were built to be as comfortable as possible. Each of them was equipped with a single bed, comfortable mattress, night stand, bookcase, lamp and decorative plants. Although the rooms were windowless, curtains covering a portion of the wall were installed to give participants the feeling that the room has windows. The ceiling lights were controlled with a dimmer, and importantly, air conditioning was centrally regulated through the hospital main system. Finally, sheets and beddings were changed every day and for each subject that participated in the study.

Upon arrival for the screening night, an olfactory threshold test was carried out to assess each individual's level of scent detection (*Sniffin'sticks*, Burghart Medizintechnik, Germany). For selected participants, this olfactory threshold was used as a covariate measure for subsequent behavioral analyses, but did not constitute an exclusion criterion *per se*. Only participants without any signs of disordered sleep and who had a sleep efficiency over 80% were selected to

participate in the study (PSG eligibility criterion) and were then invited to come back a week later for the experimental night. They were instructed to abstain from alcohol for the duration of the experiment. Subjects were asked to keep a strict sleep/wake schedule: go to bed between the hours of 10:00 p.m. and 1:00 am, wake up between 6:00 a.m. and 9:00 a.m., and abstain from taking naps during the day. To ensure that the participants adhered to this sleep/wake schedule during the week separating screening and experimentation nights, they were asked to wear an actigraph on their wrist (Actiwatch 2, Phillips Respironics). Complimentary to the actigraph, participants were also asked to complete a sleep diary. Individuals who did not follow this strict sleep/wake schedule were not enrolled in the study and did not participate in the experimental night. Out of the 135 eligible individuals, 8 were found to have at least one type of sleep disorder (e.g. bruxism, sleep apnea, periodic limb movement), 20 did not reach the 80% sleep efficiency threshold, 6 did not follow instructions regarding the sleep/wake cycles (following inspection of the actigraphy data) and 9 voluntarily dropped out of the study.

Experimental session

Thus, after completing the screening night, a total of 92 participants were selected and enrolled in the study. Importantly, participants' assignment into experimental group took place after all eligibility criteria were applied and participants were screened out. Of the 92 enrolled participants, eighteen were subsequently discarded from the analysis for the following reasons: seven were excluded due to low sleep efficiency (<75%) during the experimental night, three were due to technical problems (e.g., issue with the response box or the olfactometer), four were because they did not properly follow the instructions during the motor sequence task and four were because their performance on the MSL task was considered as outlier. Thus, 76 participants were included in the behavioral analyses of the MSL task. They were distributed as follows: 25 subjects were included in the Cond-NREM2 group (mean age: 25.42 ± 4.4 years, 11 females), 23 in the Cond-REM group (mean age: 24.77 ± 4.2 years, 9 females) and 28 in the NoCond group (mean age: 24.60 ± 4.9 years, 11 females). Of these, twelve participants were further discarded from the subsequent sleep and spindle analyses due to poorly recorded PSG data. Consequently, 64 participants were included in the sleep EEG analyses and they were

distributed as follows: 21 subjects were included in the Cond-NREM2 group (mean age: 25.5 ± 4.5 years, 8 females), 21 in the Cond-REM group (mean age: 25.13 ± 4.2 years, 9 females) and 22 in the NoCond group (mean age: 24.18 ± 4.4 years, 10 females).

Overall Experimental Design and Procedure

A week after the screening session, participants were invited again to the laboratory for the experimental night. Following proper installation of the EEG electrodes for polysomnographic recordings and the olfactometer apparatus, participants were randomly assigned to either of the three experimental groups (see next section and Figure 1B).

Prior to carrying out the MSL task, participants completed the Standford Sleepiness Scale (SSS) (Maclean, Fekken, Saskin, & Knowles, 1992) to assess their subjective levels of sleepiness. Around 10:30 pm, they were then trained on the motor task during which, depending on their experimental group, they were exposed or not to a rose-like odor through a nasal cannula. Overnight PSG recording began immediately following the training period. To increase sleep efficiency, exact timing for initiating the MSL training and for allowing subjects to sleep was adjusted according to each participant's natural sleep onset preference. After 4hrs of sleep recording time, participants were re-exposed to the rose-like odor during the subsequent episodes of the targeted sleep stage for a maximum of 60 minutes. To achieve maximum exposure time, several bouts of stimulation were necessary. Following the olfactory stimulation period, participants were allowed to complete their night of sleep until they reached 8 hours of recording time. Participants were then retested on the SSS and MSL task two hours after waking to re-assess their performance after enough time to allow for sleep inertia to dissipate.

Experimental Groups

Three groups of subjects participated in this study (see Figure 1B). The **Cond-NREM2** and **Cond-REM** groups received the olfactory stimulus during the training session. This procedure allowed participants to establish a strong association between learning of the novel motor task and the rose-like smell. These two groups were then re-exposed for a maximum of

60 minutes to the same odor during either NREM2 or REM sleep in the second half of the night in order to determine the sleep stage during which optimization of the consolidation process takes place. One additional group, which was not exposed to the odor during the training session (even though a nasal cannula was in place), but was nevertheless exposed to the olfactory stimulus during NREM2 sleep, was included to control for the presence of odor during the encoding stage and the possible non-specific effects of exposing subjects to an olfactory stimulation during NREM2 sleep (**NoCond** group). None of the subject was aware of his or her experimental group assignment, nor had any knowledge of these procedural differences.

Motor Sequence Learning: Finger Sequence Task

Motor sequence learning was tested with an adapted version of the sequential finger tapping task first developed by Karni et al. (Karni et al., 1995). Subjects were asked to practice an explicitly known 8-item sequence of finger movements (2-4-1-3-4-2-3-1, where 1 stands for the index finger and 4 for the little finger) using a procedure employed previously in the laboratory (e.g., Doyon, Korman, et al., 2009), except that subjects were asked to complete 24 blocks of practice of the sequence during the initial training session and 8 others during the retest session. In order to verify that participants had explicitly memorized the motor sequence prior to training, participants were required to repeat the sequence until they were able to reproduce it three times in a row without error. During training, participants were required to practice the sequence by executing the finger movements as quickly as possible while making as few errors as possible, without looking at their hand. To do so, participants had to use a response box comprising four buttons, and to press one button at a time with fingers of their left (non-dominant) hand. They had to practice the sequential movements for as long as a green cross (3 x 3 cm^2) was displayed at the center of a computer screen. Unknown to subjects, the green cross was displayed until 80 finger movements were recorded (one block; ideally corresponding to the production of 10 correct sequences). No information about the sequence or performance feedback was given to the participants during the task. During pre-sleep training, 24 blocks of motor sequence practice were interspersed with 30s periods of rest, during which a red cross was displayed at the center of the screen. The retest session was exactly the same as the training session, but comprised only 8 blocks of motor sequence practice and took place the

following morning. The task was coded using the Cogent2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php) and implemented using MATLAB (Mathworks Inc., Sherbom, MA).

Performance assessment and analyses of the Global performance index (GPI)

Behavioral performance at a sequence motor learning task is often reported as speed (e.g. time between key presses, time for correct sequences, time per block) and/or accuracy (e.g. number of correct key press per block, number of correct sequence). Most studies measured offline consolidation through change in speed, given that accuracy in this type of tasks is typically high and its fluctuations are minimal (Albouy et al., 2015; Debas et al., 2010). However, these small differences in accuracy at the individual level might reflect differences in motor strategy. For example, some participants might prioritize accuracy at the expense of speed while others might prefer to be faster even if it implies making more mistakes. Furthermore, the instructions provided to participants were explicitly to perform the sequence as quickly as possible while making as few errors as possible. Thus in order to reflect these requirements and to account for individual strategy differences, we measured the subjects' performance using a global performance index (GPI).

Similar to indexes in previous research (Dan, King, Doyon, & Chan, 2015; Reis et al., 2009), the GPI was built based upon the following measures of speed and accuracy:

$$speed_{block} = \frac{t_{block}}{n}$$

$$accuracy_{block} = \frac{n - \sum_{block} correct}{n}$$

where *t* corresponds to the time in seconds to complete a block of training and *n* is the number of key presses within a block (80 in this experiment). *Correct* key presses were established using an algorithm identifying correct triplets ([2,4,1], [4,1,3], [1,3,4], [3,4,2], [4,2,3], [2,3,1], [3,1,2], [1,2,4]) in the original task's sequence (2,4,1,3,4,2,3,1). The use of triplets and not pairs avoided the detection of false positive *correct* key presses. When a triplet that was not in the list was found, the last key press of this triplet was marked as incorrect.

In order to account for possible speed-accuracy trade-off, the following global performance index (GPI) was then computed:

$$GPI = e^{-speed} * e^{-accuracy}$$

where *e* is the mathematical constant, also known as the Euler's number, and is define as the base of the natural logarithm (~ 2.71828). The higher the GPI, better the performance was (see Figure 2A). The GPI was used here as it takes into account the time taken to commit and recover from an error, which is typically longer than for correct key presses.

Based on performance of the MSL task during initial training (i.e. prior to group assignment), we identified participants who were outliers, as compared with the average performance of all participants. To do so, we first used a learning curve approach to describe the performance of each participant. Each subject's GPI in the training session (24 blocks) was then fitted using this function:

$$f_{(y)} = \left((S - A) * e^{(R*x)}\right) + A$$

Performance asymptote (*A*), starting point (*S*), slope (*R*) and adjusted r-squared were extracted from this fit - one value for each of these measurements per subjects. On each of these measures, outliers were identified using the generalized extreme studentized deviate (ESD) (Rosner, 1983). The main advantage of the generalized-ESD method over other outlier tests is that it does not find a definite number of outliers, but only needs an upper bound for the possible number of outliers to be specified ("NIST/SEMATECH e-Handbook of Statistical Methods," 2012). Since there was no *a priori* concerning the expected number of outliers, the upper bound was fixed to the total number of participants tested, excluding those who did not meet the required criteria (see *Participant recruitment and selection* section; n = 80). Finally, subjects who had 2 or more values extracted from the fitting curve that surpassed this threshold were considered as outliers and were rejected from further analyses.

Olfactory threshold, stimulus delivery, and analyses

To minimize habituation to the odor, several precautions were taken. First, the olfactometer itself was kept in a separate location from the testing and sleeping rooms. Second,

the manipulation of olfactory stimuli was always conducted outside the testing room. Finally, delivery of the stimulus was carried out using an ON/OFF block design procedure (see Figure 1D). During the ON blocks, the odor was sent for 1 s every 3 s. For the MSL training session, the ON blocks consisted of the period during which subjects were practicing the sequence, while the OFF blocks corresponded to the periods of 30 s of rest in-between. During the targeted stage of sleep, the odor was delivered on a 30 s ON/ 30 s OFF block design for a maximum of 60 minutes.

A solution of phenyl ethyl alcohol (PEA - concentration: 6.31×10^{-3} [% v/v]) and heavy mineral oil (solvent - USP/FCC) was used as the odorant source. PEA has a pleasant rose-like smell and is known as a pure odorant, that is, a chemical substance that stimulates the olfactory nerve exclusively, as opposed to a mixed olfactory/trigeminal odorant that could lead to unpleasant sensations (e.g. burning, itching, cooling, etc.) (Laska, Distel, & Hudson, 1997). Importantly, several studies have shown that the presentation of an olfactory stimulus during sleep does not wake up subjects (Arzi et al., 2010; Badia, Wesensten, Lammers, Culpepper, & Harsh, 1990). The 125 ml emulsion was stored in an air-tight 750 ml glass container connected to an olfactory delivery system using Teflon-coated tubes (Tygon® SE-200, Saint-Gobain Performance Plastics) to deliver the odor to the subject via a Teflon-coated nasal cannula. Teflon does not easily bond to PEA molecules, thus maintaining a constant concentration of PEA in the airflow (Gesser, 2002).

Although odorant concentrations did not vary between subjects, the length of exposure during sleep did vary due to inter-individual differences in sleep architecture. Therefore, analyses were conducted on both sets of participants (all subjects included in behavioral analyses [n = 76] and those included in PSG analyses [n = 64]) in order to verify that there was no significant difference in amount of stimulation between groups. One-way ANOVA were performed on wake duration during cuing (within-subjects factors) and groups (between-subjects factor) to test for any differences between groups. We also investigated, with a similar analysis, the duration of cuing during REM sleep between groups. Finally, one-way ANOVA were conducted on total exposure and duration of cuing during NREM2 sleep durations, within and between groups. Results from post-hoc univariate tests between Cond-NREM2 and NoCond groups were reported to verify that there was no difference.

The PEA concentration in the odorant solution was exactly the same for each participant. However, there were inter-individual differences in terms of their olfactory threshold. Each participant's threshold was identified with the *Sniffin'sticks* test (Burghart Medizintechnik, Germany). A one-way ANOVA was thus performed to determine if there was a difference between groups (between-subjects factor) in olfactory threshold (within-subjects factor) as measured by this test.

Analyses of motor sequence learning and consolidation

Learning during the evening training session was investigated using a mixed design ANOVA for repeated-measures with blocks (n=24) as the within-subjects factor and groups as the between-subjects factor. This analysis permitted to ensure that all participants showed a learning effect during the evening session (main effect of block). It also assessed for differences in learning rate between groups (block x group interaction) and differences between groups in terms of overall MSL skill throughout the session (main effect of group).

In order to investigate the level of performance at the end of the training session (later used in the calculation for the level of consolidation), a mixed repeated-measures ANOVA was conducted with the mean GPI's from the last four blocks of the evening MSL task as the repeated within-subjects factor and groups as the between-subjects factor. This analysis allowed us to determine whether all participants reached an asymptotic performance (main effect of block). It also provided information about the learning rate (block x group interaction) and level of performance (main effect of group) between groups.

The level of consolidation was assessed through a repeated-measures ANOVA conducted with the 2 sessions (training and retest) and 8 blocks (i.e., the last 4 blocks of training and the first 4 blocks of the retest session) as repeated within-subjects factors and groups as the between-subjects factor. Four blocks were used to calculate gains in performance was selected because it has been shown in several studies that there is a warm-up effect occurring during the first block of retest (Rickard et al., 2008; Verwey, 1994). The physiological basis of the so-called *warm-up effect* are not well understood yet, but it is recognized that it tends to drastically inflate inter key-press time during the first retest block. Thus, averaging 4 blocks reduced the

inter-subject variance in performance and allowed for the inclusion of the first retest block. As it is highly possible that the duration of exposure to the olfactory stimulus and the olfaction threshold of each participant would have played an important role in the experimental manipulation occurring overnight, the latter analysis was carried out controlling for the subjects' olfactory threshold (as measured with the *Sniffin' sticks* test) and the duration of exposure to the odor during sleep. Finally, as a post-hoc analysis, we conducted a one-way ANOVA on the difference in GPI between the morning and evening sessions between the 3 groups and carried out planned contrasts analyses assessing the specific differences between groups.

Finally, the same behavioral analyses were also performed with participants who were only included in the EEG and spindles analyses in order to ensure that the results from the entire groups of participants did not differ from the sub-set who had good EEG data.

Polysomnographic (PSG) recording

PSG recordings were acquired using a 16-channel, V-Amp 16 system (Brainamp, Brain Products GmbH, Gilching, Germany) from 10 scalp derivations (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, Oz) referenced to linked mastoids (A1, A2). PSG signals were recorded continuously (at < 5KOhm) during the whole night using Recorder software (Brain Products), and were visually inspected online for quality. Signals were digitalized at 250 samples per second (high pass filter = 0.3 Hz, low pass filter = 70 Hz). PSG measurements included electroencephalogram (EEG), electro-oculogram (EOG), bipolar submental electromyogram (EMG) electrodes as well as a nasal airflow thermistor (Braebon, Ottawa, Canada) to monitor respiratory effort.

For all PSG recordings, including online scoring and stimulation periods, sleep stages were visually identified in 30-s epochs displaying EEG (high pass filter = 0.3 Hz, low pass filter = 35 Hz) from central and occipital derivations (C3, C4, and Oz) referenced to average mastoids (A1 and A2), EOG (high pass filter = 0.3 Hz, low pass filter = 35 Hz) from the lateral outer canthus of each eye, and bipolar sub-mental EMG (high pass filter of 10 Hz). Periods of cortical arousal or movement during sleep were identified using an automated detector when movement continuously exceeded 100 μV for more than 100 ms.

EEG pre-processing

Sleep architecture

PSG recordings were sleep stage scored according to standard criteria (Rechtschaffen & Kales, 1968) using 30 second epochs. Analysis of the sleep architecture was conducted on distinct parts of the night, depending on the timing of the stimulus administration and according to the experimental protocol (see Figure 1C). More specifically, the sleep period occurring before onset of the olfactory stimulation was defined as the *pre-stimulation* phase, while sleep following the beginning of the stimulation phase was defined as the *from-stimulation* phase. Finally, the period of sleep defined as *during-stimulation* comprised only the periods of stimulation in the targeted sleep stage (e.g., NREM2 or REM).

Sleep spindle detection and channel localization

Sleep spindles were automatically detected from Fz, Cz, and Pz in non-REM sleep using Brain Products (Brain Products GmbH, Gilching, Germany) Analyzer software (Version 2.1) with a method described by Ray et al. (Ray et al., 2014). The automated spindle detection technique used a complex demodulation transformation (Walter, 1968) to extract the power of each data point between 11 and 17 Hz, and is similar to the root mean square method employed to transform raw EEG signal (Mölle et al., 2002). Peak amplitude (max peak-to-peak value, in μV), duration (offset-onset, in sec) and peak frequency (max peak-to-peak distance, in Hz) were calculated from the original EEG signal filtered from 11-16Hz. Peak frequency and amplitude were extracted, for each individual sleep spindle, using fast Fourier transforms, as indicated by the power spectrogram. This represents the frequency and amplitude that had the greatest power for each spindle. Spindle density was also calculated based upon the number of spindles per minute. Measures of peak amplitude, duration and peak frequency for each spindle were extracted from all three sites (Fz, Cz, Pz) for analyses.

Given that the same spindle could be detected more or less simultaneously on multiple electrodes as a result of co-detection (Suihko, Malmivuo, & Eskola, 1993) or propagation (Andrillon et al., 2011; Nir et al., 2011; O'Reilly & Nielsen, 2014b), and in line with published

and recommended methods (O'Reilly & Nielsen, 2014a, 2014b), we sought to separate them by their principal recording sites (i.e., Fz, Cz or Pz) as a data pre-processing stage. To do so, we used the onset of each spindle as a marker to determine their primary localisation. For each detected spindle, time-lapse windows were created on the two other derivations before and after a spindle onset (200 msec. for adjacent sites - e.g. Pz and Cz; 400 msec. for non-adjacent sites - Fz and Pz). Spindles were systematically categorized into two groups. First, as *Pure* spindles, that is when an event (a spindle) occurred in only one derivation within the given time window. Second, *Multi-site* spindles were events with occurrence on at least one other electrode within the time frame. Taken together, these spindles were considered as a single event detectable from other recording sites and formed a *Multi-site* groups of spindles. Spindles from the latter class were again divided into two sub-categories: *Source* or *Rejected*. *Source* spindle were defined by their onset as the first ones to occur in a *Multi-site* group and were categorized by recording sites. Finally, the *Rejected* spindles were *Multi-site* spindles that occurred on other derivations after the *Source* spindle and weren't included in the analyses. Importantly, although some recorded events were rejected, no spindle was totally discarded *per se*, as *Source* spindles were kept for analyses. The identification and classification of spindles was carried out using software coded in Matlab (Mathworks Inc., Sherbom, MA).

Several studies have previously utilized a fast/slow spindle classification in order to investigate the function of spindles. Among others, techniques using individual threshold (Ujma et al., 2015) have been described. In contrast to the latter approach, the present technique is based solely on the spindle's derivation. This method was used, in part, because it reduces the risk of losing information from slower spindles occurring in parietal regions and faster spindles in frontal regions. To observe changes produced based upon the categorization on sleep spindle distributions, we reported the percentage of rejected spindles originally detected on Fz, Cz and Pz sites, and then analyzed with paired-sample t-tests the spindle frequency median changes of the distribution caused by the filtering on Fz, Cz and Pz. Furthermore, we investigated the categorization algorithm effect on Pz spindle frequency, by comparing the median and mean, in *pre-matched* and *during-stimulation* sleep periods (see S1 Text).

EEG Analyses

Sleep spindle analyses and stimulation period

Statistical comparisons of spindles were carried out on Fz, Cz and Pz derivations. For each derivation, peak amplitude, duration, peak frequency and density of sleep spindles were analysed. Given that stimulation during sleep was carried out towards the end of the night and that most participants had little or no SWS at the beginning of the re-exposure period, spindle analyses were conducted using NREM2 sleep only.

Furthermore, in order to be able to compare between periods with and without stimulation, a period of sleep of the same length as during-stimulation was selected from the pre-stimulation period for each subject. Starting from the last epoch of NREM2 and going backward in the recording of the pre-stimulation period, the same number of epochs as in the during-stimulation period was selected for each subject. This period was defined as pre-matched. It served as a baseline and permitted us to compare the events during the stimulation closest to the previous periods of NREM2 sleep (Figure 1C).

Given that one of our main hypotheses was that cuing during NREM2 sleep would induce changes in sleep spindles, we used one-way ANOVAs to assess the differences in spindle characteristics (within-subjects factor) between groups (between-subjects factor), first in the pre-matched period to ensure that all groups were similar before cuing, and second in the during-stimulation sleep periods. We also investigated the effect of cuing by measuring and analyzing difference (Δ% in spindle characteristics between two sleep periods: pre-matched (baseline) versus during-stimulation (cuing). This differential score was calculated by measuring the percent change for each spindle characteristic between the two periods of interest. One-way ANOVAs analyses were used to investigate the pre-matched versus during-stimulation differences (within-subjects factor) between the Cond-NREM2 and NoCond groups (between-subjects factor). We also assessed the nature of changes in spindle frequency probed by the stimulation by analyzing changes in specific bins of 0.5 Hz (11-17 Hz) between the pre-matched and during-stimulation periods for both the Cond-NREM2 and NoCond groups with Chi2 analyses (Bonferroni-corrected for the number of bins). This analysis provided information about the specific ranges of frequency that were modified by the manipulation.

In order to provide a better and unbiased estimation of the group differences regarding various spindle characteristics (frequency, amplitude, duration, density) we performed a bootstrap analysis (Lunneborg, 2001). Specifically, for each spindle characteristic (e.g. frequency) and for each group, we generated 5000 data samples (sampling with replacement), equal in size with the original sample in both groups (N=21 for Cond-NREM2 and N=22 for NoCond; see S1 Text for more details about this procedure). To control for multiple independent comparisons, a Bonferroni correction for 12 comparisons ($p<0.004$) was applied on the bootstrap results (3 electrodes x 4 spindle characteristics).

Mediation analyses

Finally, we conducted mediation analyses, using change between sleep periods in spindle characteristics as a mediator, experimental conditions as an independent variable and gains in performance as the outcome measure, using PROCESS, an SPSS add-on module (Hayes, 2013). We used a single mediator model and the mediation effect was tested using a bias corrected and accelerated bootstrap procedure (1000 samples – [BCa])(Bradley Efron, 1987).

Ethics Statement

The present study was revised and approved by an institutional ethics committee ("Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec"; ID: CMER-RNQ 09-10-026). Upon their arrival at the sleep laboratory for the screening night, all participants were asked to read carefully, and sign the written consent form.

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Supplemental Information

Article 1: NREM2 and Sleep Spindles are Instrumental to the Consolidation of Motor Sequence Memories

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Supplemental Information

1. Supplemental Data: figure S1-S2 and tables S1-S3
2. Supplemental Experimental Procedures
3. Supplemental Results
4. Supplemental References

Figure S1-S4 and Tables S1-S3

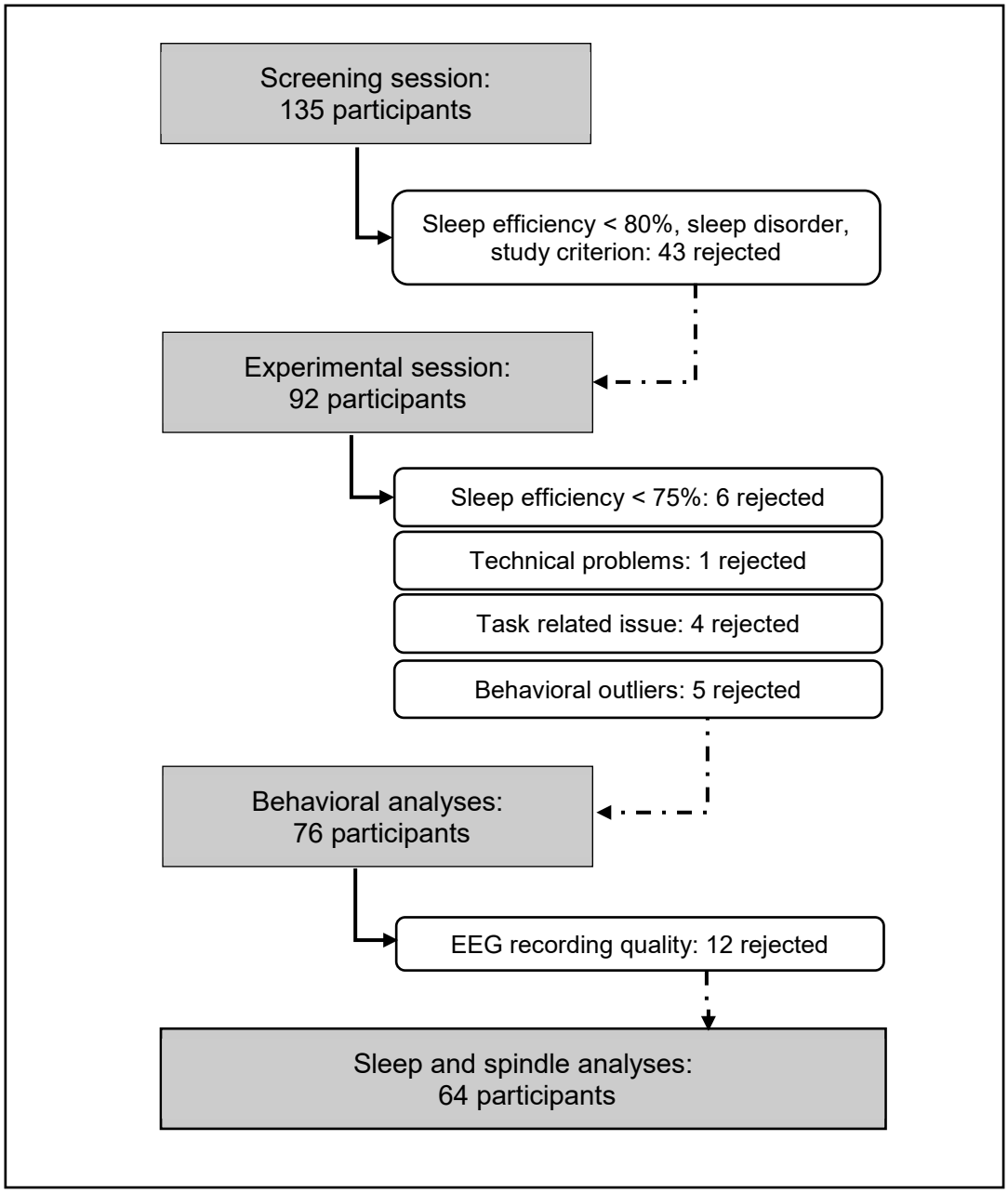

Figure S1. CONSORT diagram illustrating the selection of eligible participants across the study phases.

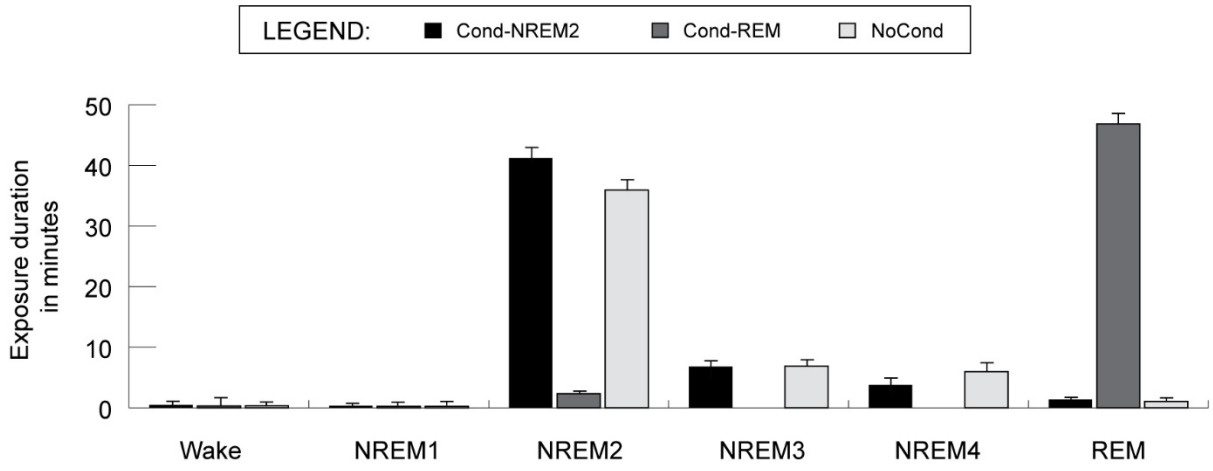

Figure S2. Duration of exposure to the olfactory stimulus during sleep stages.

The great majority of the olfactory stimulation occurred during the targeted stage in each group (Cond-NREM2 and NoCond: NREM2 sleep; Cond-REM: REM). No differences were found when assessing the total exposure time or targeted durations between the 3 groups. Also, no difference was found when looking at the duration of exposure during NREM2 sleep between the Cond-NREM2 and No-Cond groups.

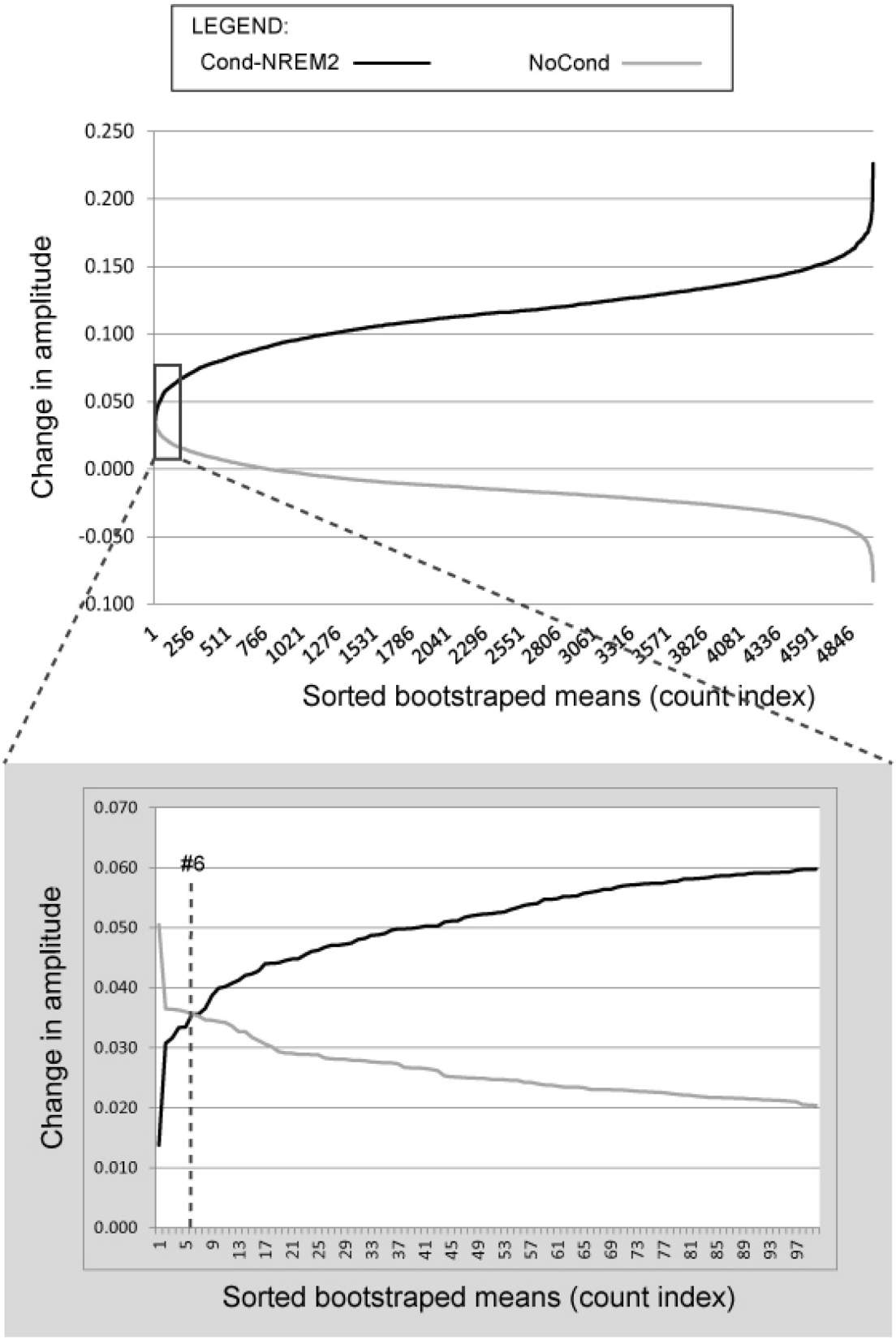
LEGEND:
Cond-NREM2
NoCond
Change in amplitude
0.250
0.200
0.150
0.100
0.050
0.000
-0.050
-0.100
1
256
511
766
1021
1276
1531
1786
2041
2296
2551
2806
3061
3316
3571
3826
4081
4336
4591
4846
Sorted bootstraped means (count index)
Change in amplitude
0.070
0.060
0.050
0.040
0.030
0.020
0.010
0.000
#6
1
5
9
13
17
21
25
29
33
37
41
45
49
53
57
61
65
69
73
77
81
85
89
93
97
Sorted bootstraped means (count index)

Figure S3. Sorted bootstrap random sampling changes in sleep spindle amplitude at Pz.

5000 random change in amplitude samples from Cond-NREM2 and NoCond groups were extracted and sorted in ascending and descending order, respectively. This procedure allowed to compare the highest value from the NoCond group with the smallest value of the Cond-NREM2. The sorted value lines crossed each other at index #6 (NoCond>Cond-NREM2 in 6; Cond-NREM2>NoCond in 4994 cases out of 5000; see inlet). This analysis yielded a significant difference between Cond-NREM2 and NoCond groups ($p = .0012$).

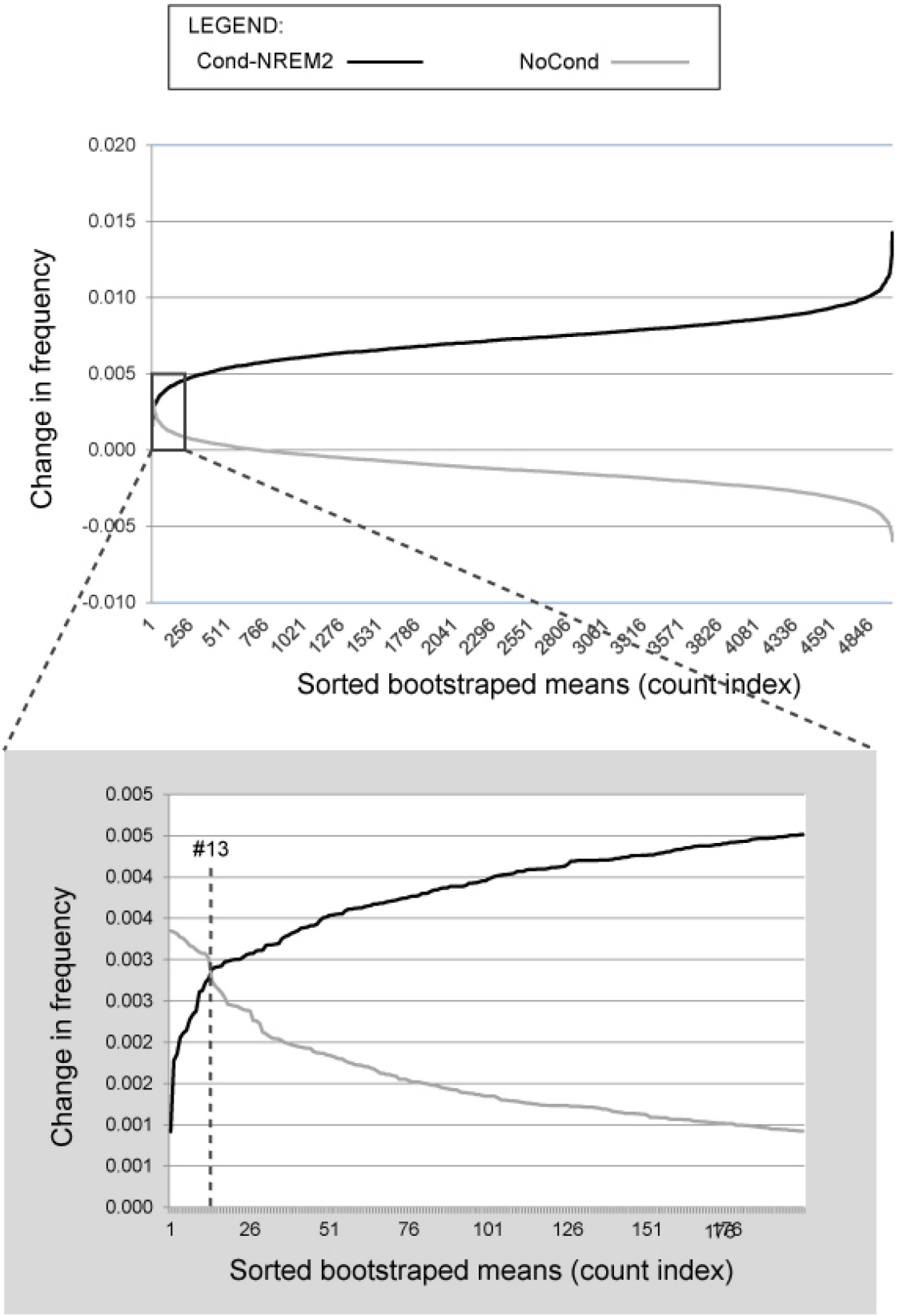
LEGEND:
Cond-NREM2
NoCond
Change in frequency
0.020
0.015
0.010
0.005
0.000
-0.005
-0.010
1
256
511
766
1021
1276
1531
1786
2041
2296
2551
2806
3061
3316
3571
3826
4081
4336
4591
4846
Sorted bootstraped means (count index)
Change in frequency
0.005
0.005
0.004
0.004
0.003
0.003
0.002
0.002
0.001
0.001
0.000
#13
1
26
51
76
101
126
151
176
Sorted bootstraped means (count index)

Figure S4. Sorted bootstrap random sampling changes in sleep spindle frequency at Pz.

5000 random change in frequency samples from Cond-NREM2 and NoCond groups were extracted and sorted in ascending and descending order, respectively. As with amplitude, this procedure allowed to compare the highest value from the NoCond group with the smallest value of the Cond-NREM2 group. The sorted value lines crossed each other at index #13 (NoCond>Cond-NREM2 in 13; Cond-NREM2>NoCond in 4987 cases out of 5000; see inlet). This analysis yielded a significant difference between Cond-NREM2 and NoCond groups ($p = .0026$) . doi:10.5061/dryad.b4t60.

Table S1. Olfactory stimulation during sleep.

	Cond-NREM2		Cond-REM		NoCond		F	p	*(Cond-NREM2 vs NoCond)* p
All subjects	Mean	S.E.	Mean	S.E.	Mean	S.E.	$F_{(2,73)}$		
Wake	0.5	0.1	0.3	0.1	0.3	0.1	0.449	0.64	1.00
NREM1	0.3	0.1	0.4	0.1	0.2	0.1	1.206	0.30	0.74
NREM2	39.0	2.2	2.7	2.3	32.0	2.1	73.127	< 0.01	0.07
SWS	12.0	1.8	< 0.1	1.9	14.6	1.7	18.446	< 0.01	0.89
REM	1.4	1.6	44.8	1.7	1.9	1.5	230.441	< 0.01	1.00
Total exposure	53.4	1.6	48.4	1.7	49.2	1.5	2.671	0.08	0.19
Only subjects in PSG analyses	Mean	S.E.	Mean	S.E.	Mean	S.E.	$F_{(2,61)}$		
Wake	0.5	0.2	0.3	0.2	0.3	0.2	0.355	0.70	1.00
NREM1	0.4	0.1	0.3	0.1	0.2	0.1	0.614	0.54	0.84
NREM2	40.9	2.7	2.7	2.3	35.6	2.2	83.794	< 0.01	0.30
SWS	10.7	1.9	0	0	12.8	1.9	12.764	< 0.01	1.00
REM	1.6	1.5	46.4	1.5	1.2	1.5	291.780	< 0.01	1.00
Total exposure	54.1	1.7	50.0	1.7	50.2	1.6	2.001	0.14	0.27

Legend: Duration is shown in minutes. Analyses were carried out separately using data from all participants included in the behavioral analyses or from the sub-set of subjects included in the PSG analyses. The two sets of data yielded a similar pattern of results. One-way ANOVAs were performed to assess whether there were any group differences in wake, sleep stages or total duration of stimulation. Importantly, the results did not reveal any difference in length of either wake or total exposure time between groups, but yielded the expected differences in exposure time between groups during the two targeted sleep stages (i.e. NREM2 and REM). Furthermore, post-hoc univariate tests on the duration of cuing during NREM2 sleep and total exposure duration between the Cond-NREM2 and NoCond groups did not reveal significant differences, showing that both groups had received a similar amount of odor during the stimulation period.

Table S2. Sleep architecture.

	Cond-NREM2		Cond-REM		NoCond		$F_{(2,61)}$	p
Pre-stimulation	Mean	S.E.	Mean	S.E.	Mean	S.E.		
Wake	27.1	5.0	28.8	4.5	34.8	6.7	0.531	0.59
NREM1	10.1	1.2	12.0	2.0	12.0	1.8	0.416	0.66
NREM2	116.9	9.0	113.7	10.1	108.9	6.9	0.217	0.81
SWS	97.2	5.3	101.5	8.4	84.1	7.4	1.635	0.20
REM	44.3	4.3	40.7	2.8	38.7	4.2	0.564	0.57
Movement	0.1	<0.1	0.1	0.1	0.3	0.2	1.356	0.27
Total Recording Time (TRT)	297.5	12.0	299.1	8.6	280.1	9.1	1.045	0.36
Total Sleep Time (TST)	268.6	10.8	267.9	6.0	243.8	9.0	2.584	0.08
Sleep Efficiency (%)	91%	<0.1	90%	<0.1	87%	<0.1	1.076	0.35
From-stimulation								
Wake	22.4	4.4	22.0	4.6	17.3	2.4	0.558	0.58
NREM1	7.6	1.3	7.3	1.0	8.0	0.8	0.109	0.90
NREM2	82.9	4.8	77.9	5.8	85.7	5.2	0.567	0.57
SWS	25.4	4.4	25.5	5.7	28.7	4.3	0.151	0.86
REM	48.2	4.8	62.9	4.6	57.4	4.7	2.442	0.10
Movement	0.1	0.1	0.0	0.0	0.3	0.2	1.239	0.30
Total Recording Time (TRT)	187.6	10.9	197.3	6.7	199.4	8.1	0.515	0.60
Total Sleep Time (TST)	164.1	10.3	173.5	8.4	179.8	8.5	0.760	0.47
Sleep Efficiency (%)	87%	<0.1	86%	<0.1	90%	<0.1	0.514	0.60

Legend: All sleep measurements are presented in minutes, except for sleep efficiency which corresponds to a percentage calculated from the ratio of TST on TRT. One-way ANOVAS were conducted for each sleep characteristic to determine whether there were any significant differences in sleep architecture between groups before, as well as from the onset of the cuing period. As expected, there were no significant group differences in any of the sleep phases and characteristics.

Table S3. Spindles characteristics for each sleep period during NREM2 at Pz.

	Cond-NREM2 m (n=21)		**NoCond** m (n=22)		t_{41}	p
Pre-matched	Mean	S.E.	Mean	S.E.		
Amplitude	67.58	9.45	73.00	10.60	-0.380	.71
Frequency	13.33	0.11	13.34	0.11	-0.082	.94
Density	3.47	0.12	3.64	0.15	-0.892	.38
Duration	0.58	0.02	0.57	0.03	0.145	.89
During-stimulation						
Amplitude	71.98	9.25	69.63	11.26	0.160	.87
Frequency	13.42	0.11	13.27	0.12	0.890	.38
Density	3.48	0.13	3.80	0.13	-1.630	.11
Duration	0.63	0.04	0.60	0.04	0.659	.51

Legend: Amplitude is reported in μV, frequency is in Hz, spindle density is in number of spindles per minute of sleep and duration is in second. Independent-samples t-tests were conducted on the mean of each spindle characteristic to test differences between groups. T-tests were also performed on Cond-NREM2 and NoCond groups for the sleep periods before and from the onset of exposure to the odor cue. It is important to note that no significant differences were found between groups in sleep spindle for any of the sleep period.

2. Supporting Experimental Procedure

Changes in sleep spindle characteristics bootstrap and control for multiple comparisons

In order to provide a better and unbiased estimation of the group differences regarding various spindle characteristics (frequency, amplitude, duration, density) we performed a bootstrap analysis (Lunneborg, 2001). Specifically, for each spindle characteristic (ex. frequency) and for each group we generated 5000 data samples, equal in size with the original sample in each group (N=21 for Cond-NREM2 and N=22 for NoCond). These samples were drawn at random, with replacement, from their respective original samples. For each of them, the mean of the spindle characteristic was computed, thus yielding a distribution of 5000 means for each spindle characteristic and group. In order to avoid any ties, we calculated each mean with a precision of six digits. Given that the overall mean of Cond-NREM2 was higher than that of NoCond, we sorted the 5000 means of Cond-NREM2 in ascending order, and the 5000 means of NoCond in descending order and we paired them. Then, we computed the group difference between each of these sorted mean pairs. This procedure allowed us to compare the highest value from NoCond with the smallest value of Cond-NREM2, the second-highest value from NoCond with the second-smallest value of Cond-NREM2, etc. Given that we expected a difference in favor of Cond-NREM2 (experimental hypothesis), the null hypothesis is reflected in the opposite situation, whenever NoCond>Cond-NREM2. Thus, following the described procedure, one can calculate the probability for the Type I error by counting in how many cases the mean of NoCond is greater than that of Cond-NREM2, out of the 5000 mean pairs. For example, if in 100 out of 5000 pairs, the NoCond> Cond-NREM2, then the probability of Type I error when we claim the opposite, that Cond-NREM2 mean is greater than NoCond mean, is 100/5000=0.02.

3. Supporting Results

Additional behavioral analyses

Additional behavioral analyses were carried out, including the data from subjects considered as outliers. Accordingly, a repeated measure ANOVA was first conducted on data from the last 4 blocks of the training session and the first 4 blocks of the retest session. Similarly to the results reported in the manuscript, this new analysis revealed a main effect of session ($F_{1, 75} = 10.033$, $p = .002$) and a session x group interaction ($F_{2, 75} = 3.997$, $p = .022$), demonstrating that while all participants showed gains in performance between the two sessions, there was a significant group difference in the amount of gains observed the next day (i.e., motor sequence consolidation). Planned contrasts analyses also revealed that the Cond-NREM2 group exhibited greater gains in performance than the NoCond group ($p = .006$), and showed a trend toward a significant difference in gains compared to the Cond-REM group ($p=.083$). Again, as previously reported, performance of the Cond-REM and NoCond groups did not differ significantly ($p = .27$).

Changes in sleep spindle characteristics bootstrap and multiple comparisons analyses

Using this procedure for each of the spindle characteristics we found the following results: for spindle amplitude (NoCond>Cond-NREM2 in 6; Cond-NREM2>NoCond in 4994 cases out of 5000; see Figure S3), for spindle frequency (NoCond>Cond-NREM2 in 13; Cond-NREM2>NoCond in 4987 cases out of 5000; see Figure S4), for spindle duration (NoCond>Cond-NREM2 in 47; Cond-NREM2>NoCond in 4953 cases out of 5000), and for spindle density (NoCond>Cond-NREM2 in 3882; Cond-NREM2> NoCond in 1118 cases out of 5000). These results yielded the following p-values: 0.0012 (amplitude), 0.0026 (frequency), 0.0094 (duration) and 0.7764 (density). These findings are consistent with those reported in our manuscript. Moreover, they indicate that, using the described bootstrap procedure, there was a significant difference between the two groups (Cond-NREM2>NoCond) for amplitude and frequency, even after correcting for multiple comparisons (using Bonferroni correction for 12 comparisons: 4 characteristics*3 electrode locations – Pz, Cz, Fz; a reference p-value of 0.0041).

Effect of categorizing sleep spindle frequencies at Pz

The categorization algorithm used in this paper had the effect of reducing the overlap between frontal and parietal spindle frequencies. Further analyses were conducted to investigate the filtering effect on sleep spindle frequencies originating specifically at the Pz recording site. As expected, the median frequency at Pz in the *pre-matched* (without filtering = 13.428 Hz; with filtering = 13.428 Hz) and *during-stimulation* (without filtering = 13.428 Hz; with filtering = 13.428 Hz) sleep periods did not change whether filtering was applied or not. Yet the same categorization process did have the effect of slightly lowering the mean frequency in both *pre-matched* (without filtering = 13.3458 Hz; with filtering = 13.3307 Hz) and *during-stimulation* (without filtering = 13.3970 Hz; with filtering = 13.3823 Hz) sleep periods. Finally, the difference in frequency between the pre-matched and during-stimulation sleep periods were again similar whether filtering was applied or not (without filtering: 0.051 Hz; with filtering: 0.052 Hz). Hence, the categorization algorithm had no major impact on the frequency of Pz spindles during these sleep periods.

Analyses conducted on the filtered spindles dataset (and reported in the main article) were also ran on all spindles (before filtering). When we compared changes in spindle characteristics between the pre-matched and during-stimulation sleep periods, the one-way ANOVA comparing percent change (Δ%) revealed a significant difference in peak amplitude ($F_{1, 41} = 4.950$, $p = .03$) and a trend toward significance in peak frequency ($F_{1, 41} = 3.043$, $p = .09$) between the Cond-NREM2 and NoCond groups. Similar to results with the filtered spindles dataset, however, one-sample t-tests revealed that only the Cond-NREM2 group had a significant increase in Δ% in peak frequency (Cond-NREM2: $t_{20} = 2.786$, $p = .01$; NoCond: $t_{21} = 1.308$, $p = .21$) and Δ% in duration (Cond-NREM2: $t_{20} = 5.667$, $p < .001$; NoCond: $t_{21} = -1.167$, $p = .23$). Results for Δ% peak amplitude did not reach significance in either groups (Cond-NREM2: $t_{20} = 1.993$, $p = .06$; NoCond: $t_{21} = -1.167$, $p = .26$). Overall the results from unfiltered spindles are thus similar in many ways to the filtered ones (i.e., results presented in the main manuscript), although some effects were weaker. However, the differences found between both set of results highlight even more the importance of applying a categorization algorithm as a preprocessing step prior to analyzing sleep spindles.

Article 2: Beyond spindles: interactions between sleep spindles and boundary frequencies during cued reactivation of motor memory representations.

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Soumis à: SLEEP
Manuscript ID: SLEEP-2017-0611

Abstract

There is now ample evidence that sleep spindles play a critical role in the consolidation of newly acquired motor sequences. Previous studies have also revealed that the interplay between different types of sleep oscillations (e.g., spindles, slow waves, sharp wave ripples) promotes the consolidation process of declarative memories. Yet the functional contribution of this type of frequency-specific interactions to motor memory consolidation remains unknown. Thus, the present study sought to investigate whether spindle oscillations are associated with low-/high-frequency activity at the regional (local) and inter-regional (connectivity) levels. Using an olfactory-targeted memory reactivation paradigm paired to a motor sequence learning task, we compared the effect of cuing (Cond) to no-cuing (NoCond) on frequency interactions during sleep spindles. Behavioral results revealed that cuing significantly enhanced performance the next day for the Cond compared to the NoCond group. Importantly, time-frequency decomposition analyses also showed that cuing induced significant differential and localized changes in delta (1-4 Hz) and theta (4-8 Hz) frequencies before, during and after spindles, as well as changes in high-beta (20-30 Hz) during the spindle oscillation. Finally, coherence analyses revealed significant increases in connectivity during sleep spindles in both theta and sigma (11-16 Hz) bands in the cued group only. These results support the notion that the synchrony between spindle and associated low-/high-frequency rhythmic activity is an integral part of the consolidation process. Furthermore, they highlight the importance of not only measuring spindles' characteristics, but to investigate such oscillations in both time and frequency domains when assessing memory consolidation-related changes.

Keywords: sleep, memory, reactivation, motor sequence learning, sleep spindle, coherence, theta, high-beta

Abbreviations list: BMI: body mass index; Cond: experimental group conditioned to the olfactory stimulus and cued during NREM2 sleep; EEG: electroencephalography; EMG: electromyography; EOG: electrooculography; ERSP: Event-related signal perturbations; GPI: global performance index; iCoh: imaginary part of coherency; MSL: motor sequence learning; NoCond: experimental group not previously conditioned to the olfactory stimulus but exposed

to the odor during NREM2 sleep; NREM: non rapid eye movement sleep. This sleep stage is comprised of four different sub-stages (1 to 4). However, the American Academy of Sleep Medicine now regroup stage 3 and 4 into a single stage: NREM3; PEA: phenyl ethyl alcohol; PSG: polysomnographic; REM: rapid eye movement sleep; SO: slow oscillation; SWA: slow wave activity; SWS: slow wave sleep (stage 3 and 4 sleep, also known as NREM3); TMR: targeted memory reactivation; TST: total sleep time; TRT: total recording time; SE: sleep efficiency.

Introduction

The seemingly effortless manner in which we successfully produce complex tasks, such as walking, driving or typing on a keyboard, involve prior training of simple, stereotyped and sequential repetitions of movements - a form of procedural memory called motor sequence learning (MSL) (Doyon et al., 2002; Karni et al., 1998). A large body of work has shown that memory traces associated with this type of learning are transformed and strengthened over time into an enduring and more accessible state. This memory consolidation process unfolds through a complex series of interactions between multiple cerebral structures (Doyon, Bellec, et al., 2009; Fogel et al., 2017; Lehéricy et al., 2005; Maquet, 2001; Edwin M Robertson, Pascual-Leone, & Miall, 2004; Robert Stickgold & Walker, 2013), and to rely upon mechanisms occurring during sleep (NREM sleep, in particular), depending on the cognitive processes needed to perform the learned motor sequence task (Doyon, Korman, et al., 2009; Korman et al., 2007; Walker, 2005).

Numerous studies have investigated the nature of the changes in electrophysiological events that are specific to certain stages of sleep (e.g., sleep spindles, slow waves, ponto-geniculo-occipital waves) and associated with procedural memory consolidation (Nishida & Walker, 2007; Rasch et al., 2007; Smith, Nixon, & Nader, 2004). Researchers have consistently reported that certain characteristics of sleep spindles (e.g., amplitude, density, duration) are modulated following MSL and that sleep spindles correlate with gains in performance following training on a MSL task (Albouy, Fogel, et al., 2013; Barakat et al., 2011, 2012; Fogel & Smith, 2006; Fogel et al., 2007; Nishida & Walker, 2007). Spindles are synchronous thalamocortical events specific to non-rapid eye movement (NREM) sleep which oscillate in the sigma band (~11-16 Hz) - particularly abundant in NREM2 compared to slow wave sleep (SWS). In support to this spindle/memory consolidation functional link, a recent targeted memory reactivation study from our group in which participants were exposed during NREM2 sleep to an olfactory stimulus previously associated to a MSL task, has confirmed the active involvement of sleep spindles in motor sequence memory consolidation (Laventure et al., 2016). More specifically, we found that only parietal spindle events were significantly involved in the consolidation of a novel motor sequence memory trace.

However, there is evidence to suggest that lasting neuro-plastic changes involved in memory consolidation are not only dependent upon sleep spindle activity, but upon brain functional dynamics involving several other types of oscillations as well (Marshall & Born, 2007; Rasch et al., 2007; M Steriade, 2006). In an influential model, called the a*ctive system consolidation model*, sleep spindles are described as a single element in a complex homeostatic process that interact with other types of oscillations such as slow oscillations (SO) and sharp wave-ripples (SWR) during the consolidation process (Clemens et al., 2007; Destexhe, Contreras, & Steriade, 1999; Klinzing et al., 2016; Maingret et al., 2016; Mölle et al., 2002; M Steriade, 1999). First, previous studies showed that non-procedural learning produces an increase in sleep spindle activity during SO up-states – corresponding to the depolarisation phase of the participating neurons (Mölle, Eschenko, Gais, Sara, & Born, 2009). Still, it is not clear whether these learning-related changes in sleep spindles, time-locked to slow wave activity (SWA), are also manifest during other forms of memory, such as MSL consolidation. Second, several studies have also revealed evidence of temporal coupling between hippocampal SWR and spindles, and have proposed that such synchronous oscillations may constitute the underlying neuronal mechanisms involved in information transfer and memory consolidation (Clemens et al., 2011; Siapas & Wilson, 1998; Sirota et al., 2003). More recently, neocortical recordings in rodents (Averkin et al., 2016) have revealed the presence of gamma activity synchronized to spindle oscillations. It was hypothesized that this high-frequency activity may be involved in the reactivation of memory traces during sleep. There is also limited evidence of similar synchronisation between spindles and higher frequency activity in humans (Clemens et al., 2011). Yet no studies have looked at inter-frequency dynamics, e.g., beta time-locked to spindles, in relation to memory consolidation. Thus, while previous human studies investigating sleep spindles mainly focused on the sigma band, it remains unclear whether task-related changes outside the spindle frequency range are involved in motor memory consolidation, and whether these boundary frequencies are coordinated with spindles. Finally, other studies looking at changes in cerebral connectivity, time-locked to spindle activity in animals (Contreras, Destexhe, Sejnowski, & Steriade, 1996) and humans (Andrade et al., 2011; Andrillon et al., 2011; Nir et al., 2011; Zerouali et al., 2014) have described the cortico-thalamic and cortico-cortical interactions between different regions during sleep spindle events. MSL-related

topographic connectivity changes occurring during spindles, however, remain to be described in humans.

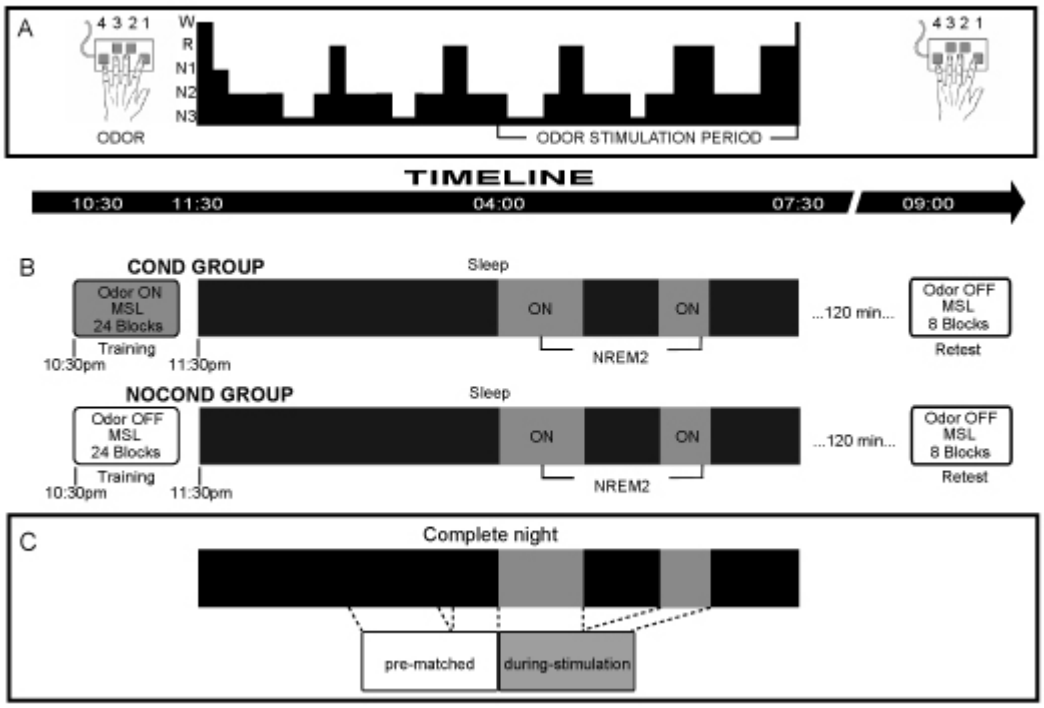

Figure 1. Experimental design.

(A) **Overview of the experimental design**. Subjects participated in a TMR protocol, which consisted of the association (or not) of an olfactory stimulus during training on a motor sequence task. During subsequent sleep in the second half of the night, subjects were then re-exposed to the associated olfactory cue. The effects of the TMR manipulation were then assessed by comparing the subjects' performance between the training and retest sessions. (B) **Experimental groups**. Subjects were randomly assigned to one of two groups: The "Cond" group was first exposed to the odor during the evening MSL training session, and re-exposed to the same stimulus during NREM2 sleep stage. By contrast, the "NoCond" group was not exposed to the odor while training, but received olfactory stimulation during NREM2 sleep. All groups were retested on the MSL task the next morning. (C) **Sleep periods**. The "*stim"* period comprised segments of sleep during which the odor was represented to the participants. By contrast, the "*pre-stim"* period consisted of NREM2 sleep episodes that occurred before the onset of the olfactory cuing and that were length-matched to the *stim* periods.

Accordingly, considering that sleep spindles are part of a larger information transfer process observable in the frequency and time domains, it is thus critical to investigate the

dynamical changes in related oscillations through spindles and their associated connectivity. Here, we examined the changes across frequency bands, from delta to beta, time-locked to spindle events, and observed spatial connectivity in relation to NREM2 parietal sleep spindles in an olfactory targeted memory reactivation (TMR) paradigm design (Laventure et al., 2016). This paradigm allowed us to investigate task-dependant changes in cortical activity associated with the reactivation of a newly acquired memory trace. Participants were exposed during NREM2 sleep to a rose-like odor, which was (or not) previously associated to a MSL task (Figure 1). The following morning, participants were then retested on the same task in order to evaluate the offline performance gains between both sessions, as an index of behavioral MSL consolidation. We hypothesized that cuing and reactivation of the motor memory trace would induce local spectral power increases in the delta band, time-locked to sleep spindles, as well as increases in sigma during spindles. Additionally, we expected that connectivity would significantly increase during sleep spindles in the sigma band in the cued group only, covering parietal and central regions related to the acquisition and consolidation of a motor sequence memory trace.

Material and Methods

Participants

Participants in the present study constituted a subset of the groups of subjects from our previous TMR experiment (Laventure et al., 2016), in which we investigated the role of sleep stages and spindles in sequence motor learning consolidation. A third group, which was stimulated during REM sleep in our previous work, was not included in the present study for lack of spindles in this sleep stage.

Pre-selection and screening session

Prior to a screening night at our sleep laboratory, participants were selected following a series of strict inclusion criteria. Eligible participants had to be right handed, between 20 and 35

years of age and free of any history of neurological, psychological, psychiatric or sleep disorders. Subjects with previous formal training in playing a musical instrument, or any training as a professional typist were excluded in order to control for pre-existing experience in tasks requiring highly coordinated finger movements. Obese individuals (BMI > 30) and, those using nicotine regularly or users of recreational drugs were also excluded. Furthermore, individuals who worked night shifts, were engaged in trans-meridian trips in the three months prior to the study, or reported taking 3 or more servings of caffeinated beverages per day, were not included in the study. All eligible participants had to have a score lower than 10 on the Beck Anxiety Inventory (Beck et al., 1988) and the short version of the Beck Depression Inventory (Beck et al., 1974). Sleep quality was also assessed with the Pittsburgh Sleep Quality Index questionnaire (Buysse et al., 1989).

Participants who met the initial eligibility criteria underwent overnight polysomnographic (PSG) screening in the sleep laboratory according to the American Academy of Sleep Medicine guidelines (Iber et al., 2007). PSG screening included EEG, electrooculography (EOG), leg and facial (submental) electromyography (EMG), thoracic and abdominal respiratory effort and airflow; all of these measures being employed to identify signs of sleep disorders (e.g., insomnia, apnea, parasomnias, etc.), which were used as exclusion criteria. In addition, the screening night allowed us to objectively quantify the subjects' sleep quality and to provide an opportunity for the participants to become acclimatized to the laboratory environment.

Upon arrival for the screening night, an olfactory threshold test was carried out to assess each individual's level of scent detection (using *Sniffin'sticks*, Burghart Medizintechnik, Germany). This olfactory threshold was subsequently used as a covariate in behavioral analyses, but did not constitute an exclusion criterion *per se*. Only participants without any signs of a sleep disorder and who had a sleep efficiency over 80% were selected to participate in the present study. They were then invited to come back one week later for the experimental night. They were instructed to abstain from alcohol for the duration of the experiment. Subjects were asked to keep a strict sleep/wake schedule, *i.e.,* to go to bed between 10:00 p.m. and 1:00 am, to wake up between 6:00 a.m. and 9:00 a.m., and to abstain from taking naps during the day. To ensure that participants adhered to this sleep/wake schedule during the week separating the

screening and experimentation nights, they were asked to wear an actigraph on their wrist (Actiwatch 2, Phillips Respironics) and to complete a sleep diary. Individuals who did not follow this sleep/wake schedule were not enrolled in the study, and did not participate in the experimental night.

Experimental session

From the selection process, a total of 58 participants were retained to complete the present study. From this group, nine were discarded from the analyses for the following reasons: two were excluded due to poor sleep efficiency (<75%), one as a result of MSL performance identified as outlier and six were discarded due to poor quality EEG recordings. Hence, 49 participants were included for subsequent analyses: 25 subjects were assigned to the Cond group (mean age: 24.8 ± 5.0 years, 11 females) and 24 to the NoCond group (mean age: 24.9 ± 4.0 years, 11 females).

Overall Experimental Design and Procedure

About a week following the screening process, participants meeting all the inclusion criteria were invited again to the sleep laboratory for the experimental session. After installation of the EEG electrodes and the olfactory delivery apparatus, subjects were assigned randomly to one of the two experimental groups (Cond, NoCond; see Figure 1B).

Prior to training on the MSL task, participants were asked to complete the Standford Sleepiness Scale questionnaire (Maclean et al., 1992) to measure their subjective levels of alertness/sleepiness. Around 10:30 pm, subjects were then trained on the motor task during which they were exposed, or not, to a rose-like odor through a nasal cannula. Following completion of the MSL task, participants were instructed to get into bed and prepare for sleep. Overnight PSG recordings started from lights out to lights on for a total maximum duration of about 8 hours. After four hours of recordings, participants were then exposed to the rose-like olfactory stimulus during NREM2 sleep periods for a maximum of 60 min. When stimulation

was completed participants were allowed to complete their 8-hour night of sleep. Upon waking, a period of two hours preceded the retest session to ensure dissipation of sleep inertia.

Experimental Groups

Two groups participated in this study (Figure 1B). The **Cond** group was exposed to the rose-like odor during the training session, and re-exposed for a maximum of 60 minutes during NREM2 sleep comprised in the second half of the night. By contrast, the **NoCond** group was not exposed to the odor during training on the MSL task, but was exposed to the same olfactory stimulus during NREM2 sleep akin to the Cond group. Having not been exposed to the odor during training, the NoCond group thus allowed us to control for potential unknown effects of post-training and sleep-related olfactory stimulation. Furthermore, it served as a control condition to test for the effect of cuing on behavior (MSL task), sleep patterns and EEG data.

Motor Sequence Learning: Finger Sequence Task

The finger tapping task used for the present study was an adapted version of the 5-item MSL paradigm (Karni et al., 1995), as described in detail in Laventure et al. (2016). Briefly, subjects were first trained to explicitly remember an 8-item sequence of finger movements (2-4-1-3-4-2-3-1, where 1 stands for the index finger and 4 for the little finger). Then, prior to the training session, participants were asked to correctly reproduce the sequence three times in a row while fixing a cross in the center of a computer screen. Following that verification procedure, subjects were asked to complete the formal training session, composed of 24 blocks of practice interspersed of 30 seconds of rest. Unknown to the subjects, each practice block was composed of 80 key presses. Prior to the beginning of the training session, participants were explicitly asked to try to reproduce the sequence "as fast and accurately as possible". The next morning, they were then asked to complete 8 blocks of the same finger sequence motor task in a retest session. The task was coded using the Cogent2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php) and implemented using MATLAB (Mathworks Inc., Sherbom, MA).

Performance assessment and analyses

Based on previous work in our lab (King, Harring, Oliveira, & Clark, 2011; Laventure et al., 2016), a global performance index (GPI) was used to assess performance on the MSL task. This index takes into consideration the requirements given to each subject regarding speed and accuracy (see *Motor Sequence Learning: Finger Sequence Task* section), and has the additional advantage of controlling for individual strategy. Outlier performance was identified by testing the learning curve characteristics from the training session of each individual using the generalized extreme studentized deviate (Rosner, 1983) as described in our previous study (Laventure et al., 2016).

The effect of the evening training session on motor abilities was measured using a mixed design ANOVA for repeated-measures with blocks (n=24) as the within-subjects factor and groups as the between-subjects factor. This allowed us to test for a learning effect during the training session (main effect of block), and for differences in learning rate between groups (block x group interaction) and differences between groups in terms of overall skill on the MSL task throughout the session (main effect of group).

Information about the end of training was examined using another mixed repeated-measures ANOVA with the average GPI from the last four blocks of this MSL session as repeated within-subjects factor and groups as between-subjects factor. This analysis assessed whether asymptotic performance was reached by participants by the end of training (main effect of block), and provided information about the learning rate (bloc x group interaction) and level of MSL performance (main effect of group) between groups. Finally, motor memory consolidation was determined using a repeated-measures ANOVA performed with sessions and blocks (i.e. last 4 blocks of training and first 4 blocks of retest) as repeated within-subjects factors and groups as the between-subjects factor. The use of four blocks instead of only one (i.e., last block of training and first of retest) was preferred to avoid fatigue effects at training, warm-up effects at retest blocks and to help reduce block-to-block performance variability (Rickard et al., 2008; Verwey, 1994).

Olfactory stimulus

A solution of phenyl ethyl alcohol (PEA - concentration: 6.31 x 10^{-3} [% v/v]) and heavy mineral oil (solvent - USP/FCC) was used as the odorant source. Delivery of the olfactory stimulus was carried out using an ON/OFF block design procedure as described in our previous work (Laventure et al., 2016). For the MSL training session, the ON blocks were comprised of blocks of practice, while the OFF blocks corresponded to the periods of 30 s of rest in-between. During NREM2 sleep exposure, the odor was delivered on a 30 s ON/ 30 s OFF block design for a maximum of 60 minutes.

Polysomnographic Recording

Sleep recordings were acquired using a 16-channel, V-Amp 16 system (Brainamp, Brain Products GmbH, Gilching, Germany) from 10 scalp derivations (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, Oz) referenced to linked mastoids (A1, A2). They were recorded continuously (at < 5KOhm) during the whole night using Recorder software (Brain Products), and were visually inspected online for quality. Signals were digitized at 250 samples per second and bandpass filtered (high pass filter = 0.3 Hz, low pass filter = 70 Hz). PSG measurements included EEG, electro-oculogram (EOG), bipolar submental electromyogram (EMG) electrodes as well as a nasal airflow thermistor (Braebon, Ottawa, Canada) to monitor respiratory effort.

For all PSG recordings, including online scoring and stimulation periods, sleep stages were visually identified in 30-s epochs displaying EEG (high pass filter = 0.3 Hz, low pass filter = 35 Hz) from central and occipital derivations (C3, C4, and Oz) referenced to average mastoids (A1 and A2), EOG (high pass filter = 0.3 Hz, low pass filter = 35 Hz) from the lateral outer canthus of each eye, and bipolar sub-mental EMG (high pass filter of 10 Hz). Periods of cortical arousal or movement during sleep were identified using an automated detector when movement continuously exceeded 100 μV for more than 100 ms (detection was visually verified).

EEG pre-processing

Sleep architecture

Sleep stages were scored by a Registered Polysomnographic Technologist (RPSGT) expert according to standard criteria (Rechtschaffen & Kales, 1968) using 30 second epochs. Sleep architecture analyses were conducted on periods defined by the onset and offset of stimulation (see Figure 1C).

Experimental sleep periods

Exposure to an olfactory stimulus during the second half of the night defined two different sleep periods called *pre-stim* and *stim*. The *stim* period refers to the exposure period during NREM2 sleep, while the *pre-stim* sleep period applies to the NREM2 epochs that occurred before the onset of the first stimulation. The *stim* and *pre-stim* periods were length-matched so that the *pre-stim* period could serve as a reliable within-group baseline for the subsequent analyses.

Sleep spindle detection and selection

Following demonstration in our previous work (Laventure et al., 2016) that only spindles originating from the parietal region showed cue-related changes, spindles were automatically detected from the Pz derivation during NREM2 using an improved version (https://github.com/Sinergia-BMZ/swa-matlab) of a previously published algorithm (Wamsley et al., 2012) and rated as a reliable detection technique (Warby et al., 2014). Detected events lasting between 0.3-2s and occurring within the 11-17 Hz frequency range were identified as sleep spindles. The toolbox was adapted to provide additional information related to spindles frequency including time markers for each oscillation within the events. Sleep spindles were then categorized by site using a previously described technique (Laventure et al., 2016). This method uses the detected onset of a given event to determine the site at which the spindle occurred first, as it is known that a single event can appear on multiple electrodes. Afterward,

each sleep spindle within the *pre-stim* and *stim* sleep periods was extracted as a five second epoch (arbitrary window of two second before and three second after onset) using the EEGLab Matlab toolbox – version 13.6.5 (Delorme & Makeig, 2004; Makeig, 1993). Finally, upon visual inspection, epochs containing artefacts, false positive detections and multiple spindle events within the five-second epoch were excluded from the analyses. This last step allowed a thorough inspection of the signal quality at each site.

EEG Analyses

Sleep spindle characteristics

Following findings demonstrating the implication of parietal NREM2 sleep spindles in MSL consolidation (Laventure et al., 2016), analyses of spindle characteristics (peak amplitude, duration, frequency and density) were carried out on Pz NREM2 events. One-way ANOVAs were used to assess the differences in spindle characteristics (within-subjects factor) between groups (between-subjects factor) in the *pre-stim* and *stim* periods.

Event-related signal perturbations processing and analyses

Time-frequency analyses were used to assess the temporal and spectral activity present before, during and after a spindle. These event-related signal perturbations (ERSP) analyses permitted to assess the mean changes in the power spectrum over baseline. Each pre-selected sleep spindle epoch was transformed into a time-frequency matrix using an ERSP function from the EEGLab Matlab toolbox. The ERSP transformation was conducted from 3 Hz to 36 Hz (3 Hz being the lower limit for this analysis) in the frequency domain and from -1000 msec to 2000 msec in the time domain on all ten electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, Oz). The function used 3-cycles Morlet wavelets at the lowest frequency (with Hanning-tapered window applied [n = 200]). ERSP matrixes were normalized using a period of time preceding the analyzed event from -1440 msec to -1000 msec.

Average spindle. A time-frequency image of an average spindle was generated using ERSP data from all selected Pz sleep spindles comprised in both conditions and groups. Data from each pixel was average across epochs.

Comparing changes between conditions and groups. The number of spindles varied between conditions (within-subject) and participants. Hence, a bootstrap analysis (B Efron & Tibshirani, 1994) was performed to generate a set of 300 samples for both conditions in each subject. With this set of samples, contrasts between the *stim* and *pre-stim* sleep spindles (independent variable) were created using Wilcoxon-Mann-Whitney comparisons in each subject, and for each pixel of the time-frequency maps (dependent variable). This resulted in a single contrast map per subject.

Single subject contrast maps were then brought to a second level of analysis to test group differences in time-frequency changes using linear regressions. This set of analyses compared the difference in changes between groups (independent variable) at each point of a time-frequency matrix (dependant variable), ultimately generating a single image per derivation. Regression weights were estimated to control for two attributes: first, the ratio of spindles from each subject compared to the total number of spindles from both groups, and second, the ratio of the number of spindles between *pre-stim* and *stim* sleep periods for each subject:

$$W = \frac{(S^i_{pre-stim} + S^i_{stim})}{\sum(S_{pre-stim} + \sum(S_{stim})}$$

where S represent the quantity of spindle events and i refers to the subject iteration. On each derivation, linear regressions assessed differences of stimulation-induced time-dependent spectral changes between groups. These regression maps, generated using plot functions provided by EEGlab, are composed of significant regression coefficients betas ($p < 0.001$) corrected with a false discovery rate (FDR) method.

Changes in topographical representations. The regression analyses yielded one map per derivation (i.e., ten maps). Topographical representations of the significant betas were estimated in specific periods of time (-1000 to 0 msec, 0 to 1000 msec, 1000 to 2000 msec) and frequency band (delta-theta: 3 to 8 Hz; sigma: 11 to 16 Hz; high-beta: 20 to 30 Hz). These

diagrams allow for a better topographical localization and lateralization assessment of the difference in changes occurring during parietal spindles between groups.

Coherence analyses

Changes in connectivity between derivations during Pz sleep spindles were investigated using coherence analyses. Thus, changes in phase and amplitude synchronization between electrode pairs that occurred between *pre-stim* and *stim* sleep spindles were tested in both groups. The same set of sleep spindle epochs as in ERSP analyses was used for the following connectivity tests. Each analyzed epoch covered a 2000 ms period, starting at the spindle onset.

Coherence and Imaginary coherence. Coherency is a standard method to determine the spectral connectivity between two signals. It is a complex valued function of frequency. A set of coherencies between electrode pairs e and e' with index n=1...N and a scalar function of frequency, f, is defined by:

$$C_{e,e\prime}(f_n) = \frac{S_{e,e\prime}[n]}{\sqrt{S_{e,e}[n]}\sqrt{S_{e\prime,e\prime}[n]}}$$

with frequency $f_n = n\, f_0$ and $f_0 = 1/T$ where $S_{e,e}[n]$ is the Fourier transform of a time domain signal of electrode e and $S_{e\prime,e\prime}[n]$ is the transform of another time domain signal of electrode e'. The coherency can be split into real and imaginary part and different quantities can be analyzed further.

The most important are the coherence $Coh_{e,e\prime}$ defined as the modulus of the coherency and the imaginary part of the coherency $iCoh_{e,e\prime}$. iCoh accounts for the portion of coherence between two electrodes sensitive to interactions with non-vanishing degree of time lag (Nolte et al., 2004).

Z-stat and average. Coherence was defined on selected frequency bands (delta, theta, sigma and high-gamma) and Z-transformed:

$$iCoh(f_n) \rightarrow Z(f_n) = \tanh^{-1}\big(iCoh(f_n)\big) - \frac{1}{df - 2}$$

where $df = 2\ P_{S,c}$ is the degree of freedom for the coherence estimate. The last term in Z corrects for the bias: $Z(f_n)$ is approximately normally distributed with mean $\tanh^{-1}\left(iCoh_{true}(f_n)\right)$ and variance $1/(df-2)$. Frequency bands were then defined (e.g., $B_i = [F_i\ , F_{i+1}]$) and finally, the coherence was computed in each band:

$$\bar{Z}_i = \frac{1}{card(B_i)} \sum_{f_n \in B_i} Z(f_n)$$

for each subject S, and for each pair of electrode e and e'.

Non-parametric statistical test of significance. First, we considered the average over each subject, in both conditions,

$$z_{i,pre-stim} = \frac{1}{n_s} \sum_s \bar{Z}_{i,s,pre-stim} \ , \ \ z_{i,stim} = \frac{1}{n_s} \sum_s \bar{Z}_{i,s,stim}$$

The contrast $\delta z_i = \left|z_{i,stim} - z_{i,pre-stim}\right|$ was then tested for significant difference from zero with a non-parametric approach based on spatial clustering of the pair-wise link. The null hypothesis was drawn from a random reallocation 'r' of the two conditions (random permutation *pre-stim* and *stim* for each subject - there is 2^{n_s} such reallocations defining fate *stim* and fate *stim'*). In each case, $\delta z_{i,r} = \left|z_{i,stim'} - z_{i,pre-stim'}\right|$ was computed and a pair of electrodes was selected for which $\delta z_{i,r} \geq 0.5 \max_{pairs} \delta z_{i,r}$. Then, the selected pair was clustered (2nd order of neighbourhood in the electrode montage) and for each cluster, the contrasts were summed and all the values were accumulated along the random resampling. This constitutes the null hypothesis distribution from which a unique defined threshold z_i^* was computed ($p < 0.00001$). The significant links were defined as the one for which $z_i \geq z_i^*$ separately in each frequency band labelled with i. For each significant pair, the direction of the effect (increase or decrease) was computed through the group mean square coherence difference between *pre-stim* and *stim*, which is defined as the amplitude of the complex-valued expression.

Ethics Statement

The present study was revised and approved by an institutional ethics committee ("Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec"; ID:

CMER-RNQ 09-10-026). Upon their arrival at the sleep laboratory for the screening night, all participants were asked to provide written consent.

Results

MSL consolidation

A mixed repeated-measures ANOVA conducted on GPI scores of the 24 blocks of training (repeated measures) showed a significant effect of block ($F_{23, 1081} = 51.397$, $p < .00001$), with no significant block x group interaction ($F_{23, 1081} = .448$, $p = .99$), or main effect of group ($F_{1, 47} = .195$, $p = .66$). These results suggest that, while all participants showed improvement in performance across the training session, both groups expressed similar overall performance and learning rates.

Additionally, a second mixed repeated measures ANOVA performed on the last four blocks of the training session did not reveal any significant main effect of block ($F_{1, 47} = 2.162$, $p = .15$), block x group interaction ($F_{1, 47} = .234$, $p = .63$), nor any main effect of group ($F_{1, 47} = .974$, $p = .33$). The latter results demonstrate that acquisition performance levelled off by the end of the training session, with all participants reaching an asymptotic level of performance.

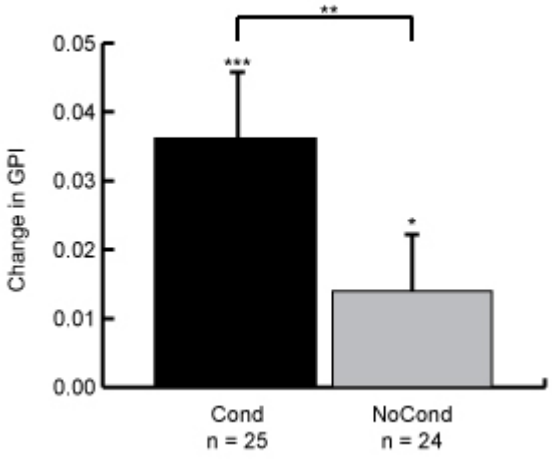

Figure 2. Stimulation-dependent MSL consolidation.

Changes in performance on the MSL task were assessed by the mean GPI differences between the four first blocks of retest and the four last blocks of training. Both groups showed offline gains in performance after a night of sleep, but the Cond group revealed significantly higher gains than the NoCond group.
* $p < 0.01$; ** $p = 0.005$; *** $p < 0.001$

Consolidation was measured by comparing the mean GPI score of the first four blocks of retest to the last four blocks of training using a repeated-measures ANOVA (Figure 2). This analysis resulted in a main effect of session ($F_{1, 141} = 44.234$, $p < .00001$) confirming that both groups showed an offline consolidation effect (pairwise comparisons: Cond, $p < 0.001$; NoCond, $p = 0.01$). Importantly, post-hoc pairwise comparisons reported a significant session x group interaction ($F_{1, 141} = 8.672$, $p = .005$) demonstrating that cued participants (Cond; mean = .036 ±.01) reached greater offline improvement in performance than those who were not conditioned to the olfactory stimulus (NoCond; mean = .014 ±.01). Complementary analyses performed on speed only (mean time per block) yielded the same pattern of results.

Sleep architecture and stimulation

Sleep and spindles were analyzed using two different sleep periods. First, the analysis comprised a period of NREM2 sleep during the stimulation phase (*stim*), and pre-stimulation (*pre-stim*) (see Figure 1C).

Table 1. Sleep architecture.

	Cond		**NoCond**		**$t_{(47)}$**	**p**
	Mean	S.E.	Mean	S.E.		
Wake	56.3	5.3	53.0	6.5	0.387	0.70
NREM1	20.1	10.4	20.3	9.4	-0.075	0.94
NREM2	197.3	34.0	194.3	41.5	0.275	0.78
SWS	123.1	36.8	115.7	35.8	0.714	0.48
REM	93.2	19.3	94.9	6.0	-0.246	0.81
Movement	3.3	0.8	3.5	0.8	-0.262	0.80
TRT	493.2	26.5	481.8	32.4	1.353	0.18

TST	433.6	30.1	425.2	46.1	0.763	0.45
Sleep Efficiency (%)	88.0%	4.9	88.2%	6.4	-0.129	0.90

Legend: All sleep measurements are presented in minutes, except for sleep efficiency, which corresponds to a percentage calculated from the ratio of total sleep time (TST) on total recording time (TRT). Standard errors (S.E.) are reported. Independent t-tests were conducted for each sleep characteristic between groups to identify whether there were any significant differences in sleep architecture. As expected, there were no significant group differences in any of the sleep periods and characteristics.

Independent samples t-tests conducted on sleep architecture did not show any difference between the two groups with regards to the total sleep time (TST), total recording time (TRT), wake duration, sleep efficiency, nor any of the sleep stages (see Table 1), hence confirming that the experimental manipulation had no differential effect ($p > 0.05$) on sleep architecture between these two groups. Another independent samples t-test was performed to compare the *stim* period duration between both groups, but again the latter analysis did not reveal any differences ($t(47) = 1.325$, $p = 0.19$; Cond: 38.7 min ±13.8 min; NoCond: 33.7 min ±12.8 min), hence showing that both groups received similar periods of stimulation.

Sleep spindle characteristics

After detection and filtering of all sleep spindles, a total of 12235 sleep spindles were selected for analyses. These events had a mean duration of 0.68 second (±0.35 sec) and their distribution showed that 81.7% were shorter than one second. In each condition (*pre-stim*, *stim*), no difference was found ($p > 0.05$) between groups in spindle duration, amplitude, frequency or density.

Sleep spindle time-frequency decomposition

Average spindle description

An ERSP average of all sleep spindle events included in the analyses is shown in Figure 3A. This time-frequency map confirmed that most events ranged from 11 to 16 Hz, although

some appeared to exceed those boundaries (~10-19 Hz), and that spindle frequency tended to decrease over the course of the spindle event (Zerouali et al., 2014). The average time-frequency decomposition showed that spindle onsets, as defined by the detection algorithm, did not represent the real event onset. Indeed, the actual spindle onsets appeared to occur earlier compared to detected onsets. This shift is to be expected, however, as the detection algorithm established onsets based on reaching a predefined threshold. When this threshold is reached, the actual spindle oscillation has already started for up to about 150 msec. Interestingly, the average spindle ERSP identified another component outside the usual sigma (11-16 Hz) range, spanning from ~ 24 to 30 Hz in the frequency domain and from 0 to 1000 msec in the time domain. This simultaneous high-beta activity, which can be described as a secondary spindle component, appeared consistently on individual spindle time-frequency decomposition.

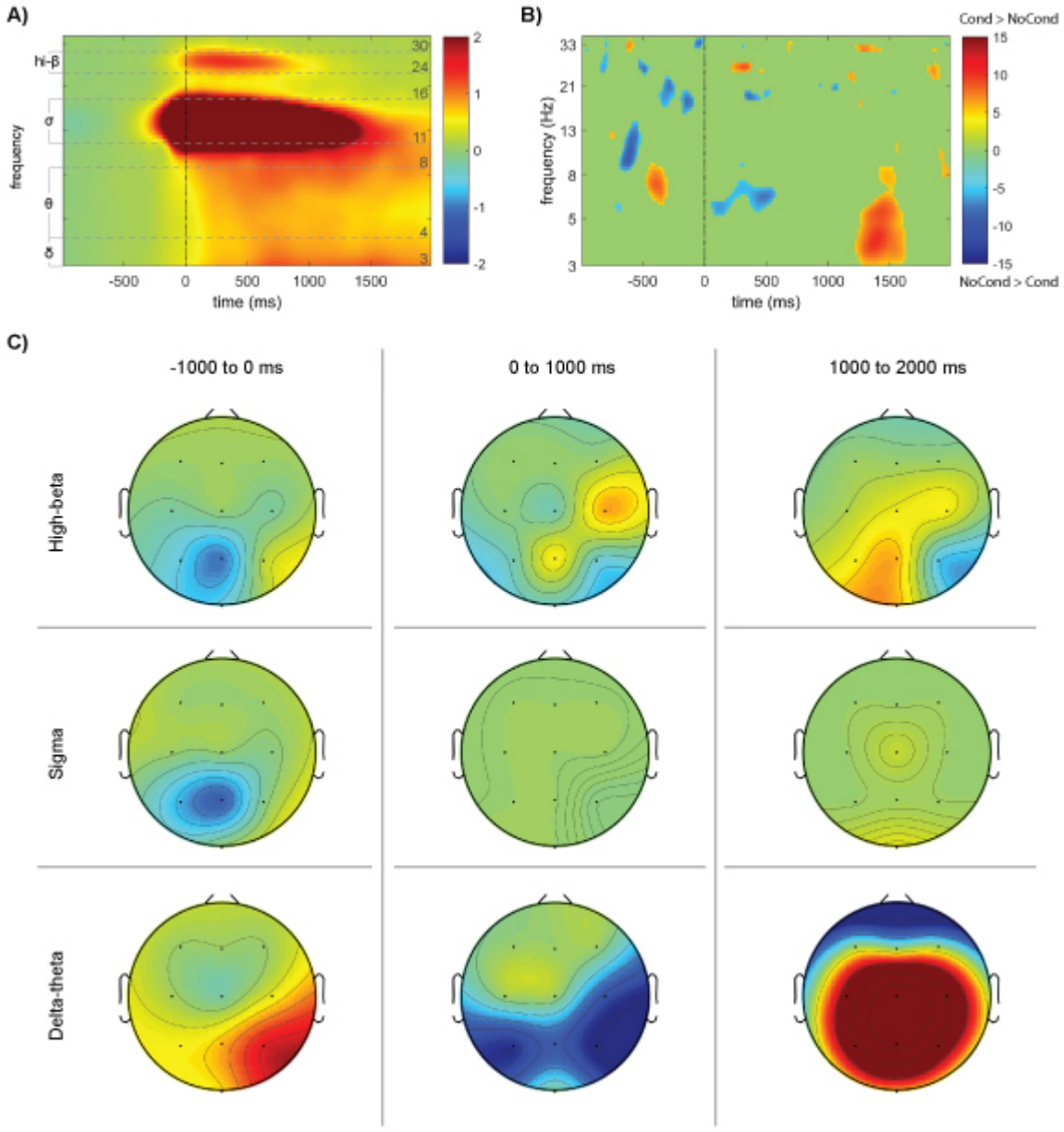

Figure 3. Stimulation-dependant sleep spindle time-frequency decomposition.

Event-related spectral perturbation (ERSP) analyses were conducted on Pz sleep spindle to investigate stimulation-dependant changes in signal around and during the events. (A) **Average spindle.** Event-related spectral perturbation average of all spindles included in the analyses. Each event was aligned using the algorithm-detected spindle onset (point zero on the x axis). The resulting time-frequency image ranged from -1000 msec to 2000 msec in reference to the onset. Frequencies (y axis) ranged from 3 to 36 Hz and an overlay allowed for the identification of predefined frequency bands used in the analyses – delta (δ), theta (θ), sigma (σ), high-beta (hi-β). (B) **Group comparison at Pz with respect to changes between *pre-stim* and *stim* periods.** Linear regression tested for

differences between groups by comparing condition (*stim* versus *pre-stim*) contrast map. Positive significant betas ($p < 0.01$, FDR corrected) identify higher ERSP changes in the Cond compared to the NoCond group while negative values indicate the contrary. (C) **Topographical representation of significant differences between groups.** Using maps resulting from linear regressions on the ten derivations, topographical representations of the significant differences between groups were generated. Results were fragmented into three time segments (-1000 to 0 msec, 0 to 1000 msec, 1000 to 2000 msec) and three predefined frequency band (delta-theta, sigma and high-beta). As for the Pz linear regression map (see panel B), significant results are represented with a color spectrum ranging from red-positive (Cond > NoCond) to blue-negative (NoCond > Cond).

Localized changes in spectral power between conditions and groups

Group differences maps of ERSP changes between the *pre-stim* and *stim* periods were generated using a linear regression corrected for multiple independent analyses (false discovery rate [FDR]) (see suppl. Information for Pz contrast maps between periods SFig 1). Only significant beta values ($p < 0.001$) were reported and detailed in the following section.

The group contrast map on Pz (Figure 3B) showed that no major significant change occurred in the sigma band during spindles (0 to 1000 msec). However, it identified significant ERSP differences (Cond > NoCond) in the theta band prior to the event onset (~ -500 to -300 msec) and, in both delta and theta bands following the end of the spindle (~ 1200 to 1600 msec; based on the average spindle in Figure 3A). Comparatively, still in the theta band, the Pz map showed higher ERSP changes in the NoCond compared to the Cond group during spindles (~ 50 to 600 msec). Altogether, these results suggest that cued memory reactivation influenced the timing, and thus power (ERSP), of lower frequencies (delta-theta) in relation to cued spindle events. Indeed, comparing both groups, while there seems to be a decrease in lower frequencies during the cued events, significant increases were identified before the onset and at the offset of cued sleep spindles. Furthermore, the regression analyses also detected segregated clusters of significant higher differences for the Cond compared to the NoCond group in the high-beta band (20 to 30 Hz) from the onset to the end of the epoch's window (0 to 2000 msec).

Figure 3C provides a topographical summary of the time-frequency linear regression significant results for all of the analyzed electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 and Oz) during Pz sleep spindles. **High-beta**. Multiple significant changes in every time segments were

identified in high-beta (20-30 Hz). First, before the event onset, the topographical map showed significantly lower ERSP differences over Pz, as well as higher difference for the Cond compared to the NoCond group in the right parietal region. Then, during the first 1000 msec following the onset, significant higher differences for the cued group compared to the NoCond group were observed in parietal (Pz) and right central (C4) areas. Finally, during the last segment (i.e., 1000 to 2000 msec), results showed that the Cond group had significantly higher differences over several posterior (P3, Pz and Oz) and central (Cz and C4) areas than the NoCond group. **Sigma**. As previously seen in Pz (Figure 3B), no major significant differences were identified in the sigma frequency band in any time period apart from a lower difference before the even onset for the Cond compared to the NoCond group. **Delta-theta**. The topographical ERSP map demonstrated strong differences in the delta and theta bands for the cued group in contrast to the non-cued group before the event onset (-1000 to 0 msec) and after the average spindle offset (1000 to 2000 msec) in central and parietal regions. Notably, the differences found before the spindle onset were predominantly lateralized in the right hemisphere and covered the primary motor (C4) and somatosensory cortex (Pz and P4). The opposite effect appeared during the event (0 to 1000 msec) as shown by lower changes for the Cond compared to the NoCond group across parietal and right central areas.

Overall, these results suggest that cuing with a conditioned stimulus is associated with increases in signal power at higher (hi-β) and lower (δ-θ) frequencies time-locked to spindle events. Additionally, these increases appear to be stronger in posterior and contra-lateral regions (in reference to the hand that performed the MSL task), and thus, may be regionally specific and use-dependent. Moreover, the contrast maps identified a stimulation-dependant decrease in delta and theta frequencies within the 0-1000ms time window, which corresponds roughly to the mean spindle duration. It also highlights that the spindles main sigma component seems to be embedded in time (δ-θ) and frequency (hi-β) by oscillations that are sensitive to the reactivation of a memory trace with a conditioned stimulus.

Changes in connectivity during sleep spindles

Coherence analyses were carried out over all derivations on four frequency bands (delta, theta, sigma and high-beta) using the same dataset of filtered events used for the ERSP analyses in order to test for changes in connectivity between cortical regions during Pz spindle events (Figure 4; $p < 0.00001$).

Delta

The results showed that the Cond group coherence in delta increased between several pairs of regions along the anterior-posterior axis. In contrast, the NoCond group showed interhemispheric, left frontal-right posterior (C4 and P4) decreases.

Theta

Analyses revealed a clear difference in pattern between the two groups. While coherence in the theta band in the Cond group seemed to increase across widespread pairs of regions covering all the deviations, the NoCond group showed a sparser mix of a few increases (three pairs) and decreases (two pairs) between regions. In the Cond group, the occipital region seemed to be a hub for connectivity between sites, since it is part of no less than seven significant increase in coherence between parietal (Pz), central (C3, Cz, C4) and frontal (F3, Fz, F4) regions.

Sigma

Coherence results demonstrated that the TMR had a significant effect on multiple regions in the sigma band. Indeed, only the Cond group showed significant changes in coherence where increases in coherence were predominantly evident on centro-parietal regions. Comparatively, the NoCond group did not show any evidence of change in connectivity in sigma.

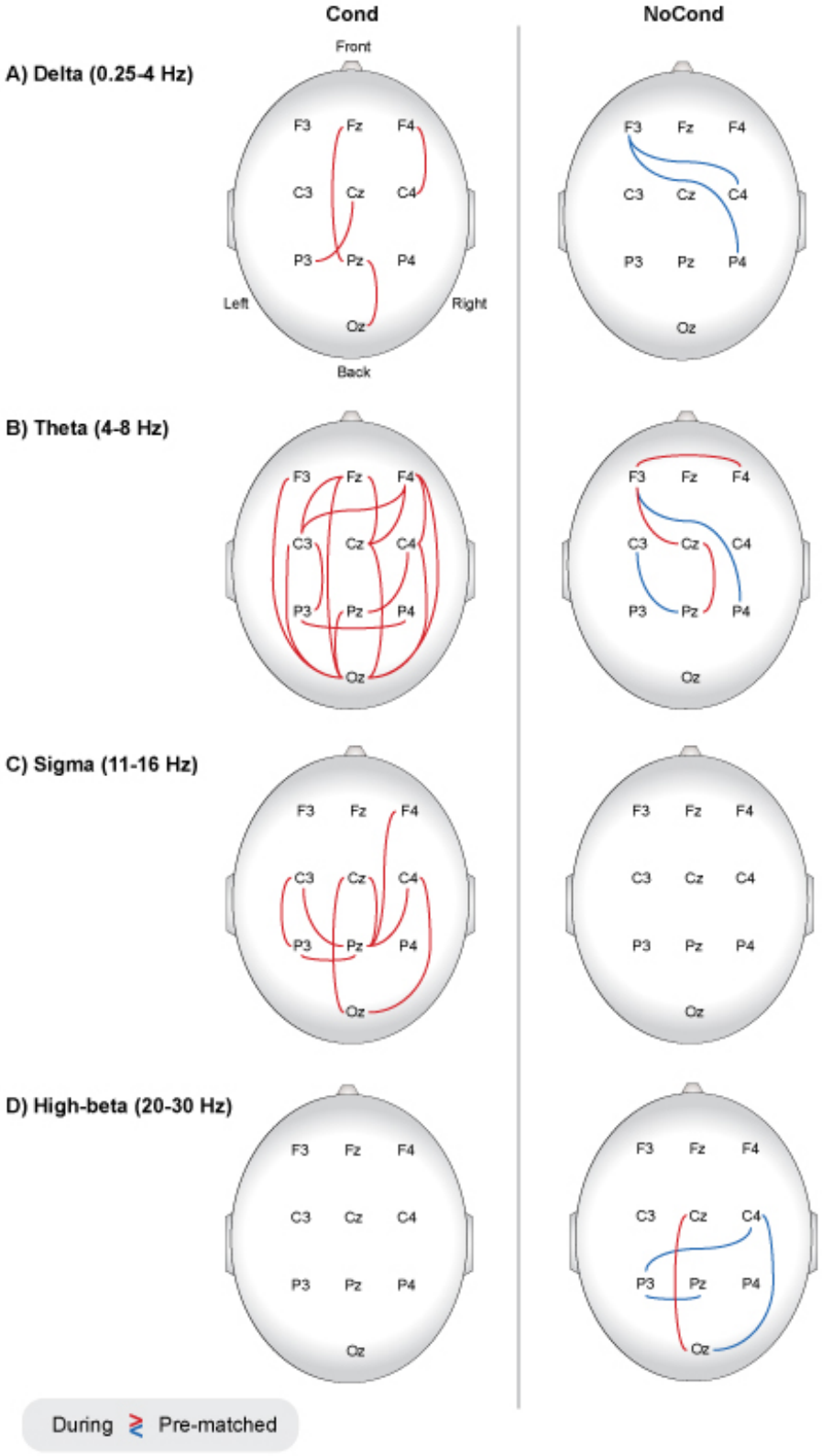
Cond
NoCond
A) Delta (0.25-4 Hz)
B) Theta (4-8 Hz)
C) Sigma (11-16 Hz)
D) High-beta (20-30 Hz)
Front
Left
Right
Back
F3
Fz
F4
C3
Cz
C4
P3
Pz
P4
Oz
During
Pre-matched

Figure 4. Changes in coherence between regions during sleep spindles.

Significant changes ($p < 0.00001$) in imaginary coherence metrics during Pz-detected sleep spindles between the *pre-stim* and *stim* periods are represented by colored link between pairs of sites - increases in red and decreases in blue – for each group. Analyses were processed over four different bands of frequencies: (A) SWA (0.25 to 4 Hz), (B) theta (4 to 8 Hz), (C) sigma (11 to 16 Hz) and (D) high-beta (20 to 30 Hz).

High-beta

Changes detected in the high-beta band were only found in the NoCond group. However, three of these four significant changes were identified as decrease in coherence (C4-P3, C4-Oz, P3-Pz).

In sum, coherence analyses demonstrated that connectivity with central-parietal regions significantly increased in the sigma band during cued NREM2 sleep spindles. This is in contrast to the absence of local changes in this band as reported above through ERSP analyses and suggests that sleep spindles might be synchronizing activity between regions during memory reactivation. Furthermore, results from this analysis reinforce the implication of theta oscillations by showing large scale increases in a global connectivity network occurring during cued sleep spindles.

Discussion

The present research builds upon previous behavioral and electrophysiological findings (Laventure et al., 2016), and suggests that sleep spindle activity interacts with multiple types of oscillations in a time-locked manner during reactivation of a newly acquired memory trace following motor sequence learning. We first showed that cued reactivation through olfaction produced a greater increase in performance for the group that was conditioned during the evening training period versus unconditioned controls. Then, time-frequency decompositions of parietal sleep spindles revealed an increase in local low frequency activity before and after spindle oscillations. The same analyses also identified high-beta activity increases during sleep spindles when subjects were re-exposed to the odor during NREM2 sleep. Finally, our results

demonstrate the presence of large increases in connectivity generated during cued spindles in the theta and sigma bands only. Our present findings thus highlights the emergence of a global mechanism temporally locked to sleep spindles supporting MSL consolidation, that involves the dynamic interplay of spindle-related activity with multiple EEG frequencies in the delta/theta and high beta bands.

As expected, analyses of MSL changes revealed that both groups elicited overnight gains in performance, hence confirming again the fact that sleep facilitates the consolidation of a newly acquired motor sequence memory trace (Ackermann & Rasch, 2014; Doyon, Korman, et al., 2009; Morin et al., 2008; Walker et al., 2002). Our results also show that cuing during post-training NREM2 sleep potentiated the consolidation process, and resulted in significantly better performance at retest for the Cond compared to the NoCond group. This is in line with studies showing similar outcomes when participants were administered a conditioned olfactory or auditory stimulus during NREM sleep (Antony et al., 2012; Cousins et al., 2014). Moreover, the absence of differences in sleep architecture between both groups suggests that the offline gains in performance were produced by the experimental manipulation rather than factors related to sleep quality.

Analyses of sleep spindle characteristics (i.e. amplitude, frequency, duration, density) on selected events did not yield any difference between groups, contrary to our previous findings (Samuel Laventure et al., 2016). This discrepancy might have been caused by a combination of factors. First, spindle detection was conducted using a different detection algorithm (Wamsley et al., 2012). Second, in order to allow for clean and unperturbed signal around each detected event for the subsequent signal analyses a pre-processing step eliminated segments containing more than a single spindle during a 5 seconds period. This resulted in sparse clusters of events that were not analyzed, and may have eliminated spindles that occur in close proximity to one another in time. Whether bursts of spindles following learning reflect more intense consolidation, was beyond the scope of the aims of the present study, and remains to be confirmed.

High frequency component during sleep spindles

The averaged spindle time-frequency decomposition (Figure 3A) allowed to identify a secondary component, nested in the high-beta band, in addition to the common sigma oscillation from spindles. This component occurred a few milliseconds after the event onset and faded out before the end of the sigma oscillation. In contrast to other studies that used time-frequency decompositions (e.g., Zerouali et al., 2014), we did not filter out the EEG signal outside the sigma band, hence allowing us to detect the existence of high-beta activity. The presence of a high-beta secondary component during sleep spindles could explain one report of beta and sigma activity occurring within the same timeframe, both time-locked to slow positive half-waves (Mölle et al., 2002). Although this is, to our knowledge, the first report of this spindle high-beta component, it is not the first characterization of such a synchronization phenomenon between sigma-band spindles and higher frequencies. Previous studies using intracranial (Staresina et al., 2015) and cortical (Clemens et al., 2011) recordings in epileptic patients and animal models (Averkin et al., 2016) have also identified evidence of hippocampal ripple (80-120 Hz) bursts of activity, time-locked to spindle troughs. Their findings suggest that the synchronization of oscillations at different frequencies resulting from communications between cortical and subcortical brain structures do underlie memory consolidation. It is thus possible that the high-beta component described here represents the activity of a population of neurons synchronized to spindle oscillations. In that case, task-related changes in this component would occur when participants are cued with a conditioned stimulus. The interaction of this high-beta component with sleep spindles and other frequency bands during cuing will be discussed further below.

Localized time-locked changes in power during sleep spindles

Parietal sleep spindle time-frequency comparison maps revealed that, in contrast to the non-cued group, spindles from the cued group were associated with higher changes in the delta band following event offset, the latter difference being possibly caused by a higher presence of SO in proximity to sleep spindles. In support of this conjecture, the time-locked association between SO and sleep spindles is well documented. Previous studies describing the relation between SO and spindles (Andrillon et al., 2011; Clemens et al., 2007; Klinzing et al., 2016; Nir

et al., 2011) have proposed that a change in SO state (e.g., from down to up-state) provides a neuronal dynamic propitious to the formation of sleep spindles and other fast frequency events (e.g., ripples). Furthermore, before spindle onset, the theta difference between our groups was mostly lateralized in the right hemisphere over an area comprising the sensorimotor regions (contralateral to the hand that performed the task), hence suggesting that cuing increased activity in task-related cortical regions. This is in line with previous studies showing that localization of spindle activity correlated with cortical regions activated during a newly learned task (Barakat et al., 2012; Clawson et al., 2016). Thus, our results suggest that cued memory reactivation increases the amount of slow frequency activity (theta and slow wave activity) time-locked to sleep spindles.

Moreover, time-frequency decomposition maps demonstrated that the cued group had a significant increase in the high-beta band during sleep spindles. This implies that the high-beta activity cluster straddling the main sigma component and described earlier might be involved in the cued reactivation of the motor memory trace. A closer look at the regions where these changes took place reveals that sensorimotor and motor areas relevant to the newly learned task show increases in high-beta, especially after spindle onset. No localized difference was detected in the sigma band between groups.

Cue-related functional connectivity changes during sleep spindles

Change in connectivity was assessed through pairwise comparisons of EEG-coherence between pre-stim and stim periods. As with the time-frequency analyses, results were divided into frequency bands. The most striking differences between the cued and non-cued groups were found in the theta and sigma bands. Surprisingly, results showed that participants who were re-exposed to the conditioned stimulus demonstrated significant and widespread increases in connectivity within the theta frequency band with occipital regions acting as a hub for connectivity. As predicted, connectivity was also significantly higher in the sigma band following re-exposure to the conditioned stimulus. Together, these results suggest that cuing produced an increase in connectivity in lower frequencies and sigma, but not in high-beta. Past studies investigating normal sleep in a non-learning context have shown that synchrony between

regions increases in sigma frequencies across NREM cycles (Achermann & Borbély, 1998a) and during sleep spindles (Achermann & Borbély, 1998b; Souza et al., 2016). The present report extends these findings by demonstrating that the reactivation of a motor sequence memory trace increases cortico-cortical functional connectivity during sleep spindles within specific frequency bands (e.g., delta, theta and sigma) over and above normal changes.

In addition, the overall delta and theta patterns suggest that cuing increased antero-posterior connectivity with less emphasis on inter-hemisphere (left-right) changes, while in sigma, most increases were found between parietal and central sites with a mix of inter-hemisphere and antero-posterior changes. This is in line with previous studies showing that delta and theta oscillations correlate with long-range communications between cortical regions, while sigma and beta bands were associated with short-range transmission and gamma bands were related to very localized exchanges (von Stein & Sarnthein, 2000). Our data suggest that long-range antero-posterior connectivity is enhanced during sleep spindles when subjects are exposed to a contextual cue conditioned to a motor task, and that this effect is led by low frequencies (delta and theta). Further, short-range, central and parietal coherence seems to be increased by the olfactory cue during sleep spindles over and above the normally high coherence previously reported between these regions (Duckrow & Zaveri, 2005). This also complement previous findings on regional task-specific changes in spindles density after motor skill learning (Nishida & Walker, 2007). Thus, our results support the notion that sleep spindles are actively participating in motor sequence consolidation by reactivating complex memory traces involving different cortical regions and that this multi-site interaction seems to rely on activity within the delta, theta and sigma bands.

Theta activity and memory consolidation

Our assessment of cortical electrical activity time-locked to sleep spindles indicated that theta activity significantly changed both locally (change in power) and between regions (increased connectivity) during cuing. The theta band has been widely studied and consistently associated to memory processing (György Buzsáki, 2002; Fogel et al., 2007; Raghavachari et al., 2006; Sauseng, Griesmayr, & Freunberger, 2010). For example, it has been shown that both

theta synchrony and power increase during recollection of past experiences (Fuentemilla, Barnes, Düzel, & Levine, 2014). It is thought that in the context of a motor learning protocol using a TMR stimulation design, as in the present study, the cued stimulus represents an episodic component triggering the motor memory trace. Hence, in such case, the reactivation of a motor memory trace associated to a contextual cue could explain the similarities in findings in this research with studies looking at declarative memory.

Although recognized as a key feature of REM, theta is also present during NREM sleep. It has been thought to correspond to a hippocampal hallmark oscillation playing a pace-maker role in memory encoding and retrieval processes (György Buzsáki, 2002), as well as to a long range communication mechanism connecting segregated brain regions (Sauseng et al., 2010). A recent report suggested that theta rhythms serve as a functional binding between the hippocampus, prefrontal cortex and the striatum during recollection of visual memories, a subtype of declarative memory (Herweg et al., 2016). Importantly, this frequency band is also thought to play a central role in the integration process of multiple mnemonic representations into a coherent whole (Fell & Axmacher, 2011; Hasselmo, Bodelón, & Wyble, 2002; Sauseng et al., 2010). In relation to our results, this particular function of the theta band could thus be instrumental in promoting the MSL memory representation integration within a given context (presentation of an odor) effectively leading to memory consolidation at a system level. Yet, such interpretations are speculative thus, studies using TMR paradigms with intra-cranial recordings should be carried out in order to shed light on the possible interaction of the hippocampus, striatum and cortex during cued sleep spindle.

From local to inter-regional changes

In sum, the current study yielded two major findings. First, together, time-frequency decomposition and coherence analyses demonstrate that the consolidation process engage not only the sigma oscillations related to sleep spindles, but also the boundary frequencies at specific stages of the spindle event. In the Cond group, the presence of significant increases in theta before spindle onset, and delta/theta at the end of spindles, is in line with aspects of the active system consolidation model (Diekelmann, Wilhelm, & Born, 2009; Marshall & Born, 2007);

more specifically, the facilitation by slower oscillations (e.g., SWA) of higher frequency activity such as sleep spindles. One of the key concepts proposed by this model is that newly learned memory traces are repeatedly reactivated during sleep, thus promoting synaptic connections within the associated neuronal network and reinforcing the associated mnemonic representation. It is thought that these reactivations are driven by SO and that the temporal grouping of neuronal depolarization during these SO up-states constitutes a favorable timeframe for memory reactivation through hippocampal sharp-wave ripples and thalamo-cortical spindles (M Steriade, 2006). Although our time-frequency analyzes did not look at SO (<1 Hz), they did highlight the presence of local power increases in lower frequencies before and after the events. This supports the notion that the mechanisms underlying cued reactivation of a newly acquired motor memory trace involve spindle activity time-locked to lower frequencies comprising theta and delta. Furthermore, despite the fact that the increase in high-beta straddling the main sigma component is composed of lower frequencies than sharp-wave ripples (which are not measurable from scalp derivations in humans), it is possible that it follows a similar generation pattern, nested inside spindle troughs (Clemens et al., 2011; Mölle et al., 2009). Thus, the high-beta component could be the result of reverberating activity within local neuronal networks triggered and synchronized by spindle oscillations.

Second, our results show a distinction between local and functional changes in terms of frequency bands. Indeed, while local sigma power was not significantly modulated by the re-exposure to a conditioned stimulus, coherence analyses identified increases in sigma connectivity between central and parietal cortical regions in this same condition. On the other hand, local increases in high-beta were observed during spindles, while connectivity changes between regions were not evident. Interestingly, both significant changes (inter-regional sigma; local high-beta) were identified over the sensorimotor regions. Yet these results do not allow us to clearly determine the exact underlying neuronal mechanisms triggering these changes. However, it could be hypothesized that during a cued spindle event, the synchrony between distinct cortical regions involved in the same motor representation is regulated by the spindle's sigma oscillations. However, no current model has yet discussed high-beta's involvement in memory consolidation. Hence, as theorized for the relationship between SO and spindles (Diekelmann et al., 2009), as well as for theta and gamma activity (G Buzsáki, 2010), we

propose that sleep spindles may be the basis for local activation of task-related networks through high-beta activity. Still, investigations using metrics such as phase amplitude coupling would be needed to confirm this hypothesis and to test the involvement of high-beta activity for motor sequence consolidation. Further analyses in studies using declarative tasks could also define if the sigma and high-beta topographic distributions are task-dependant.

Conclusion

Here we provide new evidences for the implication of sleep spindles in motor sequence consolidation. We show that cuing during NREM2 sleep does improve MSL consolidation. In addition, we demonstrate that, locally, cued reactivation increases the activity in the high-beta band during spindle events. Our results also show that lower frequencies are temporally locked to cued sleep spindles through spectral power increases before the onset and at the end of spindle events. Finally, connectivity between several cortical regions increases as a result of cuing. While low frequency bands increased connectivity throughout the cortex in an antero-posterior pattern, sigma activity seemed to influence coherence between task-related cortical areas. These findings, in relation with current theories on memory consolidation, suggest that sleep spindles are part of a complex and broad reactivation, and communication system involving multiple frequencies and brain regions. Yet, the interactions of sigma, high-beta and possibly gamma oscillations during cued sleep spindles still need to be investigated in order to elucidate the neuronal mechanisms binding these frequency bands together and their implication in motor sequence memory consolidation.

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Supplementary Material

Article 2: Beyond spindles: interactions between sleep spindles and boundary frequencies during cued reactivation of motor memory representations.

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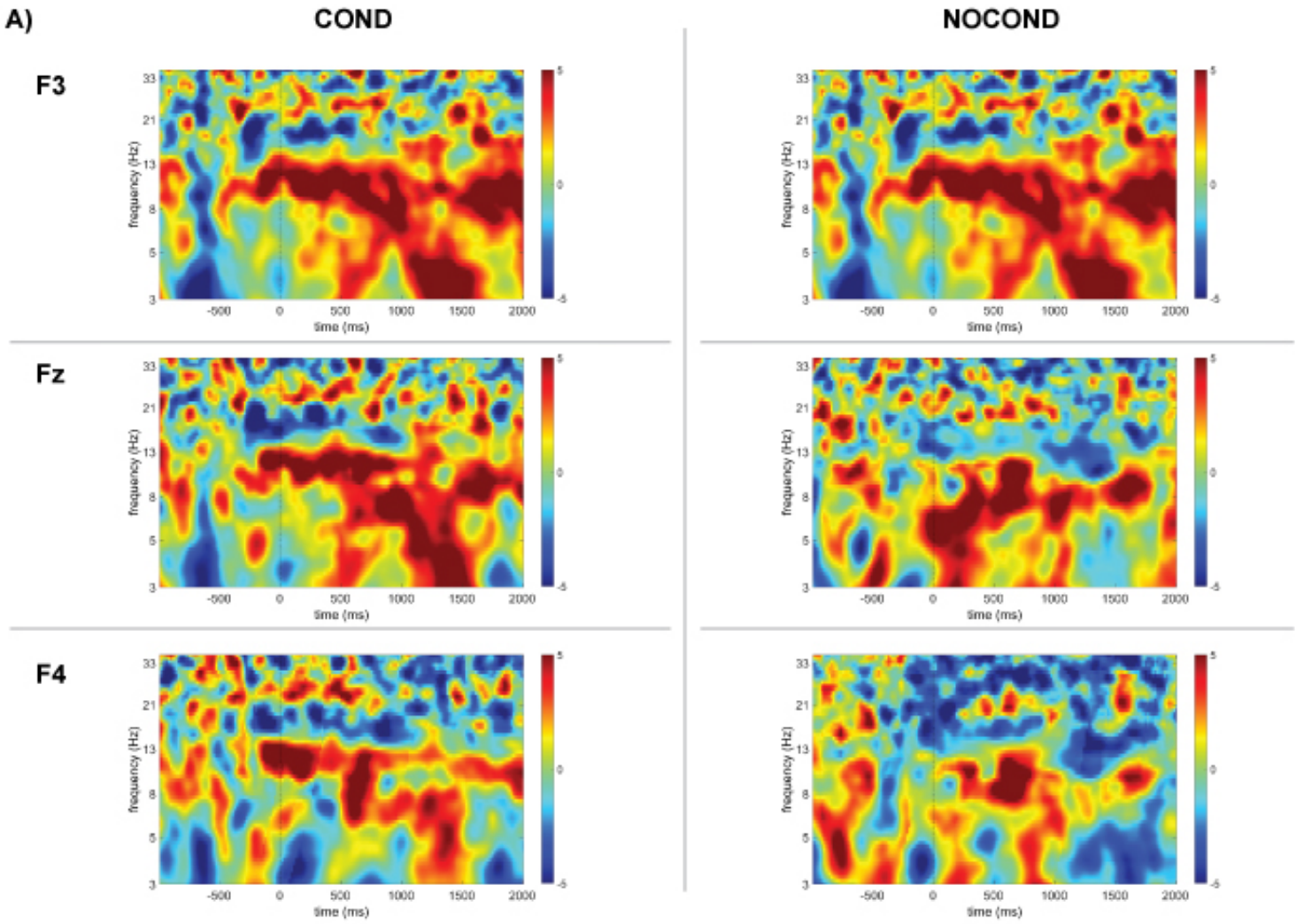
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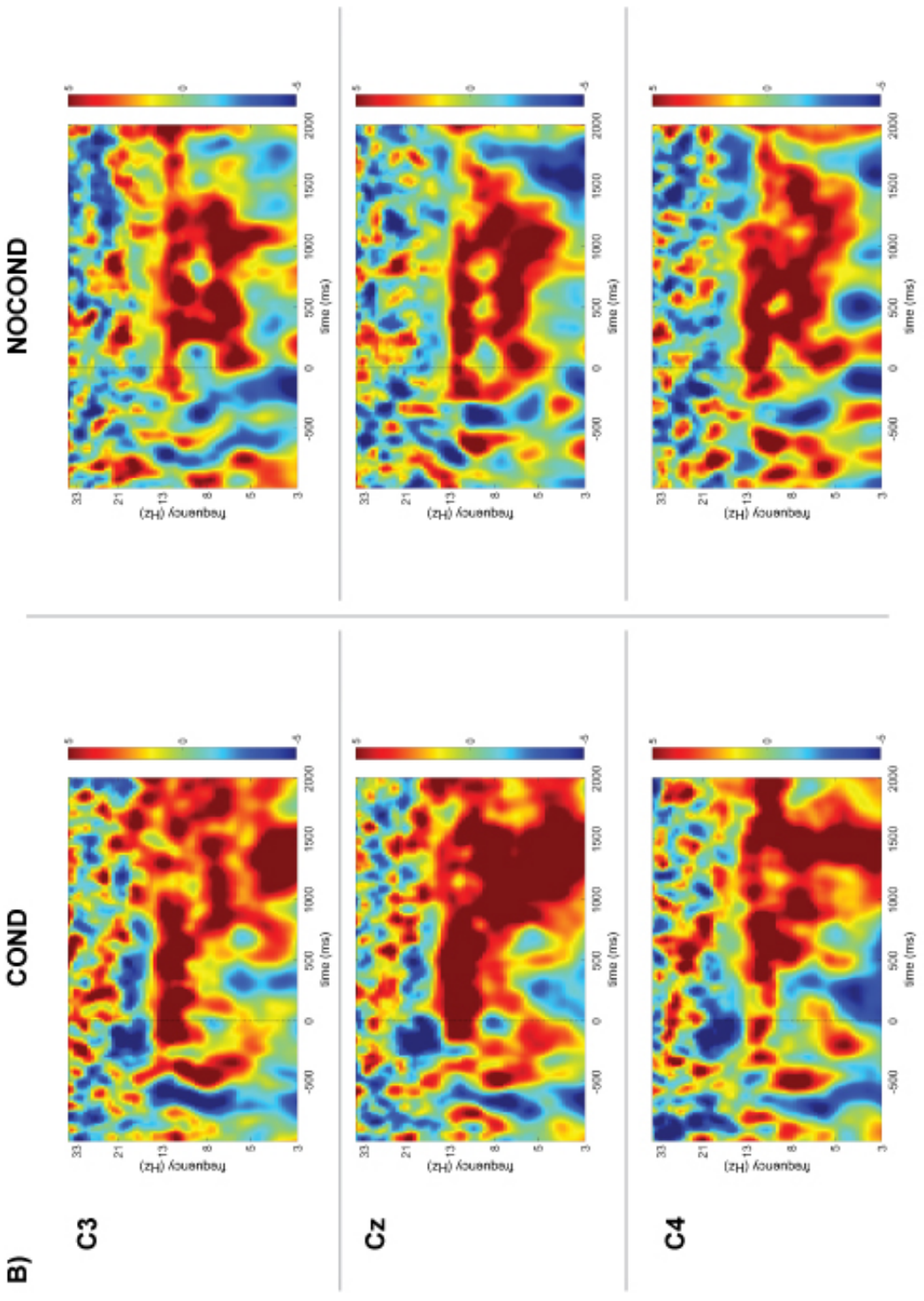
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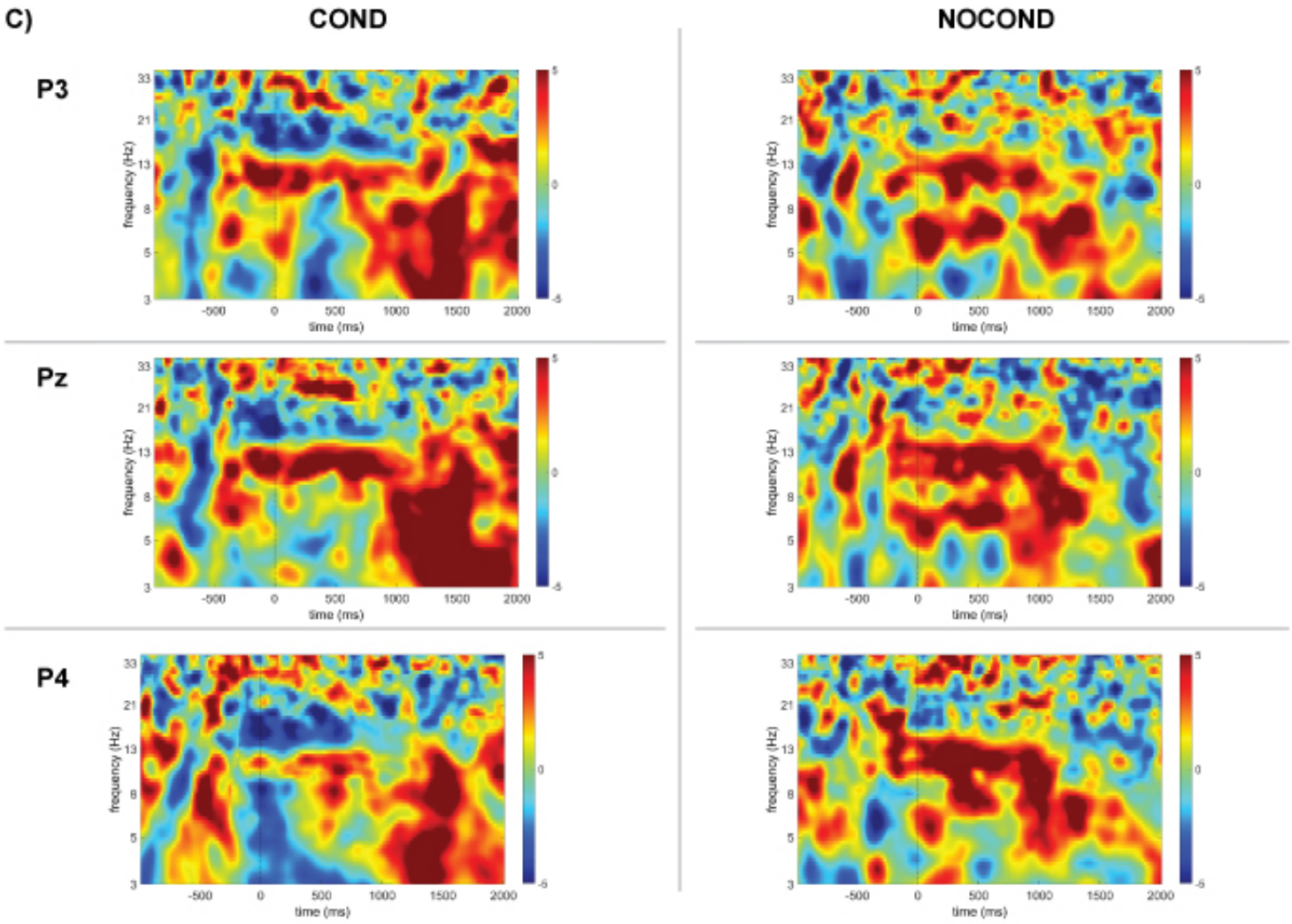
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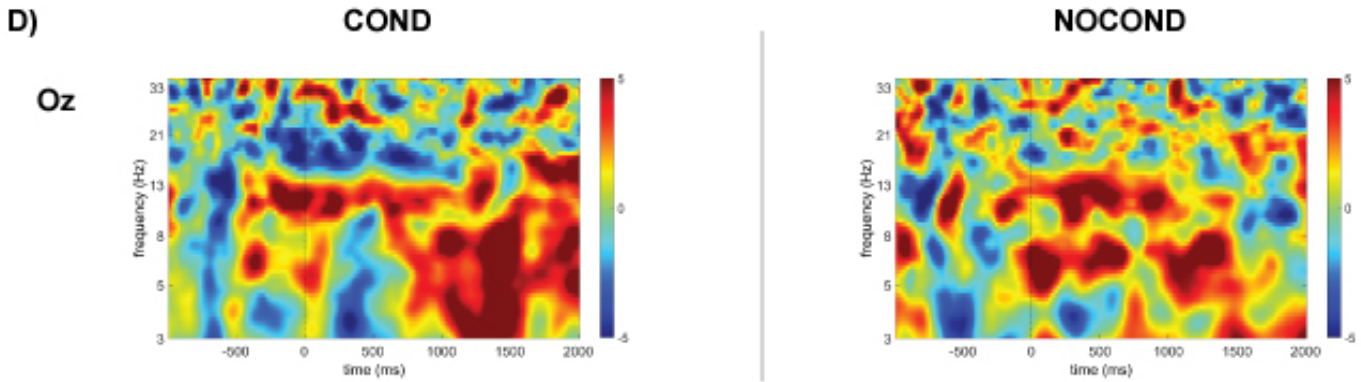
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Figure S1. ERSP maps of changes between pre-stim and stim conditions

Within group changes in sleep spindles between condition (pre-stim, stim) were assessed through Wilcoxon-Mann-Whitney comparisons in each subject, and pixel of the time-frequency map, resulting in a single contrast map per subject. These maps were averaged per group (Cond, NoCond) and site ([A]: F3, Fz, F4; [B]: C3, Cz, C4; [C]: P3, Pz, P4; [D]: Oz). Maps represent Wilcoxon-Man-Whitney values without threshold where positive values (red) represent spectral increases while negative values (blue) show spectral decreases between conditions.

Chapitre III: Discussion générale

1. Résumé et interprétation générale des résultats

L'objectif général de cette thèse était de confirmer et déterminer le rôle du stade de SNP2 et des FS dans la consolidation de la mémoire séquentielle motrice. Un second objectif était d'identifier les interactions entre FS et autres bandes fréquentielles favorisant la consolidation de la mémoire motrice. Deux études ont découlé de ce projet de recherche.

Tout d'abord, la première étude confirme l'implication importante du SNP2 dans la consolidation des AMS. En effet, nous avons observé des gains moteurs différés significativement plus élevés pour le groupe conditionné à l'odeur durant l'exécution de la tâche motrice et indicé durant le SNP2 comparativement à celui ayant été réexposé durant le SP et celui n'ayant pas été conditionné à l'odeur. Ceci témoigne du fait que le SNP2 contribue à la consolidation de la mémoire motrice séquentielle et réaffirme une implication plus importante de ce dernier par rapport au SP, à tout le moins, en termes de réactivation mnésique. L'examen détaillé des FS indicés a démontré que, dans le groupe réexposé en SNP2, la stimulation n'avait affecté que les FS de la région pariétale. Les changements observés ont pris la forme d'augmentations d'amplitude et de fréquence des fuseaux enregistrés durant la stimulation olfactive, en comparaison avec ceux précédant cette stimulation. Le fait que ces hausses étaient plus élevées chez le groupe conditionné que chez le groupe contrôle, suggère que la réactivation de la trace mnésique a eu une influence sur l'activité neuronale pariétale sous-tendant les FS. En outre, les résultats de cette étude démontrent que les changements au niveau de la fréquence des FS pourraient expliquer les différences individuelles au niveau des gains différés des sujets.

Suivant les résultats de cette première étude, nous avons par la suite exploré l'interaction concomitante entre les FS et autres bandes fréquentielles d'un point de vue local et inter-régional durant la réactivation d'une trace mnésique motrice. Globalement, cette dernière étude a identifié des changements d'activité fréquentielle apparaissant de façon synchrone avec les FS indicés. D'abord, par contraste avec les FS non indicés, elle a révélé que l'exposition à un stimulus conditionné générait des hausses plus importantes d'activité centro-pariétale de basse fréquence (delta et/ou thêta) avant et après l'occurrence des FS. De plus, elle a rapporté, la présence d'augmentations groupées dans la bande haut-bêta chez le groupe conditionné,

chevauchant l'oscillation des FS. Par ailleurs, cette étude est la première à révéler la présence d'une composante de hautes fréquences en haut-bêta simultanée à l'activité en sigma durant les FS, indicés ou non. Enfin, les analyses de connectivité ont permis de mettre à jour des changements particulièrement importants en delta, thêta et sigma, présent seulement durant les FS indicés. Globalement, les résultats des tests locaux et de connectivité inter-régionale suggèrent que les fuseaux font partie d'un processus complexe mettant en relation plusieurs types d'oscillations de façon synchrone. Ces différentes bandes fréquentielles joueraient possiblement des rôles spécifiques dans ce processus – coordination et synchronisation entre différentes régions, et activation de réseaux locaux sous-tendant la trace mnésique motrice. Tout en réaffirmant l'importance des FS dans la consolidation de la mémoire motrice séquentielle, cette étude souligne l'importance d'étudier non seulement le fuseau comme un facteur indépendant, mais aussi comme un élément faisant partit d'une interaction entre plusieurs structures produisant un large éventail de types d'activité spectrale.

2. Stades de sommeil et consolidation de l'apprentissage moteur séquentiel

La première étude de cette thèse a établi l'implication du stade SNP2 dans la consolidation de la mémoire motrice séquentielle. Bien que plusieurs études précédentes aient déjà rapporté des corrélations entre des éléments associés au SNP2 et des changements de performance à une tâche d'AMS (Genzel et al., 2009; Korman et al., 2007; Walker et al., 2002), notre étude a mise en place la toute première évidence nécessaire pour établir un lien causal entre SNP2 et consolidation motrice, soit une augmentation de performance motrice suite à une stimulation durant ce même stade. Par ailleurs, nous avons aussi observé l'effet d'un indiçage durant le stade SP sur la consolidation d'un AMS. Nos résultats n'ont démontré aucun impact significatif de ce stade de sommeil sur la consolidation.

2.1 Le sommeil paradoxal

La décision méthodologique d'examiner le rôle du stade de SP dans le processus de consolidation d'un AMS, au cours de notre première étude, se basait sur le fait que de nombreux résultats conflictuels concernant cette relation avaient été rapportés. En effet, faisant suite à l'étude charnière de Walker et collègues (2002), démontrant que la consolidation de l'AMS était dépendante du sommeil, l'identification du moment ou stade durant lequel celle-ci se produisait avait fait l'objet de multiples études. Les premiers rapports se penchant sur cette question avaient identifié le stade SP comme étant une période propice pour la consolidation des mémoires motrices durant le sommeil (Cajochen et al., 2004; Fischer et al., 2002; E M Robertson, Pascual-Leone, & Press, 2004). Cette conclusion était en partie basée sur certaines données fonctionnelles suggérant une réactivation plus importante de la nouvelle trace mnésique principalement durant le stade SP (Maquet et al., 2000). Ces résultats ont mené à la proposition d'un modèle décrivant le rôle du sommeil dans la consolidation de la mémoire dans lequel les traces mnésiques déclaratives dépendraient du stade SOL tandis que celles de nature procédurale seraient renforcées durant le stade SP (Diekelmann & Born, 2010; Marshall & Born, 2007). Cependant, les auteurs de ce modèle théorique ont aussi souligné que cette dichotomie entre SOL et SP ne reflétait pas toutes les données rapportées (Fogel et al., 2007; Huber, Felice Ghilardi, Massimini, & Tononi, 2004) et qu'il fallait user de prudence dans son interprétation.

Se basant sur ce modèle, Rasch et collègues (2007) ont alors réalisé leur fameuse expérience de réactivation de la mémoire durant le sommeil. Voulant identifier le stade de sommeil durant lequel chaque type de mémoire est consolidé, ils ont exposé les sujets à une odeur florale durant l'entrainement à deux tâches (déclarative et procédurale) et ont ensuite indicé les sujets pendant le stade SOL ou SP. En accord avec leur modèle, les expérimentateurs s'attendaient à voir des augmentations de performance à (1) la tâche déclarative dans le groupe de sujets indicés durant le stade SOL et, (2) à la tâche procédurale pour le groupe réexposé durant le stade SP. Au final, le groupe indicé en stade SOL à bel et bien démontré des augmentations significatives de performance à la tâche déclarative, mais aucun des indiçage (SOL et SP) n'a permis de produire une telle hausse de la performance à la tâche de séquence motrice.

Ainsi, le fait que dans notre première étude nous n'ayons pas observé de changements significatifs de la performance à la tâche suite à une exposition en stade SP, a confirmé ce que Rasch et son équipe avaient initialement rapporté. Cependant, l'interprétation de ce résultat exige d'être prudent. En effet, l'absence de changements significatifs du groupe indicé durant le SP par rapport au groupe non conditionné n'est pas une preuve en soi que le stade SP soit inutile au processus de consolidation. Plutôt, cela signifie que la réactivation durant le stade SP d'une trace mnésique motrice nouvellement apprise via un stimulus olfactif n'entraine pas le même effet sur sa consolidation qu'un indiçage durant le stade SNP2 (voir section 3.1 pour causes potentielles). Aussi, comme plusieurs l'ont proposé, il est probable que le processus de consolidation nécessite que le cycle SNP-à-SP soit respecté pour être pleinement efficace (Marshall et al., 2006). Cependant, à l'encontre de cette hypothèse, une étude a démontré que l'inhibition pharmacologique du stade SP après un entrainement à une tâche d'AMS n'affectait en rien la performance à la tâche le lendemain (Rasch et al., 2009). En conséquence, le rôle de ce stade dans la consolidation de la mémoire motrice séquentielle reste encore à être déterminé.

2.2 Le sommeil non-paradoxal

Par la suite, d'autres groupes ont démontré qu'il était possible d'obtenir des gains de performance à une tâche motrice séquentielle lorsque les sujets étaient indicés durant le stade SOL, en modifiant le protocole de conditionnement initialement proposé par Rasch et collègues (Antony et al., 2012; Cousins et al., 2014; Rasch et al., 2007). Notre première étude vient à la suite de cette série d'études, mais a plutôt établi que le stade SNP2 jouait un rôle instrumental dans la consolidation de la mémoire motrice séquentielle. Cette démonstration complémentait les résultats d'études précédentes démontrant des corrélations entre des aspects en lien avec le stade SNP2 et la performance à une tâche AMS (Barakat et al., 2011, 2012; Morin et al., 2008; Nishida & Walker, 2007). Ainsi, prises ensemble, les conclusions de ces différentes études RCM suggèrent que le sommeil SNP en général (stade SNP2 et SOL) est crucial à la consolidation de la mémoire motrice séquentielle.

Bien que démontrant l'implication d'un stade différent (SOL) dans le processus de consolidation, ces études à schème RCM ne contredisent pas nos résultats. En effet, tout comme

il a été précédemment proposé au sujet du stade SP, il est possible que le mécanisme de consolidation nécessite également un passage normal et cyclique SNP2-SNP3-SNP2 afin de consolider effectivement les nouvelles traces mnésiques motrices. Partant de la prémisse que le SNP était en fait composé de deux stades complémentaires — le sommeil léger (SNP1 et 2) et le sommeil profond (SOL), Genzel et collègues (2014) ont proposé un modèle de la consolidation réconciliant deux théories actuelles de la consolidation. La première, la "consolidation systémique active" soutient que, durant le SNP, les nouvelles traces mnésiques sont réactivées via une interaction entre l'hippocampe et le cortex, renforçant ainsi les connexions entre les ensembles de neurones sous-tendant cette trace (Chauvette, Seigneur, & Timofeev, 2012; Diekelmann & Born, 2010; Ego-Stengel & Wilson, 2009; Wilson & McNaughton, 1994b). L'autre, la théorie de "l'élagage" se base sur un principe d'homéostasie et avance que, suite à une période d'éveil, le sommeil permet aux réseaux neuronaux de retrouver un point d'équilibre, les rendant ainsi aptes à traiter de nouvelles information (Tononi & Cirelli, 2003). Le modèle réconciliatoire de Genzel et al. propose que durant le sommeil léger — stade dominé par les FS, SW/R et complexes K — la réactivation systématique des représentations mnésiques entraine une réorganisation globale de celles-ci à travers les différentes structures qui furent impliqués lors de l'apprentissage initial. De façon complémentaire, le sommeil profond — dominé par les OL et une rupture de la connectivité cortico-corticale (Chow et al., 2013; Spoormaker et al., 2010) — serait une période clé pour le processus d'élagage des synapses et/ou de consolidation d'une trace mnésique à l'intérieur d'une région corticale définie.

Selon ce dernier modèle de Genzel (2014), l'indiçage durant le SNP2 tel qu'effectué dans les études de cette thèse, se produirait pendant une période d'importante connectivité globale permettant une réorganisation de la trace motrice et de son contexte indicé (trace épisodique). Bien que ce modèle soit basé sur de nombreuses études et semble en ligne avec nos résultats, il demeure que cette dissociation fonctionnelle entre le soi-disant sommeil léger et le sommeil profond dans la consolidation de la mémoire motrice séquentielle se doit d'être confirmée.

3. Réactivation ciblée d'une trace mnésique d'un apprentissage moteur séquentiel

L'objectif initial et fondamental du premier article de la thèse était de faciliter la consolidation d'une tâche motrice séquentielle à l'aide d'un protocole de réactivation ciblée de la mémoire utilisant un stimulus olfactif. Cet objectif a été atteint, tel que l'a témoigné la différence significative en niveau de performance entre le groupe indicé en SNP2 comparé à celui du groupe SP et le groupe qui n'a pas reçu de conditionnement à l'odeur durant la tâche.

Cependant, ceci ne fut pas la première réussite d'augmentation de la performance motrice séquentielle à l'aide d'un paradigme RCM. En effet, lors de la publication du premier article de cette thèse, trois autres études utilisant des stimuli auditifs, plutôt qu'olfactifs, avaient atteint cet objectif (Antony et al., 2012; Cousins et al., 2014; Schönauer et al., 2014). Toutefois, aucune d'entre elles n'avait observé de modification dans les caractéristiques propres aux FS associés à l'indiçage auditifs, tel que nous l'avons rapporté dans le premier article de cette thèse. À l'origine de cette série d'études — incluant la nôtre, Rasch et collègues (2007) avaient eux aussi tenté d'obtenir, sans succès, de telles améliorations de la performance motrice en utilisant un conditionnement olfactif. À travers l'examen de ces diverses études utilisant un schème de type RCM, sous l'apparence de résultats contradictoires et inconstants, se cachent plusieurs indices pouvant nous aider à mieux comprendre le mécanisme de consolidation de la mémoire motrice séquentielle durant le sommeil. Dans la section qui suit, nous traiterons de différences méthodologiques entre ces études et la nôtre, pouvant être à l'origine de différences significatives dans les résultats rapportés. Par ailleurs, cette analyse pourra servir de guide à de futures études RCM.

3.1 Le stimulus

Dans le contexte d'une étude RCM, l'utilisation d'un stimulus comme indice contextuel conditionné, qu'il soit de nature olfactive, auditive ou même tactile, exige une analyse attentive de plusieurs facteurs méthodologiques : habituation au stimulus, inconfort à l'exposition prolongée, risque de perturbation du sommeil et efficacité du type de stimulus.

Lors d'une stimulation durant le sommeil, le choix d'un stimulus olfactif est supporté par plusieurs avantages propres à cette technique. Tout d'abord, il a été démontré que l'utilisation d'une odeur agréable n'entrainait pas d'éveil chez des sujets endormis (Arzi et al., 2010; Badia et al., 1990; Carskadon & Herz, 2004). De plus, l'emploi d'un stimulus olfactif pur, telle que celle utilisée pendant notre étude (2-phényléthanol), permet une exposition prolongée sans inconfort, puisque son interaction avec le nerf trijumeau n'entraine pas de sensations désagréables de picotement ou de brûlure lorsque sa concentration est contrôlée et faible (Frasnelli, Hummel, Berg, Huang, & Doty, 2011; Grupp, Maurer, Hörmann, Hummel, & Stuck, 2008; Laska et al., 1997; Stuck et al., 2007). Enfin, et possiblement le plus important, l'avantage de l'utilisation d'une odeur vient du fait que la réponse fonctionnelle olfactive n'est pas affectée par l'atténuation sensorielle induite par le thalamus durant le sommeil, comme c'est le cas pour l'audition et le touché (Sherman & Guillery, 2002). En effet, l'information olfactive n'emprunte pas la voie thalamique avant d'atteindre des structures critiques aux traitement et stockage du contenu mnémonique telles que l'hippocampe (Carmichael & Price, 1996). Cette caractéristique lui permettrait peut-être d'agir plus efficacement comme indice épisodique lors de la stimulation durant le sommeil, comparativement à un autre type de stimulus.

Cependant, il est important de noter que l'utilisation d'un stimulus olfactif comporte aussi certains désavantages. Premièrement, une odeur est un indice diffus, c'est-à-dire qu'une fois le sujet exposé, celui-ci restera en présence du stimulus durant une période plus ou moins longue. Ainsi, la résolution temporelle des analyses investiguant l'effet du stimulus sur le sommeil est plutôt basse, consistant en périodes de plusieurs minutes comparativement à quelques millisecondes pour un stimulus auditif. De plus, certaines études chez le chat suggèrent que la réponse fonctionnelle olfactive est différente entre les stades SNP et SP, étant plus faible durant le dernier (Hernández-Peón, O'Flaherty, & Mazzuchelli-O'Flaherty, 1965; Homeyer, Sastre, Buda, & Jouvet, 1995). Si ce même effet se retrouve chez l'humain, ceci pourrait avoir un impact sur l'efficacité de la stimulation durant le SP. Finalement, la manipulation et préparation du soluté olfactif nécessitent plusieurs précautions propres à l'utilisation d'une odeur, afin d'éviter tout contact entre les sujets et l'odeur avant le moment prédéfini pour la stimulation. Par surcroît, dépendant du type de molécule utilisée, l'utilisation de certains produits cosmétiques (parfums, savons, crèmes, shampoing, etc.) doit être évitée par les expérimentateurs avant tout contact

avec le participant. En effet, plusieurs molécules utilisées dans les expériences RCM (par exemple, lavande et 2-phényléthanol) font communément partie de la composition de plusieurs produits cosmétiques. Ainsi, bien que la nature du stimulus puisse expliquer certaines différences entre les résultats provenant de ce groupe d'études RCM et la nôtre, d'autres facteurs sont possiblement en cause.

3.2 Stade de sommeil et période ciblé pour la stimulation

Dans notre première étude, nous avons démontré l'importance du stade SNP2 dans la consolidation de la mémoire motrice séquentielle. Ce stade spécifique a été choisi comme cible dû au fait que les FS, qui ont été à maintes reprises associés à la consolidation de l'apprentissage moteur séquentiel (Barakat et al., 2011, 2012; Fogel & Smith, 2011; Morin et al., 2008; Nishida & Walker, 2007), sont générés principalement durant ce stade de sommeil (Luigi De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005). Cependant, trois des quatre autres études mentionnées précédemment ont ciblé le stade de SOL (Antony et al., 2012; Cousins et al., 2014; Rasch et al., 2007), alors que dans la quatrième, la stimulation a eu lieu durant le sommeil, sans distinction du stade (Schönauer et al., 2014). Si le FS est bel et bien un élément crucial dans le processus de consolidation de l'apprentissage moteur durant le sommeil, il est possible que le choix des stades ciblés ait influencé les résultats rapportés.

Outre le stade de sommeil ciblé pour la stimulation, le moment d'exposition que nous avons choisi diffère de celui de ces autres études. Ainsi, les sujets prenant part à notre expérimentation ont été exposés à l'odeur durant la dernière moitié de la nuit, alors que dans le cas des quatre autres études, la stimulation a plutôt eu lieu durant la première moitié de la nuit, débutant toujours avec le premier cycle de sommeil. Ce choix méthodologique, nous a permis de comparer l'effet de l'indiçage sur des événements propres au sommeil tels les FS, à une période de référence où ces mêmes événements n'avaient pas encore été influencées par la stimulation durant le sommeil. Il est donc possible que ceci explique en partie les changements détectés dans les caractéristiques des FS seulement dans notre étude.

3.3 La tâche d'apprentissage

La tâche d'apprentissage utilisée lors des études formant cette thèse consiste en une séquence de mouvements de doigt sur un clavier à quatre boutons, cette dernière constituant une version adaptée de la tâche d'AMS développée par Avi Karni et al. (1995). L'une des caractéristiques principales de cette tâche est que les sujets connaissent explicitement la séquence avant de la produire. En contraste, trois des quatre études RCM ont plutôt choisi d'employer des tâches d'apprentissage moteur séquentiel implicite (Antony et al., 2012; Cousins et al., 2014; Schönauer et al., 2014), consistant en une suite de mouvements dans laquelle se cache une séquence qui est inconnue des sujets. Cependant, il a été démontré que la consolidation des apprentissages d'AMS découlant de tâches explicites est dépendante du sommeil, alors que celle provenant de tâches implicites ne l'est pas; le simple passage du temps étant suffisant (E M Robertson, Pascual-Leone, & Press, 2004). Ainsi, ceci implique que les processus neuronaux sous-tendant la consolidation de ces deux types de traces mnésiques sont, à tout le moins, en partie différents. Il est donc possible que cette différence dans la nature de l'apprentissage initial explique la variance entre ces études et les nôtres.

Cependant, il n'y a pas que la nature de la tâche qui peut être en cause. Les sujets participant à l'étude de Rasch et collègues (2007) étaient en fait entrainés à deux tâches différentes, l'une à la suite de l'autre, sans permutation. La première tâche était une tâche visuospatiale de pairage d'image (mémoire déclarative) alors que la deuxième correspondait à une tâche d'AMS (mémoire procédurale). Fait important, durant toute la durée de ces deux entrainements, les sujets étaient exposés au stimulus olfactif. Ainsi, il est possible que l'association entre le stimulus et la tâche ait été efficace seulement pour la première tâche, celle impliquant la mémoire déclarative. Ceci est d'autant plus possible étant donné le haut risque d'habituation lors d'une exposition prolongée à un stimulus olfactif, découlant d'une diminution graduelle de la réponse neuronale (Croy, Maboshe, & Hummel, 2013; Poellinger et al., 2001). Par conséquent, dans le cas de cette étude, bien que la tâche d'apprentissage et la nature du stimulus étaient les mêmes que celles utilisées durant notre expérimentation, l'addition d'une tâche déclarative dans le protocole peut expliquer l'absence de gains moteurs dans leur étude.

4. Le fuseau de sommeil: un élément clé du processus de consolidation

Ayant établi que le SNP2 était instrumental à la consolidation de traces mnésiques motrices séquentielles, l'objectif suivant de cette thèse était d'investiguer le rôle des FS dans ce processus. Dans le premier article, nous avons observé les changements induis par l'indiçage sur les caractéristiques des FS, tandis que dans le deuxième, nous avons mesuré et décrit l'interaction entre les FS et d'autres signaux concomitants aux niveaux locaux et interrégionaux. Les résultats découlant de ses deux études ont permis d'éclaircir différentes facettes du mécanisme de la consolidation à travers l'action des FS.

4.1 Modifications des fuseaux de sommeil par indiçage

Avant la publication du premier article de cette thèse, plusieurs études suggéraient déjà l'implication des FS dans la consolidation de la mémoire motrice séquentielle. Cependant, cette hypothèse se basait sur la corrélation entre les caractéristiques des FS et les gains en performance à la tâche d'AMS, et/ou les changements mesurés dans les caractéristiques des FS suite à un entrainement à une tâche d'AMS (Barakat et al., 2011, 2012; Fogel & Smith, 2011; Morin et al., 2008; Nishida & Walker, 2007). Bien que ceci ne diminue en rien l'importance de ces résultats, les preuves accumulées alors étaient uniquement de nature corrélationnelle. Ainsi, il est devenu important de confirmer si ces résultats reflétaient bel et bien l'action des mécanismes de consolidation de la mémoire. Comme il a été mentionné précédemment, certains groupes ont alors tenté de confirmer l'implication des FS dans la consolidation de la mémoire motrice en utilisant des protocoles de RCM (Antony et al., 2012; Cousins et al., 2016, 2014; Rasch et al., 2007; Schönauer et al., 2014). Deux de ces équipes ont rapporté des corrélations entre les gains de performance à une tâche motrice et le nombre ou la densité des FS. Cependant, aucune d'entre elles n'a observé de changement significatif à travers les différents attributs des fuseaux suite à la stimulation durant le sommeil.

La démonstration faite dans l'étude initiale de cette thèse était donc la première à identifier de telles modifications à travers les caractéristiques des FS induites par une stimulation

exogène. Plus précisément, l'amplitude et la fréquence des FS d'origine pariétale ont significativement augmenté suite à l'indiçage durant le SNP2 en comparaison avec ceux du groupe non conditionné. Fait important, ces changements n'étaient pas dus à des différences d'architecture de sommeil ou des FS présents avant la stimulation, mais ont plutôt été déclenchés par l'indiçage olfactif durant le SNP2. Des analyses supplémentaires ont permis d'identifier une bande de fréquence spécifique (13,5 à 14 Hz) dans laquelle nous avons observé une augmentation significative du nombre de FS chez le groupe indicé en comparaison avec le groupe non indicé. Nous avons aussi démontré à l'aide d'une analyse de médiation que les changements dans cette même bande de fréquence expliquaient la relation entre les groupes expérimentaux et les différences en performances à la tâche motrice.

Il est à noter que, comparativement à plusieurs études précédentes (Antony et al., 2012; Barakat et al., 2011, 2012; Cousins et al., 2014; Fogel & Smith, 2006; Nishida & Walker, 2007), cette première étude ne rapporta pas de changements au niveau du nombre de fuseaux (nombre ou densité) suite à l'entrainement à la tâche AMS et/ou à la stimulation. De fait, puisque nos groupes n'avaient pas effectué de nuit de base, permettant la comparaison des FS avant et après entrainement, il nous était impossible de mesurer l'impact de l'AMS sur le nombre de fuseaux. Ainsi, nous devons assumer que si la tâche a eu l'effet d'augmenter le nombre de FS, elle a eu la même incidence sur tous les groupes (indicé et non indicé). Par ailleurs, tous changements observés suite à l'indiçage, significativement différent par rapport au groupe non indicé, était donc au-delà de l'effet de base d'une tâche d'AMS. Le fait que nous n'ayons pas observé de hausses de densité des FS suite à la stimulation est en accord avec l'hypothèse suggérant que les changements au niveau des FS même (amplitude, fréquence, durée) soient potentiellement plus importants pour la consolidation de la mémoire que le nombre de FS (Manuel Schabus et al., 2004, 2006, 2008). De plus, puisqu'il est proposé que l'activité rythmique des FS facilite l'apparition de conditions favorables à la plasticité synaptique (Contreras et al., 1997; Rosanova & Ulrich, 2005; Sejnowski & Destexhe, 2000; Yang et al., 2014), il est possible que, sans la nécessité d'un plus grand nombre de FS, l'augmentation de la fréquence et de l'amplitude des fuseaux soit suffisante pour générer plus efficacement des changements synaptiques à long terme, assurant une meilleure synchronie de la boucle thalamo-corticale, et ainsi faciliter la consolidation de la mémoire motrice séquentielle.

Tel que mentionné précédemment, cette première étude ne représentait pas la première tentative de manipulation des FS dans un contexte de RCM. L'absence d'effet sur les caractéristiques physiques des FS durant le sommeil au cours de ces autres études (Antony et al., 2012; Cousins et al., 2014; Rasch et al., 2007) est possiblement due à deux raisons principales. Tout d'abord, puisqu'ils ont effectué leurs stimulations durant le stade de SOL, et que les FS sont beaucoup plus nombreux en stade de SNP2 qu'en SOL, il est possible que la densité différentielle des FS dans ces deux stades explique la différence de résultats entre notre étude et ceux des autres groupes de recherche. Enfin, contrairement à notre protocole expérimental, les segments non indicés et indicés de leur groupe conditionné s'entrecoupaient en succession. Considérant la courte durée de ces segments, l'indiçage d'une période donnée pouvait donc potentiellement contaminer l'activité du segment non indicé lui succédant. Le terme contamination renvoie à la possibilité que la stimulation durant une période donnée (indicée) puisse avoir un effet qui perdurera pendant la période suivante (non indicée). Lors de notre expérimentation, la période comparative reflétant le segment non indicé du groupe conditionné se retrouvait en totalité avant le début de la stimulation olfactive, évitant ainsi la contamination de la période de base non indicée.

4.2 Rôle du cortex pariétal dans la consolidation de la mémoire motrice séquentielle

Tel que présenté dans le premier article de cette thèse, les analyses sur les caractéristiques des FS ont d'abord été effectués sur les dérivations de la ligne médiane du cortex — c'est-à-dire, les cortex frontal, central et pariétal. Au final, nous n'avons identifié des changements significatifs suite à la stimulation durant le SNP2 que dans les régions pariétales. À ce point, considérant les limites méthodologiques de notre expérimentation, nous ne pouvons que spéculer sur les raisons possibles expliquant l'implication du cortex pariétal dans la réactivation et la consolidation de la mémoire motrice séquentielle associé à la génération de FS. De fait, la littérature scientifique actuelle propose certaines pistes de réponses potentielles.

D'abord, afin de faire la lumière sur l'importance apparente des régions pariétales dans la consolidation de la mémoire motrice séquentielle, il faut se pencher sur les différentes facettes comprises dans un tel apprentissage. En effet, celui-ci comporte non seulement l'exécution motrice de chacun des mouvements de la séquence, mais aussi le développement d'une représentation spatiale de ces mouvements, un contexte épisodique qui s'y rattache (olfaction, vision, audition) et un affect, sans compter les composantes motivationnelles et attentionnelles lors de l'entrainement. Pour que la consolidation d'une trace mnésique soit complète, l'intégration de ces modalités en un tout cohérent est nécessaire. Depuis longtemps déjà on reconnait le cortex pariétal comme une structure ayant une fonction associative (Critchney, 1953; Hyvärinen, 1982; Mountcastle, 1975). On y retrouve le cortex somatosensoriel, responsable du traitement des sensations corporelles, telles que le toucher, la douleur, l'équilibre. De plus les aires associatives pariétales reçoivent et traitent plusieurs afférences de types visuels, moteurs, auditifs et olfactifs (Andersen, Snyder, Bradley, & Xing, 1997) et sont responsable de leur intégration en une représentation globale et concrète (Kurata, 1994).

L'une des pistes de solution expliquant l'implication prépondérante du cortex pariétale dans la consolidation de mémoire motrice provient donc du fait que, dès le début de l'entrainement à une tâche d'AMS, la représentation de la séquence est subdivisée en deux formes (spatiale et motrice), qui sont indépendamment associées à des changements neuro-plastiques dans des réseaux distincts (Albouy, King, et al., 2013; Genzel et al., 2015). L'apprentissage de la représentation motrice de la séquence recrute en partit, le striatum, le cortex moteur et le cervelet (Dayan & Cohen, 2011; Doyon et al., 2011; Doyon, Bellec, et al., 2009; Hikosaka et al., 2002) alors que la forme spatiale de cette représentation nécessite principalement l'activation de l'hippocampe ainsi que les cortex préfrontal et pariétal (Albouy et al., 2015; Albouy, King, et al., 2013; Hikosaka et al., 2002; Wilber, Skelin, Wu, & McNaughton, 2017a). La forme spatiale de la tâche serait donc le versant « déclaratif » de ce type de tâche procédurale, ce qui expliquerait le recrutement de ces structures typiquement associées à la mémoire déclarative. Par ailleurs, la consolidation de ce dernier type de représentation est reconnue pour être associée au FS durant le SNP (Albouy et al., 2015). Pareillement, d'autres études RCM utilisant plutôt une tâche visuospatiale ont rapporté que l'indiçage olfactif pendant le stade de SOL induisait des changements dans les FS rapides (14-

16 Hz) enregistrés dans les régions pariétales (Cox et al., 2014; Rihm et al., 2014). De plus, certaines études chez l'animal ont démontré l'association entre activations pariéto-hippocampiques et consolidation de mémoires de nature spatiale (Maingret et al., 2016; Qin, McNaughton, Skaggs, & Barnes, 1997) et motrice (Wilber, Skelin, Wu, & McNaughton, 2017b).

Considérant qu'un stimulus olfactif est un indice de nature épisodique, et donc déclaratif, la coactivation de l'hippocampe et du cortex pariétal appert comme étant fortement probable. Il est alors possible que lors de la stimulation olfactive, l'odeur préalablement associée à la nouvelle trace mnésique spatiale réactive de façon préférentielle la représentation spatiale de la séquence recrutant ainsi les régions pariétales.

4.3 Électrophysiologie de la consolidation de la mémoire motrice séquentielle

Suite à la démonstration de l'importance des FS dans la consolidation des traces mnésiques motrices, nous nous sommes penchés sur (1) l'interaction entre FS et autres bandes de fréquences ainsi que sur (2) les changements en connectivité corticale associés aux FS pendant l'indiçage. Au cours de cette seconde étude, nous avons confirmé que les FS indicés étaient précédés et suivis par des changements spectraux associées aux bandes delta et thêta. Nous avons aussi identifié des augmentations dans la bande haut-beta apparaissant durant ces mêmes FS indicés. Enfin, nous avons rapporté que durant les FS indicés, la connectivité entre plusieurs régions corticales augmentait de façon différentielle, dépendant de la bande de fréquence observée — delta, thêta et sigma. Durant les FS indicés, alors que nous avons observé des augmentations de cohérence couvrant toutes les régions corticales en thêta, celles-ci étaient restreintes aux régions habituellement reliées à l'apprentissage moteur en sigma. Par ailleurs, les hausses en connectivité dans les bandes delta et thêta formaient un patron antéro-postérieur, alors que celles en sigma étaient à la fois interhémisphériques et antéro-postérieures tout en étant ségrégées aux régions motrices et associatives. Ces résultats complémentent d'autres études démontrant que les oscillations delta et thêta soient associées à la communication entre régions

corticales éloignées, tandis que les oscillations sigma sous-tendraient l'activité entre régions voisines (von Stein & Sarnthein, 2000). Ils sont aussi en accord avec d'autres études rapportant que, suite à un AMS, on observait des augmentations de la densité des FS dans ces régions ainsi que des hausses de connectivités entre celles-ci (Duckrow & Zaveri, 2005; Nishida & Walker, 2007). Ainsi, le deuxième article de cette thèse appuie l'hypothèse que les FS participent activement à la consolidation de la mémoire motrice séquentielle par la réactivation d'une série de régions cérébrales sous-tendant la trace mnésique et que cette interaction complexe nécessite une activité que l'on peut observer dans les bandes delta, thêta et high-beta, concomitante à la génération de FS.

Tel que nous l'avons démontré, des modifications de la bande thêta, reliées à l'indiçage, ont été observées localement et entre différentes régions. Cette bande fréquentielle, typique du stade de SP, est aussi présente durant le SNP et est généralement associée à l'activité hippocampique soutenant les processus mnésiques (György Buzsáki, 2002; Sauseng et al., 2010). Certains auteurs ont suggéré que l'activité neuronale dans la bande thêta était le produit de l'interaction entre l'hippocampe, le cortex et le striatum durant la récupération de souvenirs de nature épisodique (Fuentemilla et al., 2014; Herweg et al., 2016). De plus, plusieurs études ont proposé que le thêta jouerait un rôle central dans l'intégration de multiples représentations (par exemple : spatiale, motrice, auditive) en un tout cohérent, rôle semblable à celui accordé au cortex pariétal tel que décrit précédemment (Fell & Axmacher, 2011; Hasselmo et al., 2002; Sauseng et al., 2010). Comme il a été mentionné plus haut, étant donné que le stimulus olfactif représente un indice épisodique, il est donc possible que cet indiçage explique les augmentations en synchronie entre fuseaux et thêta, et les hausses en connectivité corticales durant les FS, résultant ultimement dans une consolidation plus effective et une meilleure performance le lendemain matin.

L'interaction temporelle apparente entre FS et les fréquences delta que nous rapportons ici concorde avec ce qui est décrit dans la littérature. En effet, plusieurs études décrivant la relation entre FS et AOL ont proposé que le passage d'état inactif (*down-state*) à actif (*up-state*) lors d'AOL fournirait un environnement propice à la formation de FS et autres oscillations rapides, telles que les SWRs (Chauvette et al., 2012; Diekelmann & Born, 2010; Ego-Stengel & Wilson, 2009; Wilson & McNaughton, 1994b). Ces interactions de synchronies et de

facilitation entre différents types d'oscillations sont au centre même du modèle de « consolidation systémique active » tentant d'expliquer les mécanismes qui sous-tendent la consolidation mnésique durant le SNP (Diekelmann et al., 2009; Marshall & Born, 2007). Par conséquent, les hausses enregistrées localement dans la bande delta, précédant et suivant les FS, appuient ce modèle tout soulignant la possibilité qu'un autre type d'oscillation soit impliqué dans la réactivation : c'est-à-dire le haut-beta.

Plusieurs études récentes suggèrent que la période durant l'activation d'un FS est un moment d'activité propice à l'apparition d'activité neuronale très rapide et synchrone, telle que les SWRs (Averkin et al., 2016; Clemens et al., 2011; Staresina et al., 2015). Cependant, l'identification, dans notre deuxième article, d'îlots d'activité haut-beta durant les fuseaux, et ce sans indiçage, constitue une première dans la littérature scientifique. Par la suite, nous avons démontré que ces rafales de haut-beta étaient modulés significativement par l'indiçage dans des régions généralement associées à l'apprentissage et la consolidation d'une tâche motrice. Cela suggère que ces bonds ponctuels d'activité pourraient être causés par la réactivation de la trace mnésique lors de la présentation du stimulus conditionné durant le SNP2, ouvrant la porte à une toute nouvelle avenue de recherche. Toutefois les outils d'enregistrement utilisés lors de ce protocole expérimental ne nous permettaient pas de définir la nature des structures neuronales et réseaux qui sous-tendaient cette activité en haut-beta. Ainsi, le rôle de l'activité haut-beta imbriquée dans l'oscillation des fuseaux et la consolidation de la mémoire reste à être étudiée.

Néanmoins, l'analyse globale des changements locaux et interrégionaux peut apporter des indices quant à leur origine. Contrairement aux analyses locales (temps/fréquence), l'examen des changements en cohérence entre régions corticales n'a identifié aucune hausse significative dans la bande haut-beta. En fait, le schéma inverse a été observé dans la bande fréquentielle des fuseaux, où des changements ont été identifiés uniquement lors des analyses de connectivité associées au FS indicés, et non lors des analyses locales (changements spectraux). Globalement, cela suggère que l'influence de l'activité en haut-beta durant les FS serait ségrégée à un réseau local. En revanche, il appert que l'indiçage olfactif ait plutôt influencé la connectivité en sigma entre régions voisines; régions supportant les processus somatosensoriel et moteur. Ensemble, ces résultats suggèrent que les FS synchroniseraient l'activation d'un réseau global comprenant plusieurs régions corticales supportant la

représentation de la tâche motrice, et entraineraient ainsi une activité locale concomitante de fréquence rapide (haut-beta). En outre, il est possible de faire l'hypothèse que cette activité, produit de la réactivation de la trace mnésique et répétée durant le sommeil, induirait des modifications neuro-plastiques sous-tendant le processus de consolidation de la mémoire motrice séquentielle.

4.4 Le rôle des fuseaux dans le processus de consolidation

Enfin, cette dernière étude apporte aussi des éléments de réponse concernant une problématique récurrente liée à l'association entre FS et consolidation de la mémoire. En effet, bien qu'il existe une panoplie d'études s'entendant sur le fait que les fuseaux sont impliqués dans la consolidation de la mémoire déclarative et procédurale, celles-ci ne s'accordent pas quant à l'identification de la ou les caractéristiques (c.-à-d., amplitude, durée, fréquence, densité) pouvant servir de marqueurs du processus de consolidation pour ces deux types de mémoire.

À même le champ restreint de la littérature scientifique au sujet de l'apprentissage moteur, certains auteurs ont rapporté des changements en amplitude (Barakat et al., 2012), durée et/ou densité (Barakat et al., 2011; Fogel et al., 2007; Morin et al., 2008) des FS suite à l'apprentissage d'une tâche motrice. Plusieurs études ont également identifié des corrélations entre les gains en performance motrice et l'une ou plusieurs de ces mêmes caractéristiques (Albouy, Fogel, et al., 2013; Barakat et al., 2011, 2012; Fogel & Smith, 2006; Lustenberger et al., 2016; Nishida & Walker, 2007; Peters, Ray, Smith, & Smith, 2008). En outre, des changements ou corrélations ont aussi été rapportés concernant la fréquence de FS, bien que plusieurs études utilisent en prétraitement une catégorisation se basant sur la fréquence des FS (lents [~11-14Hz]; rapide [~14-16hz]) pour ensuite tester les changements des attributs des FS et corrélations entre ces attributs et la performance (Astill et al., 2014; Barakat et al., 2011; Fogel & Smith, 2011; Laventure et al., 2016). Par conséquent, bien que ces analyses confirment que les FS post-entrainement soient modifiés suite à l'entrainement moteur et/ou soient ensuite corrélés avec les gains de performance, il n'est toujours pas clair quel aspect des fuseaux représente un marqueur clair et stable de la consolidation.

Dans leur ensemble, les résultats rapportés dans cette thèse démontrent que, bien que certaines caractéristiques des FS sont modifiées (amplitude et fréquence) lors d'une réactivation induite par indiçage, celles-ci ne sont probablement pas la seule cause de la génération de gains en performance enregistrés lors d'une pratique subséquente. Effectivement, tel que discuté précédemment et démontré par d'autres études, le fuseau n'est pas un événement thalamo-cortical isolé d'autres activités et rythmes neurologiques. Plutôt, comme nous l'avons démontré au cours de cette thèse, son déclenchement, maintien et désengagement s'insèrent dans un cadre temporel et fréquentiel distinct, incluant l'interaction, la facilitation et la synchronie de plusieurs bandes fréquentielles, incluant le delta, thêta et haut-beta. Cette interrelation multi-fréquentielle semble être au cœur même du processus de consolidation, tel que le témoigne l'activité synchrone entre différentes zones corticales motrices et associatives sous-tendant les apprentissages moteurs. Conséquemment, nous posons l'hypothèse que toute tentative d'identification d'un marqueur unique et stable de la consolidation de la mémoire durant le sommeil par le seul examen des FS et de leurs caractéristiques est vouée à l'échec, sans une analyse systématique de leur contexte spatio-temporel et fréquentiel.

5. Fuseaux de sommeil, consolidation et causalité

Le principe de causalité représente l'apothéose de toutes les sphères de la recherche scientifique (Granger, 1969; Wiener & Masani, 1957). Dans le domaine de la physique, ce concept s'appuie sur l'assomption que la connaissance de l'état d'un matériel à un moment donné permettra la prédiction exacte de son état à un moment subséquent (Bohr, 1950). Dans sa plus stricte application, pour qu'une interaction soit dite causale, deux critères doivent être rencontrés : elle doit être à la fois nécessaire et suffisante à l'apparition de l'effet (Epp, 2011). Cependant, en neurosciences, ce concept est difficile à appliquer en raison de la complexité des interactions entre les systèmes impliqués et à notre manque de connaissance à leur sujet – sans parler de l'effet d'interférence de l'observation sur ces mêmes systèmes. Par exemple, l'activation synchrone de plusieurs systèmes peut être nécessaire à l'apparition d'un phénomène, mais ce dernier aura tout de même lieu, peut-être seulement avec une moins grande intensité, si l'un des systèmes n'est pas impliqué. Afin de pallier cette lacune du modèle de

causalité dans le domaine de la médecine, le concept de cause contributoire a été proposé (Cartwright & Hardie, 2012; Riegelman, 1979). Selon ce modèle, un événement n'a ni besoin d'être nécessaire ou suffisant pour être défini comme causal. Plutôt, il doit (1) précéder l'effet et (2) son altération doit entrainer une modification de l'effet. Appliquée à la neuroscience, la causalité contributoire d'un événement/structure sur un effet doit refléter sa nature probabiliste (Mahoney, 2008).

Dans la présente thèse, nous avons conditionné l'apprentissage d'une nouvelle tâche motrice séquentielle à une odeur. En nous basant sur l'hypothèse que cette odeur était associée à la trace mnésique motrice, nous avons utilisé celle-ci pour réactiver les réseaux sous-tendant cette trace. Tel que démontré par les analyses sur les FS avant et pendant la stimulation, l'indiçage a eu comme effet de produire (1) une augmentation dans la fréquence et amplitude des FS, (2) des augmentations spectrales dans des bandes de fréquences voisines précédant, pendant et suivant les FS, (3) une augmentation de la connectivité entre autres dans des régions corticales impliquées dans la tâche et finalement (4) une augmentation des gains hors-ligne à la tâche motrice. De plus, nous avons démontré que le changement en fréquence dans les FS prédisait les gains de performance au retest, mesure indirecte de la qualité de la consolidation.

Ainsi, puisque les deux critères de la causalité contributoire sont remplis, nous pouvons tout d'abord inférer que la stimulation à l'aide d'un stimulus conditionné durant le SNP2 a causé les changements mesurés au niveau des FS et autres fréquences voisines (delta, thêta, high-beta). Nous pouvons tirer la même conclusion au sujet de l'effet de ces changements sur la performance à la tâche motrice. Cependant, il est plus difficile d'établir cette relation causale contributoire des FS sur la consolidation de la mémoire puisque cette dernière ne suit pas l'apparition des FS (premier critère) — plutôt, elle débute dès le début de l'apprentissage. Par conséquent, si les changements mesurés dans les FS suite à la stimulation ont un effet causal contributoire sur la qualité de la consolidation, ceux-ci agissent en fait sur un sous-mécanisme de la consolidation que nous n'avons pas encore identifié. Ultimement, cette action (sur un sous-mécanisme) faciliterait la consolidation de la trace mnésique. En établissant l'importance des interactions oscillatoires temporelles et fréquentielles autour des FS, le deuxième article de cette thèse fournit une piste de recherche concernant la nature de ce sous-mécanisme associé à la consolidation de la mémoire motrice. Par conséquent, les travaux exposés dans cette thèse

établissent les premiers fondements de la démonstration causale de l'effet des FS dans la consolidation de la mémoire motrice séquentielle, tout en soulignant l'importance de leurs interactions complémentaires avec d'autres fréquences.

6. Limites des études

Quelques points pouvant limiter l'interprétation et la généralisation des résultats sont à noter. Tout d'abord, bien que la taille de l'échantillon soit respectable pour ce type de protocole expérimental, son petit nombre limite tout de même la généralisation des résultats à la population générale. De plus, la sélection des sujets dépendait d'une liste exhaustive de critères couvrant leurs habitudes de vie, santé mentale et physique, habiletés motrices, consommation de substance (ex. café, cigarette) ainsi que leur capacité à dormir dans un laboratoire de sommeil. Le grand nombre de sujets potentiels ayant été éliminés à travers l'application de ses critères confirme la difficulté de transposer les conclusions, concernant l'effet d'un sommeil sain sur l'apprentissage d'une tâche motrice, à la population générale qui pour la plupart, ne rempliraient pas ces critères sévères.

Bien que notre protocole nous ait permis de comparer une période pré-stimulation à une autre, durant la stimulation, l'absence de nuit d'enregistrement pré-entrainement ne nous a pas permis de faire la comparaison des nuits de chaque individu par rapport à lui-même. Ce type de comparaison nous aurait offert la possibilité d'identifier les changements électrophysiologiques propre à l'apprentissage de la tâche d'AMS (nuit pré-AMS versus nuit post-AMS). De plus, il aurait alors été possible de faire une double démonstration de l'effet de l'indiçage sur la consolidation. C'est-à-dire, une première, inter-groupe telle que présentée dans cette thèse ainsi qu'une seconde, intersujet, ajoutant ainsi de la puissance aux analyses et facilitant possiblement l'interprétation des résultats.

Également, tel que présenté plus haut, l'utilisation d'une odeur comme choix méthodologique pour le conditionnement comportait des limitations propres à ce type de stimulus. Bien que l'initiation et la terminaison de la présentation d'une odeur pouvaient être faites quasi instantanément, il fut impossible de contrôler le moment exact où les molécules

d'odeur entrent en contact avec l'épithélium olfactif de la cavité nasale, ni celui où elles n'étaient plus détectables. Durant le sommeil, le ralentissement de la respiration fait en sorte que plusieurs secondes peuvent s'écouler avant que le stimulus ne soit détecté. De plus, lors de l'arrêt de la stimulation, le stimulus, de nature aérienne et diffuse, peut prendre un certain temps à se disperser et ne plus être détectable. Ceci influença le pré-traitement des données et l'interprétation des résultats — par exemple, l'utilisation de segments étendus sur plusieurs minutes de stimulation au lieu de blocs de quelques secondes. En outre, puisque les périodes de stimulation étaient définies en direct (pendant le sommeil), la précision en termes de stades ciblés n'était pas parfaite. En effet, certains segments de stimulation ont eu lieu à l'extérieur des stades ciblés. Il est possible que ce fait, particulièrement pour ce qui est des segments d'odeur envoyés durant le stade de SOL, au lieu de SNP2, ait pu avoir une influence sur la consolidation de la mémoire. Bien que nous n'ayons détecté aucune différence inter-conditions (*pre* et *during-stimulation*) dans les FS durant ces périodes additionnelles de SOL, la réactivation a pu entrainer des modifications non testées durant notre étude et ainsi avoir un impact lors du stade SNP2 suivant.

Pour des considérations méthodologiques et de faisabilité, nous n'avons pas testé l'effet de l'indiçage durant le stade SOL. Nous ne pouvons donc pas conclure que seulement le SNP2 est impliqué, via les FS, dans la consolidation de la mémoire motrice. Plutôt, nous pouvons conclure que l'effet des FS et des fréquences concomitantes voisines sur l'apprentissage moteur séquentiel se joue durant le SNP en général, et de façon certaine durant le SNP2.

Fait intéressant, un raisonnement complémentaire se doit d'être appliqué au SP. Spécifiquement, la démonstration faite dans cette thèse de l'importance du SNP2 et des FS n'implique pas, par défaut, l'inutilité du stade de SP dans le processus de consolidation de la mémoire comme nous l'avons mentionné plus haut. Bien que faible, il existe la possibilité que certains aspects neurophysiologiques reliés à l'état particulier du cerveau durant le SP ne permettent pas la réactivation de la trace mnésique de la même façon qu'en SNP. Dans un tel cas, nous pourrions nous attendre à ce que le groupe indicé en SP démontre une performance similaire au groupe non-conditionné et stimulé en SNP2, comme il a été le cas dans notre étude. D'autre part, puisque le sommeil est un processus homéostatique, il est probable que, pour que la trace d'une mémoire motrice séquentielle soit efficacement consolidée, il soit nécessaire que

le cerveau fasse la transition entre tous les stades composant un cycle normal, et que la perturbation de l'un de ces stades puisse entrainer des failles dans le processus de consolidation. Malgré le fait que des études cliniques pharmacologiques (Rasch et al., 2009; Siegel, 2001; Vertes & Eastman, 2000) et de privation (Genzel et al., 2009) contredisent cette hypothèse, au moins un rapport optogénétique récent suggère que le SP jouerait possiblement un rôle dans la consolidation de la mémoire via la génération de l'oscillation thêta (Boyce, Glasgow, Williams, & Adamantidis, 2016; Boyce, Williams, & Adamantidis, 2017). Il reste maintenant à reproduire ce résultat divergeant et surprenant. Le débat est toujours ouvert.

7. Contributions originales de la thèse

Le protocole expérimental à la base de cette thèse a permis l'exploration du rôle des FS dans la consolidation de la mémoire motrice comme aucune autre étude ne l'avait fait auparavant. Tout d'abord, cette thèse représentait la toute première tentative de réactivation de la trace mnésique d'une tâche motrice durant le SNP2 par l'emploi d'un protocole de RCM. Grâce à celui-ci, nous avons confirmé l'importance, non seulement du SNP2, mais des FS dans le processus de consolidation de ce type de mémoire. D'ailleurs, ce fut la première démonstration de changements des caractéristiques des FS provoqués par un indiçage olfactif. Par ailleurs, elle a aussi été la première à induire des gains de performance avec l'aide d'une RCM olfactive.

La deuxième partie de cette thèse a décrit pour la toute première fois l'existence d'une composante dans la bande haut-beta, générée localement durant les FS et sensible à l'indiçage. Cette même étude a permis la première analyse exhaustive en temps/fréquence, et en cohérence de l'effet de la réactivation de la trace mnésique durant les FS. Ces analyses ont mis à jour des interactions multi-fréquentielles et topographique encore mal comprises et définies dans la littérature scientifique concernant la consolidation de la mémoire, et de la mémoire procédurale en particulier.

Enfin, certaines nouveautés méthodologiques ont été développés lors des analyses composant cette thèse. Premièrement, la création d'un index de performance motrice globale

(GPI). Précédant l'élaboration de cet index, des mesures évaluant distinctement la vitesse (temps inter-touche, par bloc, par séquence réussie), la précision (nombre d'erreurs, de séquences réussies) et de force étaient utilisés pour établir le degré de performance (Doyon, Korman, et al., 2009; Karni & Sagi, 1993; Nishida & Walker, 2007). L'utilisation d'un index global de performance nous a permis d'avoir une mesure combinée et unique décrivant plus écologiquement ce que représente réellement une habileté motrice. C'est-à-dire, une mise en contexte commune et dépendante de la vitesse et de la précision tenant compte de la stratégie d'exécution choisie par chacun des participants. Deuxièmement, prenant en compte les récentes avancées dans la recherche sur les FS (Andrillon et al., 2011; Nir et al., 2011; O'Reilly & Nielsen, 2014a, 2014b; Suihko et al., 1993), une classification topographique plutôt que fréquentielle a été implémentée. Sans cette catégorisation topographique, il ne nous aurait probablement pas été possible de détecter les changements d'amplitude et fréquentiels causés par l'indiçage.

8. Avenues de recherches futures

Suite à cette série d'études, deux avenues de recherche principales peuvent être proposées. La première, chez l'humain, devrait s'intéresser aux changements en connectivité fonctionnelle entre régions corticales et sous-corticales, particulièrement l'hippocampe, le thalamus et le striatum, lors de la génération de fuseaux de sommeil indicés. Il serait intéressant de mettre à jour la façon dont les interactions fréquentielles décrites dans cette thèse se traduisent en relation avec ces structures. Par exemple, d'autres études sont nécessaires pour répondre aux questions suivantes : 1) est-ce que le couplage entre les FS et l'activité fréquentielle delta ou thêta est associé à une plus grande connectivité fonctionnelle entre régions sous-corticales (e.g., hippocampe, thalamus, striatum) et corticales supportant la représentation de la tache; 2) est-ce que cette même association est modifiée lors de la présentation d'un stimulus indicé; 3) quelles sont les structures différentiellement impliquées entre périodes indicées et non-indicées? Des projets de la sorte nécessiteraient l'utilisation d'enregistrements EEG/IRMf ainsi que d'un protocole RCM simultané. Une autre piste de recherche prometteuse inclurait l'enregistrement à haut taux d'échantillonnage afin d'investiguer comment les FS, l'activité en haut-beta et les

SWRs interagissent, sans et après apprentissage. Ceci pourrait permettre de faire la lumière sur les mécanismes neuronaux locaux sous-tendant la consolidation de la mémoire. Enfin, il serait également intéressant de tester la dynamique menant à l'échec de la consolidation. Il serait alors utile de vérifier si la perturbation de la génération et/ou de l'activité d'événements tels que les FS ou les OL est suffisante pour empêcher le processus de consolidation de se produire normalement. Ce même principe pourrait aussi s'appliquer aux interactions entre ces diverses oscillations. Parmi les multiples questions en suspens, il serait important de vérifier les points suivants: 1) est-ce qu'une inhibition artificielle de l'amplitude ou durée des FS est suivit d'une diminution de la consolidation effective (absence de gains ou chute de performance); 2) est-ce que la perturbation de l'interaction entre FS et AOL affecte pareillement la consolidation; 3) est-ce que l'inhibition complète de FS est délétère à la consolidation?

La seconde avenue de recherche consiste en la démonstration causale, chez l'animal, de l'implication des fuseaux dans la consolidation de la mémoire motrice séquentielle. Grâce à un protocole optogénétique, il serait possible de comparer l'effet de facilitation/rehaussement à celui de perturbation de l'oscillation des fuseaux, sur la performance motrice de l'animal à l'éveil. De plus, ce type d'expérimentation permettrait l'enregistrement en haute définition temporelle et spatiale de régions sous-corticales telles que l'hippocampe et le thalamus ainsi qu'un accès aux différentes couches corticales. Ceci pourrait potentiellement faire la lumière sur les mécanismes neuronaux et systémiques sous-tendant la consolidation de la mémoire motrice. Point important, ce type de stimulation (optogénétique) éliminerait l'utilisation d'un indice contextuel, en le remplaçant par une modulation plus ou moins directe de l'événement à l'étude, le FS, permettant d'éliminer une partie de l'effet épisodique relié à l'usage d'un stimulus conditionné.

9. Conclusion

Le sommeil, et plus particulièrement les FS d'origine pariétale, durant le SNP2 joue un rôle fondamental dans la consolidation des mémoires motrices séquentielles. Il est d'ailleurs maintenant établi que les FS ne sont pas l'unique moteur favorisant la consolidation durant le

sommeil. En fait, nous savons que les FS, accompagnés d'un nombre d'événements fréquentiels concomitants, sous-tendent la réactivation des traces mnésiques nouvellement acquises. Ces événements fréquentiels apparaissent à des moments distincts de la génération des fuseaux, facilitant et accompagnant ainsi l'activité de ces derniers. Cette découverte souligne l'importance, dans le cadre de l'étude de la relation entre apprentissage et sommeil, d'observer et d'étudier les FS dans leurs contextes fréquentiel, topographique et temporel, et d'éviter de les analyser comme des événements singuliers et isolés. L'accroissement de notre connaissance relatif aux interactions entre événements électrophysiologiques et structures, ainsi que le développement des outils méthodologiques, laisse entrevoir un avenir prometteur concernant l'étude de ces apprentissages simples, innombrables et vitaux à la qualité de notre vie quotidienne; tel que le simple fait de porter un verre d'eau à nos lèvres.

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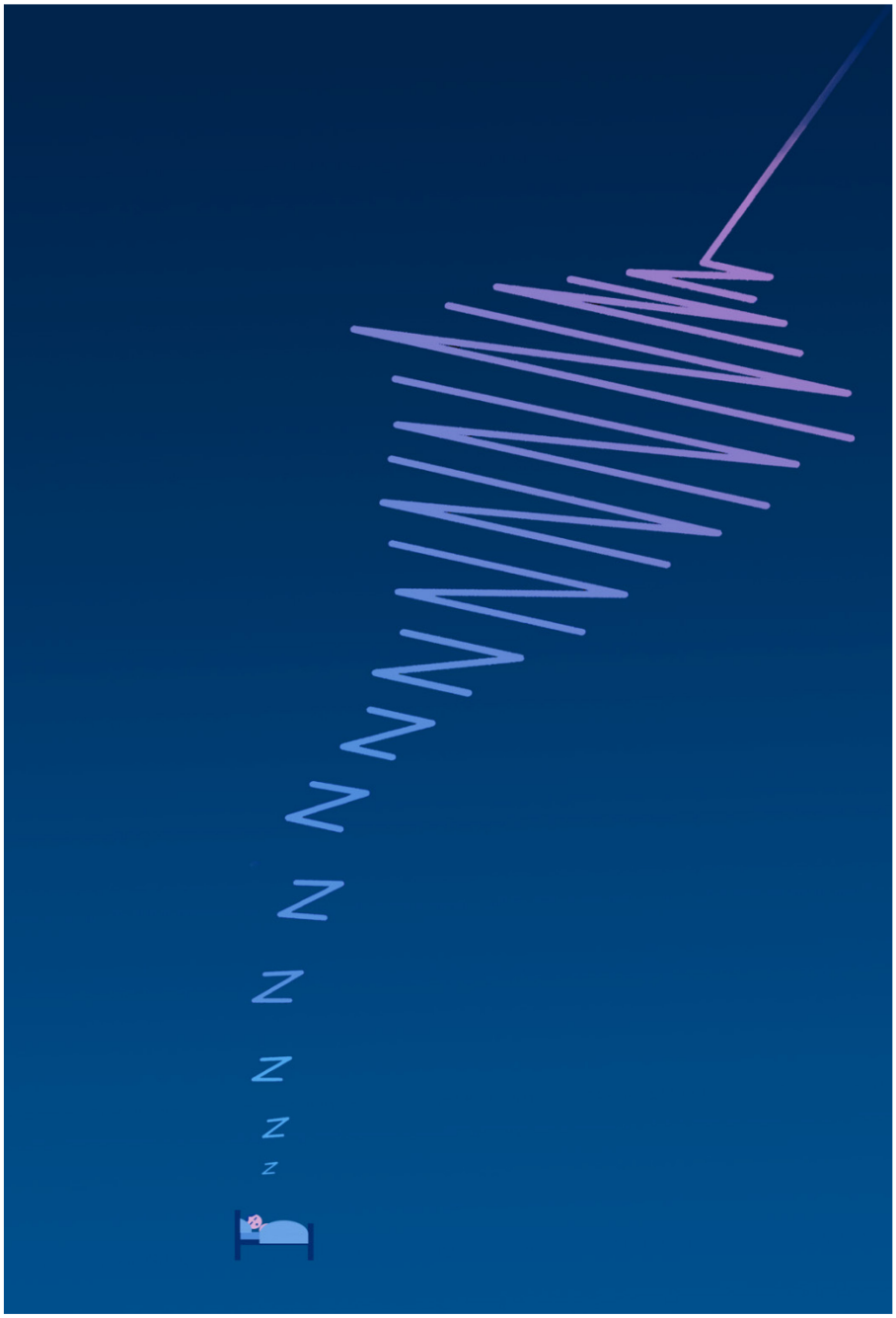
Annexe I

Image de couverture, article 1 (PLoS Biology)



Artiste: Michel Mergaerts

Annexe II

Premier croquis du système olfactif