Les performances saccadiques, un biomarqueur pertinent des troubles de l'humeur

I.1. Pourquoi utiliser les performances saccadiques comme biomarqueur des troubles de l'humeur ?

L'utilisation des performances saccadiques et plus particulièrement des performances en antisaccades (AS) comme biomarqueur des troubles de l'humeur, repose sur le fait que la réalisation d'AS met en jeu des structures clés impliquées dans la dépression. Ainsi réaliser une AS requiert d'inhiber le déclenchement d'une saccade réflexe vers une cible et de programmer une saccade sur la position en miroir. L'inhibition des saccades réflexes est médiée par le cortex préfrontal dorso-latéral (CPFDL) (chapitre 3). Or les patients souffrant de troubles de l'humeur présentent fréquemment un hypométabolisme du CPFDL (chapitre 1). D'où l'idée, au niveau oculométrique, que ces patients devraient montrer un déficit de performance en AS par rapport aux sujets sains contrôles.

I.2. Que dit la littérature ?

La littérature met en évidence un taux d'erreurs en antisaccades plus important pour les patients en dépression unipolaire et en dépression bipolaire que pour les sujets contrôles (chapitre 3), avec toutefois quelques études contradictoires probablement dues à des différences méthodologiques sur lesquelles nous reviendrons plus tard. Retenons ici que la majorité des études amène à conclure que les performances saccadiques constituent un marqueur *trait* pertinent des troubles de l'humeur. En revanche, l'idée que les performances saccadiques puissent également être un marqueur *état* de ces troubles n'a quasiment pas été explorée.

Dans le cadre du trouble bipolaire, le terme de marqueur *état* fait référence aux différentes phases (maniaque, dépressive et euthymique). Seules deux études (Garcia-Blanco et al., 2013 ; Malsert et al., 2013) ont été réalisées ; elles montrent toutes deux, malgré là encore quelques données contradictoires, que les performances saccadiques peuvent être un biomarqueur *état* du trouble bipolaire, c'est-à-dire permettant de distinguer les différentes phases du trouble. A notre connaissance, aucune étude ne s'est intéressée à la possibilité que les performances saccadiques puissent être une mesure assez sensible pour non seulement distinguer des phases d'état mais également des variations sur un état, autrement dit renseigner sur l'amélioration thymique des patients. C'est à cette question, qui renvoie à la problématique cruciale en psychiatrie de pouvoir disposer d'outils permettant d'objectiver la réponse (ou la non réponse) à un traitement et donc d'en évaluer son efficacité, que nous nous sommes intéressés. Voyons maintenant un résumé de nos principaux résultats.

I.3. Que montrent nos résultats ?

Dans l'étude « Dep-Bip », des patients en dépression bipolaire pharmaco-résistante étaient traités par un protocole rythmé de stimulation magnétique transcrânienne répétée (iTBS), appliqué de façon excitatrice sur le CPFDL gauche pendant trois semaines. Le test saccadique était réalisé avant et après une séance d'iTBS, le premier jour de chaque semaine de traitement. Les résultats de cette étude ont indiqué une corrélation entre amélioration des symptômes dépressifs et amélioration des performances. Les performances saccadiques peuvent donc constituer un biomarqueur, ou plus exactement un marqueur psychophysique, de l'amélioration thymique. De plus, nous avons montré que, juste après la séance iTBS, seuls

les patients recevant la stimulation active amélioraient leurs performances, la stimulation placebo n'avait quant à elle aucun effet sur les performances. Ce résultat démontre, pour la première fois, que les performances saccadiques peuvent constituer un marqueur psychophysique de l'effet neuromodulateur à court-terme de séances rTMS, condition sine qua non d'une neuromodulation plus globale à long terme, issue de la cumulation des séances. Toutefois dans l'étude « Dep-Bip », les résultats étaient obtenus en moyennant les résultats de trois jours de passation. Nous avons donc ensuite étudié l'effet d'une seule séance de stimulation, chez des sujets sains en stimulant (en miroir des patients) de façon inhibitrice le CPFDL, et avons pu montrer que les performances saccadiques étaient un marqueur suffisamment fin pour détecter l'effet neuromodulateur à court-terme **d'une seule séance** de de rTMS, qu'il s'agisse d'un protocole rythmé ou conventionnel de stimulation.

I.4. Prospectives

L'étude des performances saccadiques semble être un outil très précieux en Psychiatrie apportant bon nombre de renseignements pour l'aide au diagnostic, pour objectiver l'amélioration thymique, et pour évaluer l'efficacité des traitements, notamment rTMS, en soulignant toutefois que si les oculomètres actuels sont très opérationnels, pouvant donc être utilisés par des non-spécialistes de la psychophysique, il reste toutefois coûteux et requièrent un accompagnement technique pour leur programmation et l'analyse des résultats. En outre, optimiser leur usage en clinique psychiatrique requiert d'améliorer certaines caractéristiques métrologiques afin de diminuer l'hétérogénéité des résultats entre les études et améliorer la sensibilité du test saccadique afin qu'il puisse fournir des informations fiables sujet par sujet.

I.4.1 Améliorer les caractéristiques métrologiques du test saccadique

La méta-analyse de Smyrnis (2008) met en évidence une grande variabilité des performances saccadiques entre les études, avec, notamment des taux d'erreurs en AS variant entre 2 et 30 %. Pour l'auteur, une part de cette hétérogénéité est d'ordre méthodologique, dû à l'hétérogénéité des paramètres expérimentaux d'une étude à l'autre. Smyrnis montre par exemple que la durée de présentation du point de fixation avant l'apparition de la cible ainsi que l'excentricité de la cible par rapport au point de fixation, ont un impact majeur sur le taux d'erreurs en AS. Face à ces différences méthodologiques, Smyrnis préconise le recours à un protocole saccadique standardisé. Ce n'est que cinq ans plus tard que ce protocole standardisé

sera proposé par Antoniades et collaborateurs (2013). Différentes consignes sont données dans ce protocole : ne travailler qu'avec des saccades horizontales, présenter le point de fixation pendant une durée comprise entre 1 et 3.5 secondes avant l'apparition de la cible, qui doit elle-même apparaitre entre 8 et 10° angulaires du point de fixation avec une durée d'une seconde ; ne pas donner de feedback au participant sur ses performances pendant le test, sauf si ce dernier commet plus de quatre erreurs consécutives, réaliser dix essais d'entrainement avant les prosaccades et 4 avant les antisaccades. Enfin, réaliser au total 240 saccades, 120 prosaccades et 120 antisaccades, en bloc, comme le résume la figure 39.

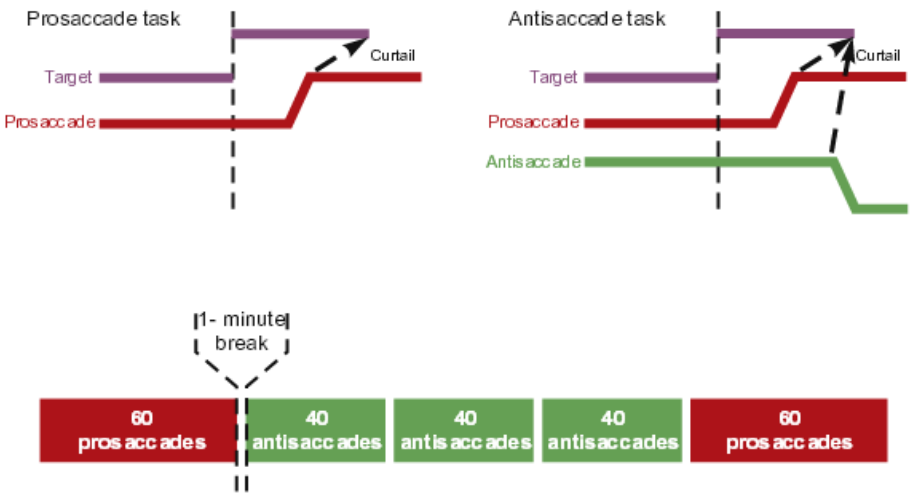

Figure 39 : Représentation du protocole standardisé de saccades. Reproduit d'après Antoniades et al. (2013).

L'utilisation d'un tel standard diminuera probablement la variabilité des résultats inter-études mais il présente, selon nous, une imperfection : le nombre de saccades. Selon les auteurs, la réalisation de 240 saccades est un bon compromis entre fatigabilité des participants et nombre d'essais suffisants pour une puissance statistique suffisante. Cependant, nous avons pu observer dans notre pratique que la réalisation de deux blocs de 80 saccades, espacés par 10 minutes de pause était déjà éprouvant pour nos patients. En dépit du fait que l'augmentation du nombre de saccades permettrait d'améliorer la sensibilité de l'outil oculométrique pour qu'il puisse fournir une information qui soit valide et fiable sujet par sujet, nous émettons quelques doutes sur les 240 saccades proposées dans ce protocole.

II. L'excitabilité corticale, des doutes sur son utilisation comme biomarqueur des troubles de l'humeur…

II.1. Pourquoi utiliser les mesures d'excitabilité corticale comme biomarqueur des troubles de l'humeur ?

L'utilisation des mesures d'excitabilité corticale comme biomarqueur des troubles de l'humeur repose sur le fait que certaines des mesures réalisées mettent en jeu des neurotransmetteurs impliqués dans la dépression. Ainsi, l'inhibition intracorticale courte (SICI) et la période de silence corticale (CSP) mettent respectivement en jeu la neurotransmission GABAa et GABAb, et la facilitation intracorticale (ICF) met en jeu la neurotransmission glutamatergique (chapitre 4). Les patients présentant des troubles de l'humeur présenteraient un déséquilibre de cette neurotransmission (chapitre 1). Plus précisément, le taux de glx (reflétant le glutamate) serait diminué dans la dépression unipolaire et augmenté dans la dépression bipolaire, quelle que soit la phase thymique, en comparaison au taux de glx de sujets contrôles. Le taux de GABA serait diminué pour ces deux pathologies. Selon ces hypothèses, les patients en dépression unipolaire et en dépression bipolaire devraient présenter une moins bonne inhibition que des sujets contrôles. A l'inverse, la facilitation intracorticale pourrait discriminer ces deux groupes, avec une facilitation diminuée pour les patients déprimés majeurs, et une facilitation accrue pour les patients bipolaires, en comparaison à des sujets contrôles.

II.2. Que dit la littérature ?

Selon une méta-analyse récente (Radhu et al., 2013), les patients en dépression unipolaire présenteraient effectivement des déficits d'inhibition, reflétés par des SICI plus faibles et des CSP plus courtes que les sujets contrôles. Ces résultats semblent indiquer que l'excitabilité corticale puisse être un marqueur ***trait*** des troubles de l'humeur, mais cette conclusion est à considérer avec précaution car moins de cinq études ont été incluses dans la méta-analyse. La pertinence de l'excitabilité corticale comme marqueur ***état*** des troubles de l'humeur a été encore moins étudiée. Dans le cadre du trouble bipolaire, seules deux études ont été publiées et révèlent un déficit de SICI et de CSP pour les patients bipolaires en phase dépressive par rapport aux sujets contrôles (Levinson et al., 2006, Malsert et al., 2012). La seconde étude

(Malsert et al., 2012) met, de plus, en évidence une asymétrie interhémisphérique dépendante de la phase thymique pour les mesures d'inhibition et facilitation intracorticale. A notre connaissance, seules deux recherches ont testé la pertinence de l'excitabilité corticale comme marqueur de l'amélioration thymique. La première (Bajbouj et al., 2005) montre que les Répondeurs (à un traitement rTMS) ont des CSP plus longues et un meilleur SICI que les non-Répondeurs. La seconde (Fitzgerald et al., 2004) trouve une corrélation négative entre la durée de la CSP et l'amélioration des symptômes : plus la durée de la CSP est importante moins bonne sera la réponse clinique. Ces deux études suggèrent donc que les mesures de CSP et de SICI pourraient être utilisées comme marqueur et prédicteur de l'amélioration thymique pour des patients unipolaires. Cependant, face au manque cruel de données de la littérature, il est difficile de statuer définitivement sur la pertinence de l'excitabilité corticale comme marqueur *trait* des troubles de l'humeur et encore plus comme marqueur *état*. Les déficits d'inhibition observables sur les mesures de SICI et d'ICF se normalisent-ils avec l'amélioration thymique comme le suggèrent Bajbouj et collaborateurs (2005) ? C'est à cette question que nous avons tenté de répondre au travers de nos études. Abordons maintenant un résumé de nos résultats.

II.3. Que montrent nos résultats ?

Dans l'étude « Dep-Bip », portant sur des patients bipolaires en phase dépressive et traités par une cure iTBS (excitatrice) appliquée sur le CPFDL gauche, nous n'avons pas retrouvé les résultats de Bajbouj et al. (2005). Les mesures d'excitabilité corticale ne différaient pas entre le début et la fin de traitement, quelle que soit la réponse clinique des patients au traitement. Dans l'étude « KétaDep », nous avons étudié les effets de la rémission clinique dans la dépression unipolaire. Mais là encore, contrairement à l'étude de Bajbouj et al. (2005) nous n'avons pas observé de modification des mesures de SICI et de CSP en lien avec l'amélioration clinique, et contrairement à Fitzgerald et al. (2004) nous n'avons pas pu mettre en évidence que la durée de la CSP était un prédicteur de la réponse clinique. Par ailleurs, nous n'avons trouvé de différence sur les mesures d'excitabilité corticale entre patients en dépression unipolaire et sujets contrôles (résultats non présentés dans cette thèse). Bien que l'absence de preuve ne soit pas la preuve de l'absence, l'ensemble de nos résultats questionne l'utilisation de l'excitabilité corticale comme marqueur *état* ou marqueur *trait* des troubles de l'humeur. Sur ce dernier point, rappelons que dans la méta-analyse de Radhu et collaborateurs

(2013), seules cinq études seulement étaient disponibles. Cela traduit-il un manque de recherches dans le domaine ou un manque de publications lié à l'absence de résultats dans les recherches réalisées ?

II.4. Questionnements sur l'utilisation de l'excitabilité corticale comme marqueur des troubles de l'humeur

Deux hypothèses peuvent expliquer l'absence de résultats, soit l'excitabilité corticale est une méthode valable mais il faut l'optimiser en contrôlant le « State-Dependency », i.e., l'état des sujets pendants les stimulations, induit une trop grande variabilité dans les mesures, et masque les différences ; soit l'excitabilité corticale n'est pas une mesure valable car elle mesure des déficits de neurotransmission sur une zone non intrinsèquement impliquée dans ces déficits. Présentons maintenant ces deux points.

II.4.1. Optimisation des mesures d'excitabilité corticale : le « State-Dependency »

Nous l'avons vu lors de notre pratique, l'attitude des patients varie largement d'un patient à l'autre pendant les mesures d'excitabilité corticale et les séances de rTMS. Certains sont en état de vigilance amoindrie, d'autres ruminent leurs pensées et pleurent. Ces variations d'état pourraient expliquer la grande hétérogénéité intra- et inter-individuelle des PEM (Kiers et al., 1993) et ainsi l'absence de différence entre patients et contrôles, et entre Répondeurs et non-Répondeurs. Face à ce constat, nous avons tenté de contrôler l'état des sujets pendant les stimulations. Nous pensions alors que le fait d'uniformiser « l'état » des sujets, via une tâche, permettrait une diminution de la variabilité intrinsèque des PEM. Deux expériences ont été réalisées, l'une manipulait l'état cognitif des sujets, l'autre, l'état émotionnel. Contrairement à notre hypothèse, nos résultats n'ont pas montré de différence sur la variabilité des PEM, mais nous avons mis en évidence que la mesure de SICI semblait très sensible (i) à l'état cognitif et (ii) à l'état émotionnel des sujets pendant les stimulations. Or, c'est sur cette mesure de SICI que reposent les principales hypothèses pour l'utilisation de l'excitabilité corticale comme marqueur des troubles de l'humeur. Il est donc juste de penser que la non prise en compte du « state-dependency » pourrait nuire aux mesures d'excitabilité. Comprendre et maîtriser le phénomène de « state-dependency » est un enjeu scientifique important, intrigant, pour la recherche expérimentale et clinique en TMS, même si le caractère multidéterminé du phénomène limite intrinsèquement la validité opérationnelle des investigations expérimentales

et questionne la nécessité scientifique de pouvoir déterminer un « état contrôlé » du sujet soumis à la TMS.

II.4.2. Validité de l'excitabilité corticale comme marqueur des troubles de l'humeur ?

Comme nous l'avons vu dans le premier chapitre, la troubles de l'humeur sont souvent associés à des déséquilibre de neurotransmission GABA/glutamatergique mais les structures impliquées sont frontales (e.g. CPFDL) et interne (e.g. hippocampe). A notre connaissance, aucune étude n'a mis en évidence de déficit de neurotransmission au sein du cortex moteur. Il est alors juste de se demander si l'utilisation de l'excitabilité corticale du cortex moteur est un choix judicieux. Peut-on considérer que les déficits de neurotransmission GABA/glutamate présents dans une zone se retrouvent dans l'ensemble du cerveau, et notamment au sein du cortex moteur ? Autrement dit, existe-t-il un fonctionnement générique de cette neurotransmission ? La recherche menée par Boy et al. (2011) montre que non. En effet, les auteurs ont trouvé une corrélation entre des traits d'impulsivité et le taux de GABA mesuré dans le CPFDL, mais pas dans les autres structures cérébrales. Ces données militent en faveur d'un fonctionnement non générique du GABA questionnant donc fondamentalement l'utilisation de l'excitabilité du cortex moteur comme marqueur des troubles de l'humeur.

La recherche de biomarqueurs nous a également amené à étudier l'efficacité de la rTMS comme traitement de la dépression. Abordons maintenant ce point.

III. L'efficacité de la stimulation magnétique transcrânienne répétée comme traitement des troubles de l'humeur : utilise-t-on les bons paramètres de stimulation, les bons modèles ?

La stimulation magnétique transcrânienne répétée (rTMS) est une alternative thérapeutique non médicamenteuse proposée pour les patients pharmacorésistants, i.e. ne répondant pas aux traitements antidépresseurs classiquement utilisés. Revenons maintenant brièvement sur le but de son utilisation et sur son efficacité comme traitement de la dépression.

Nous l'avons vu dans le premier chapitre, les troubles de l'humeur sont sous-tendus par différentes anomalies structurelles et fonctionnelles, et notamment par déséquilibre interhémisphérique dû à l'hypométabolisme du CPFDL gauche. Le but de la rTMS comme traitement des troubles de l'humeur, est de rétablir l'équilibre interhémisphérique. Pour ce

faire, la rTMS peut être appliquée de façon excitatrice sur le CPFDL gauche, ou de façon inhibitrice sur le CPFDL droit. L'effet excitateur on inhibiteur de la rTMS dépend, dans le cadre des protocoles conventionnels de la fréquence de stimulation. Ainsi, appliquée à haute fréquence (> 5 Hz) la rTMS génère une excitation de la zone cérébrale stimulée, et appliquée à basse fréquence (< 1 Hz), la rTMS inhibe la zone corticale ciblée. Dans le cadre des protocoles rythmés de stimulation (TBS), ce n'est plus la fréquence qui détermine le type d'effet neuromodulateur, mais le caractère continu ou intermittent des stimulations. Appliquée de façon continue, la cTBS induit une inhibition de la zone ciblée ; de façon intermittente, une facilitation de la zone ciblée.

Différentes méta-analyses ont été réalisées pour évaluer l'efficacité de la rTMS comme traitement de la dépression unipolaire et concluent à une efficacité significative mais modérée des protocoles conventionnels de rTMS (Dell'Osso et al., 2011 ; Kedzior et Reitz, 2014). Concernant l'efficacité de la rTMS comme traitement de la dépression bipolaire, seules cinq études sont actuellement disponibles, il est donc difficile de statuer sur son efficacité ; il en est de même pour l'efficacité des protocoles rythmés de stimulation.

Des raisons méthodologiques peuvent expliquer l'efficacité modérée de la rTMS comme traitement des troubles de l'humeur. Comme nous l'avons vu il n'existe pas de consensus concernant les paramètres de stimulation (e.g. intensités de stimulation, nombre de pulses par séance, nombre de séances par jour, nombre de jour de traitement.) De même, le manque de système de neuronavigation basé sur l'IRM des patients est également un problème. En effet, nombre d'études n'ont pas de neuronavigation et utilisent encore la règle « des cinq centimètres » pour localiser le CPFDL, ce qui, comme déjà dit, conduit dans 60 % des cas à une stimulation du cortex prémoteur plutôt que du CPFDL (Ahdab, Ayache, Brugières, Goujon et Lefaucheur (2010). Enfin, comme rappelé précédemment le phénomène de « state-dependency » n'est jamais pris en compte dans les études ; or, il semble que l'effet des stimulations dépende de l'état d'activation des populations neuronales en lien avec l'état cognitif et émotionnel des sujets. On peut donc penser que contrôler (contraindre) « l'état » des sujets pendant les cures de rTMS soit une piste méthodologique pour optimiser l'efficacité de la rTMS comme traitement des troubles de l'humeur.

Au-delà de ces raisons méthodologiques, il existe aussi des raisons théoriques. Toutes les propriétés concernant le post-effet des stimulations rTMS chez l'homme sont basées sur

l'étude du cortex moteur. Le choix des intensités des stimulations est également basé sur la réactivité du cortex moteur. Mais la réactivité de ce cortex est-elle la même que celle d'autres aires cérébrales, et plus particulièrement du CPFDL ?

Pour répondre à cette question, nous allons présenter une recherche menée avec Sylvain Harquel (ingénieur d'étude au LPNC, actuellement en thèse) utilisant le couplage TMS-EEG (Harquel, Beynel, et al., submitted). Dans cette étude, nous nous sommes intéressés aux modifications de l'activité électroencéphalographique consécutives à l'application d'une TMS single pulse. Dix-huit aires cérébrales ont été stimulées (neuf par hémisphère : le gyrus frontal moyen, le gyrus frontal inférieur, le CPFDL, l'aire motrice supplémentaire, le cortex moteur primaire, le gyrus temporal supérieur, le lobe pariétal supérieur, le lobe pariétal inférieur et le lobe occipital supérieur). Dans ce résumé, afin de savoir si la réactivité du cortex moteur est la même que celle du CPFDL, nous décrirons seulement l'activité de ces deux aires. 22 sujets sains ont été inclus dans cette étude. Une acquisition de l'IRM anatomique de chaque sujet a d'abord été réalisée. Les sites corticaux ont été marqué sur les IRM de chaque sujet en utilisant les coordonnées MNI et la procédure de transformation inverse de SPM (cf. chapitre 1, partie 2, étude « NeuroMod »). Pour chaque cible, 90 stimulations single-pulse étaient délivrées à une intensité de 120 % du seuil moteur au repos.

En partant de l'hypothèse que les premières millisecondes (< 60 ms) de la réponse EEG à la TMS représentent la **réactivité corticale locale** de l'aire stimulée, nos résultats montrent que le cortex moteur (M1) est hyperexcitable par rapport au CPFDL. En effet, M1 présente une activation forte et très rapide (à 30 ms après la stimulation), alors que la réponse du CPFDL reste très faible pendant ces premières millisecondes. L'analyse multivariée des réponses locales montre, de plus, que la réponse du cortex moteur est très singulière, ne partageant aucune similarité avec les autres aires corticales quant à leurs caractéristiques dynamiques. Cette même analyse fait apparaitre le CPFDL au sein de plusieurs réseaux distribués (réseaux frontal droit et fronto-pariétal). Cette étude met donc en évidence (i) des réactivités locales dissemblables pour le cortex moteur et pour le CPFDL et (ii) des caractéristiques dynamiques de réponse différentes, traduisant de fortes hétérogénéités anatomiques (cyto-, myelo-, recepto-architecturales). De fait, les paramètres choisis pour la stimulation du CPFDL sont-ils pertinents ? Comme le cortex moteur primaire parait être une aire très singulière dans sa réponse à la TMS, n'est-on pas en train de biaiser la stimulation du CPFDL en utilisant des

protocoles de neurostimulation basés sur le cortex moteur ? Ce constat pourrait expliquer l'effet modéré de la rTMS dans le traitement des troubles de l'humeur

Mapping dynamical properties of cortical microcircuits using robotized TMS and EEG

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Abstract

Transcranial Magnetic Stimulation (TMS), a non-invasive cortical stimulation technique, is a powerful tool regarding the functional exploration of the human brain. Moreover, the coupling between TMS and concurrent Electro-Encephalographic (EEG) recordings have recently given new insights regarding the ability of TMS to reveal the properties of both the local neuronal microcircuits and the long range connectivity of a stimulated area. The understanding and the mapping of these properties are essential in several neuroscience domains, like the study of functional parcellation or brain networks. They become even more critical in the TMS field, where all the delivered stimulation powers are tuned on the cortical excitability (CE) level of the primary motor cortex, regardless of the final stimulation site. For these reasons, we develop here the first attempt to map dynamical properties of local cortical mircrocircuits by using the coupling between robotized TMS and EEG. Robotized TMS allowed us to complete the recording of the activity evoked by the stimulation of 18 cortical targets covering the whole brain within one session on 22 healthy volunteers. The analysis of the earliest components of the evoked responses reveals that local CE levels are symmetrically but in-homogeneously distributed among cortical areas. Moreover, far from being isolated, the multivariate analysis of local source activity (LSA) maps reveal that cortical areas could be gathered into symmetric networks sharing common dynamical properties. The spatial organization of these networks highly correlates with resting state networks (RSN) already found using other neuroimagery techniques. These results could call the exclusive use of motor CE as a global indicator of brain CE into question. Furthermore, they suggest that this mapping technique could be used as a novel RSN segregation or functional parcellation methodology, based on the spacial clusterization of the dynamical properties of LSA.

Keywords: robotized TMS, EEG, Cortical excitability, Cortical microcircuits

1. Introduction

Transcranial magnetic stimulation (TMS) consists of the generation of a transient magnetic field by a coil placed over the scalp, which induces electrical currents on the cortical surface [1]. Its applications are numerous, ranging from fundamental studies on cortical networks involved in sensorimotor [2, 3, 4, 5] or cognitive [6, 7, 8] tasks, to clinical studies where TMS is applied both as a diagnosis tool [9**?** , 10] and as a promising therapeutic treatment in several psychiatric disorders [11, 12]. Importantly, measuring cortical excitability (CE) is a critical step in nearly every TMS protocol.

CE has originally been assessed on the motor cortex, because neuronal responses to TMS can easily be evaluated from the motor evoked potentials (MEP) [13, 1]. MEPs are generated through the activation of the whole cortico-spinal track, resulting from both the direct stimulation of pyramidal track neurons (D waves) and their indirect activation by excitatory and inhibitory interneurons projecting on their dendritic trees (I waves) [14, 15]. The evaluation of the motor CE is nowadays the gold standard to assess safety limits and to normalize the stimulation power between subjects [16]. The standard procedure is to determine the resting motor threshold (rMT), which is defined as the minimal stimulation power to elicit a MEP on half of the TMS pulses [17]. However, because the cytoarchitecture differs from one cortical area to another, CE is likely to differ between cortical regions and it is thus suboptimal to tune TMS power using the rMT as sole indicator. Using concurrent electroencephalographic (EEG) recordings is the only way to study the spatial properties of TMS neuronal responses and to assess local variations of CE.

Since the late 90s, TMS-EEG coupling has been used to study (i) neuronal waves at rest [18] or during sensorimotor [19, 20, 21] or cognitive tasks [22, 23, 24] ; (ii) human

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brain connectivity [25, 26] ; (iii) rTMS after-effects due to induced plasticity [27, 28, 29]. In particular, TMS-EEG coupling has provided new insights regarding CE, through the analysis of TMS evoked potentials (TEPs) [**?**]. TEPs is actually a highly reproducible [30] and sensitive measure [31, 32]. Several of TEP components have been shown to correlate with classical CE markers [33, 34, 35], and to be indirect indicators of cortical excitatory or inhibitory circuits activation [25, 36, 37]. TEPs have been recorded over a large diversity of cortical areas including M1, frontal, parietal, and occipital lobes. As expected from the heterogeneity of cortical microcircuits and long range connectivity, TEPs showed distributed spatio-temporal patterns specific to each stimulated area, in terms of both spectral and spatial signatures [18, 38, 39]. However, existing literature suffers from the diversity of the TMS parameters and of the EEG signal processing methods employed, which prevents an accurate understanding of CE properties amongst cortical regions.

In this study, we fully revisited the methods required to obtain an accurate mapping of CE and of other dynamical properties of local microcircuits. Our methodology was based on the coupling of EEG recordings with neuronavigated and robotized TMS. Robotized TMS was critical because it allows the automatic and precise positioning of the coil over a series of cortical targets [40], thereby offering the possibility to stimulate a large number of cortical targets within a unique recording session in a fast and convenient way. EEG processing techniques were developed to estimate the early components of cortical current densities generating TEPs, locally for each cortical target. Further spatial clustering on time-frequency properties of such local source activity (LSA) was used to estimate the main cortical modes underlied by the regional differences in cytoarchitecture and local microcircuitry. We believe that such methodology could provide a new way of assessing functional parcellation of the superficial cortex, or resting state network (RSN) segregation.

2. Materials & Methods

2.1. Participants

This study was approved by the ethical comity of Grenoble University Hospital (ID RCB: 2013-A01734-41), and registered on ClinicalTrials.gov (number NCT02168413). All the subjects gave their written consent prior to the experiment. Twenty-two healthy volunteers participated to this experiment (14 males, aged 29.6 ± 10.1 years old). None of them had neither histories of psychiatric illness or neurological disorders, nor history of alcohol or substance abuse. All were free of any medicinal treatment likely to modulate their cortical excitability levels.

2.2. Acquisition parameters

Protocol design

First, brain anatomical MRIs were acquired at 3T (Achieva 3.0T TX, Philips, Netherlands). The subjects were then prepared for the TMS-EEG experiment (EEG cap hanging), while their MRI were being processed in order to define the cortical targets. A co-registration step, necessary for the neuronavigation system, was performed. The resting motor threshold (rMT) was assessed during a classical motor CE session. Finally, one TMS-EEG mapping session per hemisphere was performed (30 min each), separated by a 15 min break.

TMS parameters

TMS was delivered using a Magpro Cool B65-RO butterfly coil (MagVenture A/S, Denmark) plugged in a MagPro x100 TMS stimulator (MagVenture A/S, Denmark), and guided by a Localite neuronavigaiton system (Localite GmbH, Germany). The coil was handled automatically using a TMS-robot (Axilum Robotics, France). The rMT was assessed on the "hotspot" position, defined as the optimal target to elicit the greatest motor evoked potential (MEP) in the contralateral first dorsal inter-osseous muscle, on a stimulation grid centred over the hand knob of the motor cortex. The MEP were recorded using a Dantec Keypoint portable electromyographic (EMG) recording system (Natus Medical Inc., USA). Resting motor threshold (rMT) was then defined using the threshold hunting method (Awiszus, 2003) as the minimal stimulation intensity to evoke a $50\mu V$ MEP in half of the trials. The rMT was assessed either on the left or right hemisphere, depending on the stimulation side order, counterbalanced between subjects.

EEG-TMS mapping of a single hemisphere was performed in one session and included the recording of the EEG activity evoked by the stimulation of 9 cortical targets (Figure 1A). Both hemispheres were symetricaly stimulated. Sites included the inferior frontal gyrus (IFG), the dorso lateral prefrontal cortex (DLPFC), the middle frontla gyrus (MFG), the anterior part of the supplementary motor area (SMA), the primary motor coretx (M1), the superior temporal gyrus (STG), the superior and inferior parietal lobes (SPL and IPL respectively), and the superior occipital lobe (SOL). The target coordinates were preliminary defined in the standard MNI coordinate space (Table 1), and were projected back on each subject's individual anatomy using the inverse spatial transform given by the normalization procedure of SPM8 (Wellcome Department of Imaging Neuroscience, UK, `www.fil.ion.ucl.ac.uk/spm/`). The coil was placed on a posterior to anterior direction, with an angle of 45° to the nasion-inion axis, except for M1 (perpendicular to the primary motor gyrus), STG and SOL (90°). The coil followed a predefined robotized sequence of stimulation, going from the anterior to the posterior part of the brain (Figure 1B). The sham condition consisted of stimulating 3 to 5cm above one of the cortical targets (randomly distributed between subjects) at 95% of the maximal stimulator output, in order to produce a clic sound of a maximum intensity. Each cortical target was stimulated during 2 min 30 s at a randomized frequency of 0.5-0.7 Hz, leading to an average number of

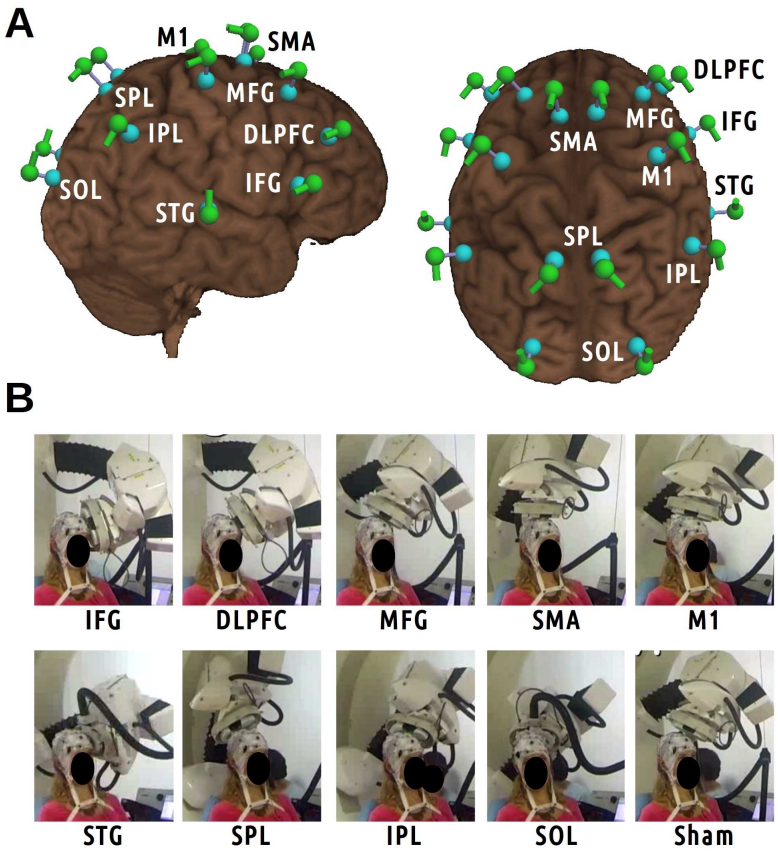

Figure 1: Cortical mapping procedure. A: cortical targets used for the mapping procedure. The brain meshes are taken from the neuronavigation system on one individual subject. Entry points and coil orientations are depicted in green, whereas cortical targets are in blue. Targets are symmetrically distributed on both hemispheres. B: robotized sequence of stimulation. The snapshots show the position of the robotized arm trhoughout the mapping procedure of the left hemisphere, from the anterior to the posterior sites. Snapshots are sorted into time order from top left to bottom right, except for Sham condition (see text).

90 trials per stimulation point. The intensity was fixed at 120% of rMT, corrected for the scalp-cortex distance following Stokes formula [41]. During each stimulation sequence, the subject was told to relax (resting state) and to stare at a black cross located on the opposite wall. Subjects were also listening to white noise through active noise cancellation intra-auricular earphones (QC 20, Bose, USA) in order to limit the influence of the auditory processing of the TMS click on the ongoing EEG activity. The sound level was adjusted individually to each subject, until the TMS click delivered at 95% of the stimulator output became barely inaudible. A thin layer of soft plastic was placed on the coil surface in order to limit both sensory and auditory feedbacks to the subject.

EEG acquisition

EEG was recorded on a 64 channels TMS compatible system using the BrainAmp DC amplifier system together with BrainCap TMS 64 electrodes caps (Brain Products GmbH, Germany). The EEG cap was placed at the beginning of the experiment over the subject's head following the 10-20 standard system. Electrooculogram (EOG) of the right eye was recorded using one of the 64 electrodes. The electrode impedances were adjusted and kept under 5 kOhms using conduction gel. The impedance levels were checked and corrected if needed before the two TMS-EEG sessions. The signal was DC corrected, filtered using a 500 Hz anti-aliasing low-pass filter, and finally digitized at 1 kHz sampling frequency. Fz was used as reference during the recording. The channels spatial positions relative to the subject's scalp were measured at the end of the experiment using the neuronavigation system.

2.3. EEG processing

EEG signals were processed using the Fieldtrip [42] and Brainstorm 3 [43] toolboxes, and other custom scripts written in Matlab (The MathWorks Inc., USA).

Preprocessing

EEG signals were preprocessed semi-automatically based on the methodology described in [44], for each condition (18 targets and 1 sham) and each subject. First, the channels showing electrical noise (flat signal or an overall dynamic superior to $100\mu V$) on more than 15% of the trials were discarded from the analysis (mean 1.53 ± 2.08 per condition). EEG signals were then epoched around the TMS pulse, using a -200 to +1000 ms time window of interest. TMS artifacts were discarded by cutting out the -5 to +15 ms period surrounding the TMS pulses. Two rounds of independent component analysis (ICA) were then applied in order to remove noise remaining in the signal. The first ICA allows for the suppression of the muscle artifact, while the second is dedicated to the decay, ocular, auditory-evoked potentials (AEP) and other noise-related artifacts (see [44]). Before the second ICA, the signal was interpolated over the -5 to +15ms period, band-pass filtered (1-80 Hz), re-referenced using the average reference, and cleaned from artifactual trials (leading to a mean of 77.7 ± 7.2 trials left per condition). The ocular components were automatically identified using the correlation product ρ between the spatial topographies of the components and a template of typical horizontal eye movements and blinks ($\rho > 0.7$) build from our own database by averaging over subjects. Other artifactual components (decay, AEP and other noises) were detected by thresholding above 4 the z-score of their mean activity against the pre-stimulus period, and by visual inspection. Cleaned EEG time series were reconstructed using the remaining components and any isolated channel still showing remaining noise was discarded from further analysis. Time series of rejected channels were finally inferred using the activity averaged over their neighbouring channels.

TMS evoked potentials (TEPs)

TEPs were computed for each condition and subject by averaging over trials, using a baseline normalization over the -200 to -5 ms period (removing the mean and z-scoring). The grand average TEP was obtained for each TMS target by averaging across subjects.

TEP source reconstruction

TEP source reconstruction was performed following the default procedure proposed in the software Brainstorm 3. First, the cortex and head meshes (15 000 and 10 000 vertices respectively) of each individual were generated using the automated MRI segmentation routine of FreeSurfer [45]. The location of EEG electrodes were co-registered on each subject's anatomical MRI. The forward model was then computed using the symmetric Boundary Element Method (BEM) developed in the openMEEG freeware, using the default values of conductivity and layer thickness [46]. The full noise covariance matrix was then computed for each subject using the temporal concatenation of the baseline periods of all conditions. Sources were distributed orthogonally to the cortical surface and their amplitudes were estimated using the default values of the Brainstorm implementation of the whitened and depth-weigthed linear L2-minimum norm solution. The absolute source amplitudes were finally spatially smoothed using a Gaussian filter of 20 mm width and normalized (Z-score against baseline).

Local source activity maps

Local source activity (LSA) maps were constructed in order to represent the cortical response to TMS within the region of interest (ROI) centered on each target, for all the 18 stimulated sites at the same time (Figure 2). ROIs were created on each individual anatomy using a mean spatial extent of $10cm^2$, covering about 50-60 vertices of cortical mesh. The LSA time series of ROI i, $|S_i(t)|$, was obtained by averaging absolute source time series within ROI i. For display purposes, LSA maps were created by projecting back LSA of each ROI on a canonical brain (using Colin27

Lobe	Cortical targets	BA	MNI coordinates (Left)	MNI coordinates (Right)
Frontal	Inferior frontal gyrus (IFG)	45	-59 22 13	62 26 13
	Dorsolateral prefrontal cortex (DLPFC)	46	-44 41 31	41 44 30
	Middle frontal gyrus (MFG)	8	-33 15 62	35 12 62
	Supplementary motor area (SMA)	6	-3 8 72	9 8 73
	Primary motor cortex (M1)	4	(HS) -36 -35 63	35 -32 64
Temporal	Superior temporal gyrus (STG)	22	-66 -23 10	68 -23 9
Parietal	Superior parietal lobule (SPL)	40	-52 -53 51	55 -50 51
	Inferior parietal lobule (IPL)	7	-9 -62 71	6 -62 70
Occipital	Superior occipital lobe (SOL)	19	-21 -87 34	29 -87 32

Table 1: Characterization of the cortical targets used for the mapping procedure. Primary motor cortex (M1) was targeted on the hot-spot (HS) position (see text).

template) and LSA was interpolated in between ROIs using the Shepard's weighting of 3D nearest-neighbor interpolation in order to assign an LSA value to every node of the cortical mesh.

LSA group analysis

We performed a group ICA analysis on individual LSA in order to extract the main time-frequency modes of the local neuronal activity and to evaluate its spatial distribution. First, we extracted the signed values of the source amplitude $S_i^j(t)$ within each ROI i and subject j, for each time bin $t \in [1, N]$ corresponding to the -50 to +400ms period. The signed (instead of absolute) values were needed here in order to take the oscillatory properties of the different neuronal populations into account. Since we assumed that the spatial location of the ROI was consistent between subjects, we computed a group ICA with temporal concatenation (see ref). This led to a LSA matrix M, of size $L \times (N * K)$, L being the number of stimulated targets (18), and K the number of subjects (22). M thus aggregates all the individual LSA, such as $M(i) = [S_i^1 ... S_i^k ... S_i^K]$, with $k = 1, ..., K$. M was finally decomposed into 18 independent components (data dimension) using the "runica" method. The dynamics of each component was finally assessed on each individual through a time-frequency (TF) analysis, using a wavelet decomposition (width of 7 oscillation cycles) between 9 and 50 Hz (0.5 Hz bandwidth). Individual TF maps were then normalized (Z-score against baseline) and averaged across subjects.

Statistics

Significant spatial differences in the LSA map across stimulated area were assessed through time using the Skillings-Mack test (ref). This test is derived from the Friedman test (non-parametric equivalent of the repeated measures ANOVA test) and can handle missing data. Differences were considered as significant at $p < 0.05$ for at least 20 consecutive time bins (ref). Statistical dependences between LSA and other experimental values were computed using Spearman correlations. TF maps were analyzed using comparisons against baseline. One t-test was performed per time-frequency bin, the resulting p-values were corrected for the number of tested frequencies (83) using a Bonferroni procedure.

3. Results

All the subjects went through the entire mapping procedure without any major complication. However, three subjects reported painful sensations during the stimulation of IFG and STG. Accordingly, the stimulation intensity was lowered down (minimum of 105% of rMT) for those three subjects when targeting IFG and STG, but the stimulation remained painful for one subject and was stopped. In addition, one subject experienced drowsiness during the stimulation of some targets. Finally, we removed from the analysis the data of four subjects for left IFG, of two subjects for the left and right STG, and of one subject for the left and right IPL, left and right SOL, right IFG, right DLPFC, right SMA, and right M1.

3.1. TMS evoked potential

Figure 3 shows grand-average TEPs for the stimulation of the left hemisphere. The sham condition did not show any significant activity. It clearly suggests that the responses observed for real stimulations were not due to confounding auditory and somatosensory responses to TMS clicks. First, it is important to note that the earliest components (< 60 ms) were rather focal under the target, indicating the activation of local neuronal populations. The largest activity within this period was generated by the stimulation of M1 (P30 component). In opposite, IPL was the least activated area, showing no activity pattern above baseline level. Second, larger activity patterns could be observed after 60 ms for each condition, peaking around 100, 200 and 280 ms. Whereas the 100 and 280 ms components were essentially generated after the stimulation of MFG and parieto-occipital areas, and of IFG, DLPFC and STG respectively, the 200 ms central component could be observed in nearly all the conditions. These late components could reveal the level of efferent connectivity of each stimulated area. In particular, the stimulation of the DLPFC, IFG and STG, which are 3 cortical areas highly involved in inhibitory circuits and language processing respectively,

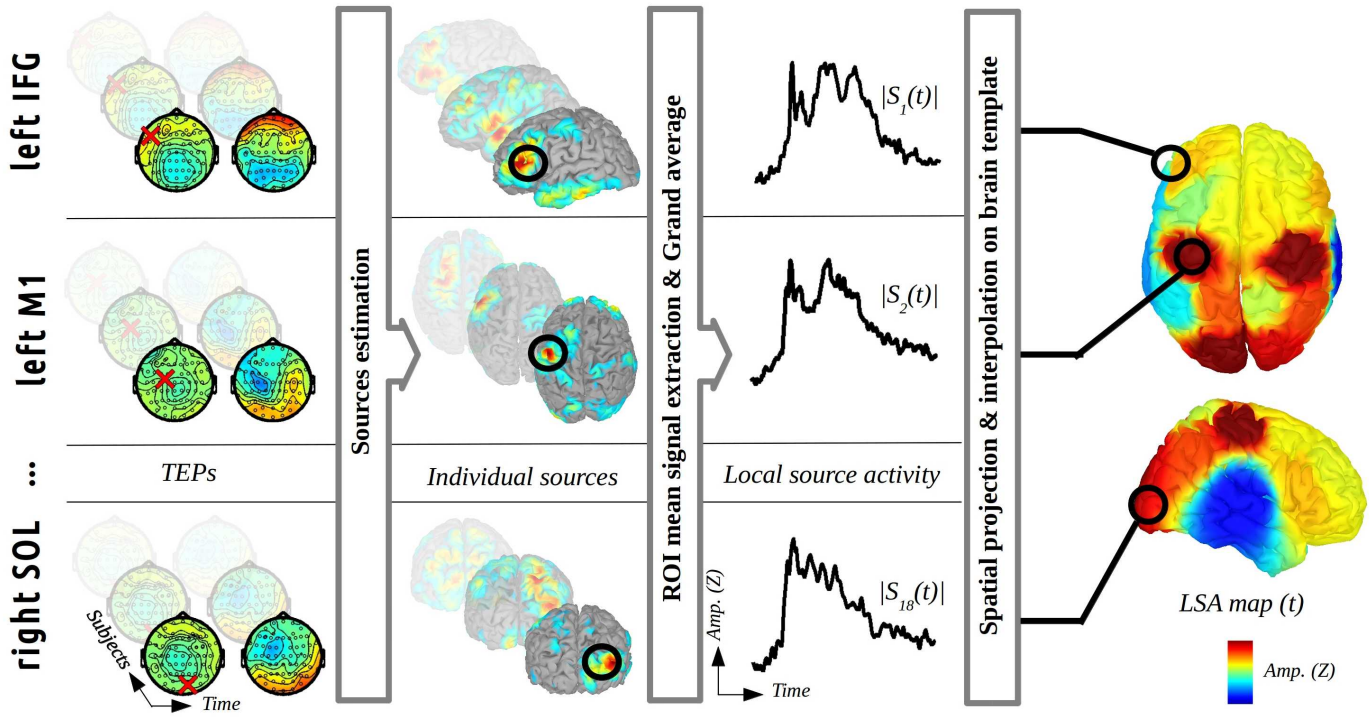

Figure 2: Generation of the local source activity (LSA) map, in function of time. Sources of TEPs to each stimulated region (red cross) are first localised. Local cortical responses (LSA time series) are then inferred from source time series averaged within ROIs centred on each cortical targets (black circles). Using spatial interpolation of LSA time series, the LSA map is finally generated.

generates the largest and longest activity (up to 340ms). In opposite, M1 stimulation leads to the smallest response, possibly due to the lesser proportion of cortical efferents.

3.2. Local source activity

Figure 4 shows LSA for all TMS targets. Interestingly, whatever the TMS target, LSA time series did not show any significant activity beyond 250 ms (Figure 4A), which was in contrast with TEPs (Figure 3). This strongly supports the hypothesis that the later components of TEPs were generated by neuronal populations remote from the neuronal population directly activated by TMS.

Secondly, each stimulation site has its own temporal pattern of response to the TMS. The local response differs significantly across sites within all the period of interest, except for 3 periods ranging from 49 to 53ms, from 104 to 121 ms, and from 164 to 174ms. Besides, the LSA maps appear to be highly symmetric during all the analysis window, as no significant difference between right and left hemispheres activation levels has been found. The only substantial asymmetry can be observed in SOL around 70ms.

Chronologically, M1 and SOL are the two first areas to respond at 30ms, followed by SMA and MFG at 45 and 70ms, the frontal and temporal areas (IFG, DLPFC, and STL) being activated later. The IPL is the least activated area throughout all the period of interest.

Two analysis can be derived from this LSA map. A attempt to map CE is first proposed, while the variability in the dynamic of responses is then assessed through a group ICA analysis.

Cortical excitability map

In order to assess the homogeneity of CE, we averaged the LSA maps on the very first time period, from +15 to 60ms after stimulus onset. The very first components could indeed reveal the cortical reactivity of the local neuronal circuits. The CE map is shown in Figure 5A. First, we can observe that CE is not homogeneous, but differs significantly across brain areas ($p = 1.27e^{-8}$). The motor areas (SMA and M1), the MFG, SPL and SOL show the greatest reactivity, whereas the STL, IPL and other frontal areas (IFG and DLPFC) show a lack of excitability. The ratio between the least activated area (right STG, $\bar{Z} = 3.1$) and the most activated one (left SOL, $\bar{Z} = 5.6$) reaches 1.8. Secondly, CE levels seems to be symmetric, since no difference has been found between the two hemispheres ($p = 0.53$).

Since we corrected the stimulation amplitudes for the scalp to cortex distances, we computed the correlation between CE levels and the stimulation powers used in order to discard any side effects (see Figure 5B). No significant correlation was found between the two values ($\rho = 0.08, p = 0.13$).

Finally, we tested the between subjects variability and

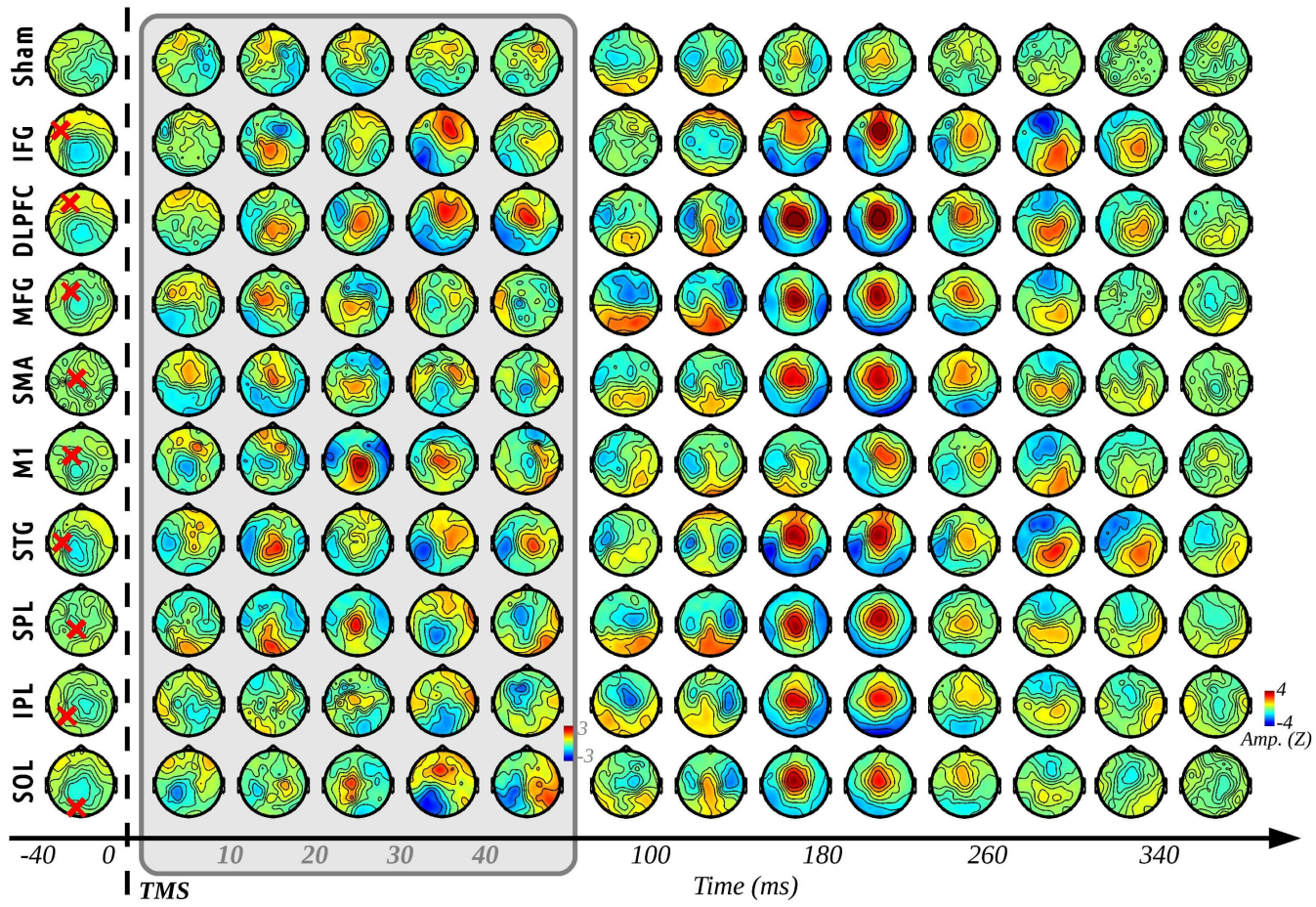

Figure 3: Grand-average TEPs for the stimulation of the left hemisphere. The grey insert emphasizes the earliest components. The z-score limits are -3 to +3 within this period. Topographies were obtained by averaging TEPs within a 40ms time window (10 ms in the grey insert). Red crosses on the left column indicate the stimulation sites

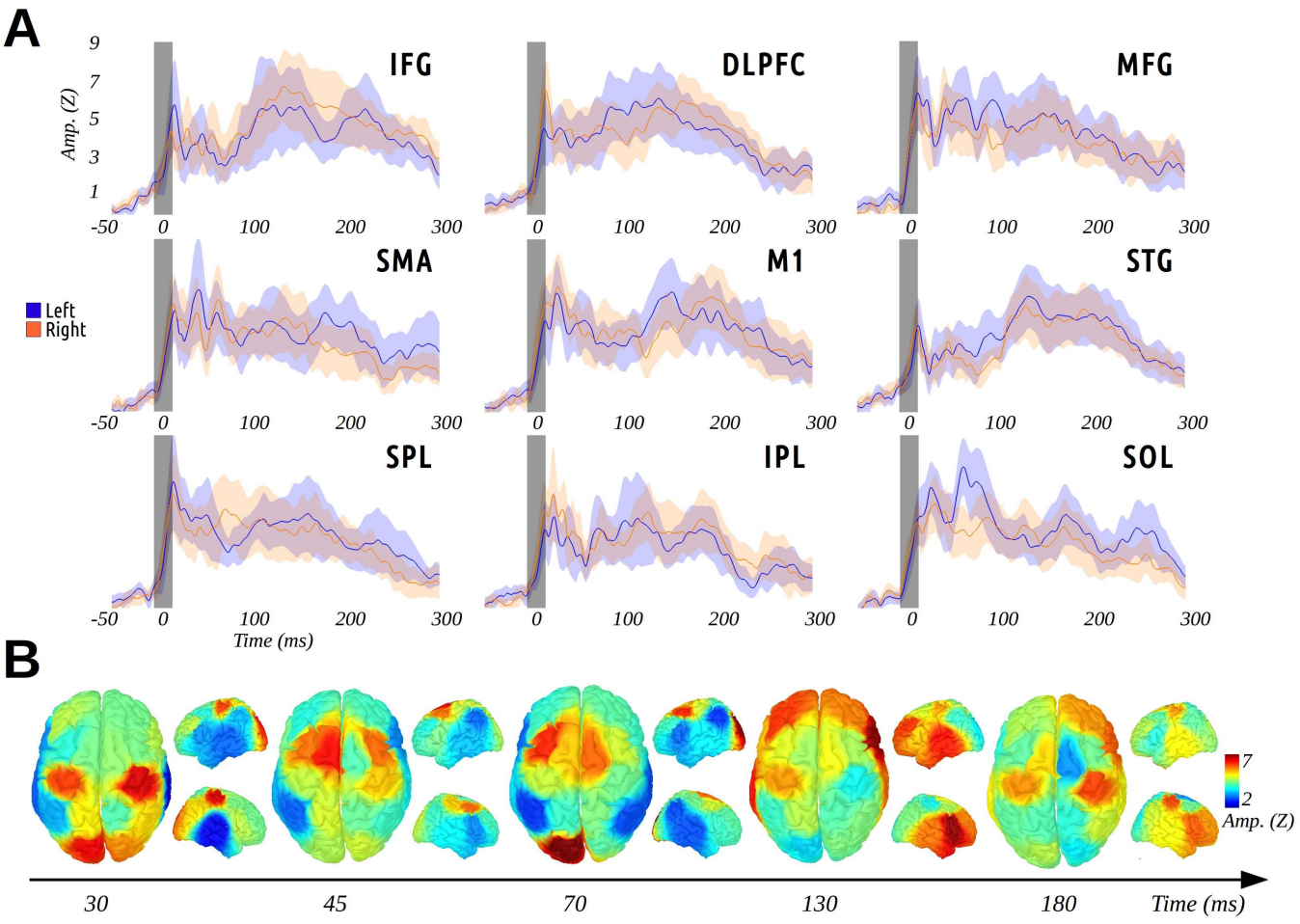

Figure 4: Group average of LSA. A: LSA time series. Colored areas represent the 95% confidence intervals. The grey shadowed area indicates the -5 to +15ms interpolation period due to the TMS artefact. B: LSA maps generated for the 5 time periods presenting the highest overall activity.

reproducibility of this map by computing correlation coefficients between the CE map obtained for all the 22 subjects and CE maps obtained from random subsets of subjects. 200 maps were computed using random groups between 5 and 20 subjects. The correlation and its 95% confidence interval is plotted in Figure 5C for each group sizes. The CE map seems to be highly reproducible ($\rho > 0.9$) for group of 16 and more subjects, while a good score ($\rho > 0.75$) can still be obtained for group of at least 10 subjects.

Spatial clusterization of LSA dynamic properties

A group ICA on LSA time series was performed in order to detect cortical regions sharing common neuronal signatures. Figure 6 shows the first five components that best explained the data variance. The spatial pattern of each component is shown on the left. On the right, the temporal signature of each component is shown using a time-frequency decomposition based on a wavelet transform in order to identify their main frequencies. Interestingly, we could identify networks that were essentially symetrical. The first component was driven by the SPL and by the STL in a lesser proportion, while a large temporo-parieto-frontal network emerged from the second one. The third component mainly involved frontal areas (right DLPFC and IFG, left MFG). The two primary motor cortex were represented in the fourth component, and a large parieto-occipital cluster composed the fifth component.

Interestingly, each component had a specific dynamical signature. The large parieto-occipital cluster (comp. 5) was associated with a sustained alpha rhythm from 50 to 500 ms after stimulation onset. The two other components involving parietal areas (comp. 1 and 2) were also characterised by a short burst of alpha oscillations between 100 to 300 ms. We could also observe a burst of low and high beta oscillations on the two primary motor cortex (comp. 4), looking like a beta rebound in the 100-250 ms latency. Finally, the frontal cluster (comp.3) shows a low gamma (35 Hz) burst of oscillation at 50 ms. Interestingly, the highest frequency of oscillation of each component seems to be sorted in ascending order from posterior to anterior areas.

4. Discussion

We developed here the first attempt aiming to map the dynamical properties of human cortical microcircuits in a non-invasive and automatic way, using the coupling between robotized TMS and EEG. The results regarding the spatial organization of local microcircuits properties are promising, and could possibly lead to a new way of assessing RSN segregation or functional parcellation of the human superficial cerebral cortex. However, several technical issues have still to be addressed in the TMS-EEG field, that could limit the conclusion of this work. We thus finally present future works that have to be done in order to confirm and develop our findings.

4.1. Protocol feasibility

The 22 recorded subjects went through the whole experimental procedure without any major complications. The mapping in itself can be done in a fast (30 min/hemisphere) and convenient way using a robotized system. However, the whole process remains expensive in terms of time (3h15) and budget, regarding all the different neuroimaging techniques to be used. One of the longest step lies in the TMS compatible EEG cap preparation (about 1h), and further technical improvement of these systems could drastically reduce the duration of our procedure. The mapping procedure is nevertheless operative and can be applied on other group of subjects or patients in the future.

4.2. Spatial organization of local microcircuits properties

CE homogeneity

The results showed that the CE of the human brain seems to be spatially heterogeneous, as the amplitude of the local neuronal responses differs among cortical areas 15 to 60 ms after being stimulated. The primary motor cortex is moreover one of the area presenting one of the highest excitability level, especially around 30 ms. As a consequence, our data could question the exclusive use of motor CE as an indicator of the global brain excitability. In particular, stimulating the frontal, temporal or inferior parietal lobes using intensity based on the rMT could lead to a systematic undershooting of the stimulation effect. Furthermore, these maps could be turned into biomarkers of the integrity of the cortical tissues, in the context of strokes for example. It could also be studied in the context of psychiatric diseases, in order to define possible hyper- or hypo-excitable cortical areas.

From the spatial clusterization of LSA dynamics properties...

Far from being randomly organized among cortical targets, the multivariate group analysis of LSA showed the emergence of several organized spatial patterns, like parieto-temporal, parieto-occipital, frontal, or motor networks. By definition, the cortical areas composing these networks thus share common properties regarding the LSA evoked by TMS, like the oscillatory activities of their local neuronal populations. The time frequency analysis revealed that these networks have their own oscillatory signature, in accordance with previous findings in the EEG and TMS-EEG fields [18, 38]. For example, the parieto-occipital network showed a resonant frequency in the alpha band, whereas the motor cortex mainly oscillated in the beta band. As for CE maps, the analysis of these cortical networks and their oscillatory patterns could be turned into biomarkers of their integrity. A recent study supports this idea, by showing that the resonant frequency of the premotor area could be modulated in the context of several psychiatric diseases [47].

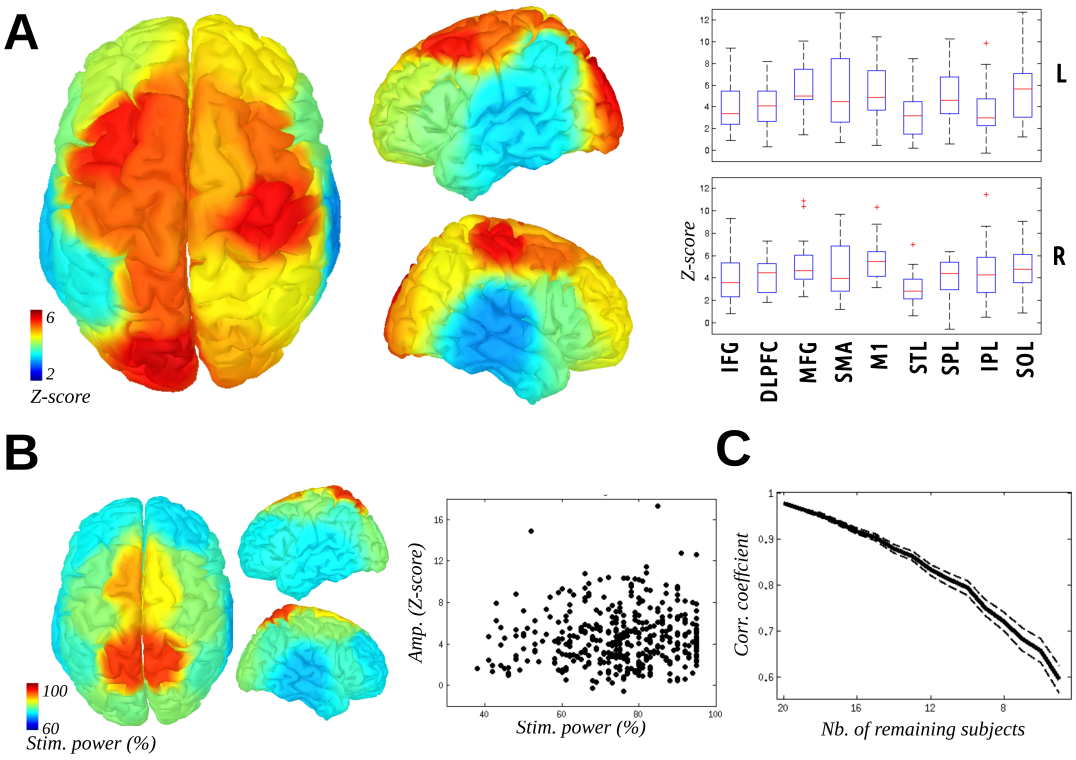

Figure 5: Cortical Excitability map. A, from left to right: CE map, CE level distributions used for this map against cortical areas. B, from left to right: map showing the mean stimulation power used, correlation between CE levels and stimulation powers. C: reproducibility of the CE map regarding the number of subjects used (see text).

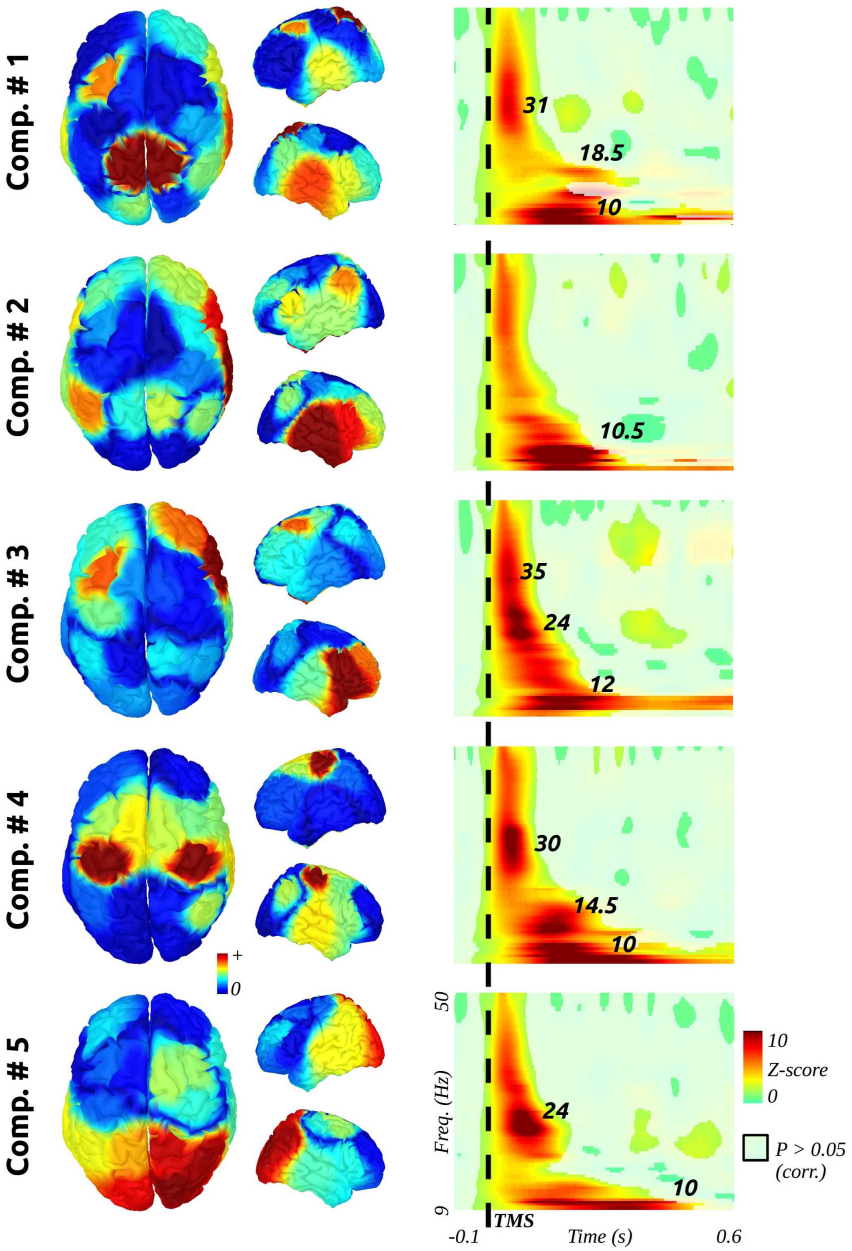

Figure 6: Group ICA decomposition of LSA. ICA components were sorted by the amount of explained variance in descending order from top to bottom. Their topography is shown on the left, and their time-frequency profile on the right. Frequencies corresponding to local maxima of power are indicated in black figures.

...toward a non-invasive functional parcellation method of the human cerebral cortex...

Furthermore, the methodology we developed could be turned into a new non-invasive way to parcel the human superficial cerebral cortex regarding the dynamics of its local neuronal circuits response. Parcellation of the cortex is one of the most studied field in neuroscience since its beginning (ref). The search for precise anatomical boundaries, based on local cytoarchitectural, myeloarchitecural, or else receptoarchitecture specificities, derived from the fact that structure determines function (ref). If this property can be verified on primary areas, it is now commonly agreed that higher cognitive functions rather requires the involvement of complex and widely distributed networks. Moreover, several studies have shown that the connectivity pattern of a cortical area can even induce change in its local cytoarchitecture and neural response dynamics. This is one of the reasons that steered one branch of this field to go from purely anatomical parcellation to functional parcellation. Non-invasive functional parcellation methods, based on in vivo neuroimagery, essentially rely on MRI techniques, such as resting-state (ref), and diffusion imaging - tractography (ref). These methods are able to parcel a defined brain area in respect to a connectivity score, using both functionnal and/or anatomical connectivity. However, there is only few equivalent based on electrophsyiology recordings, although several studies using invasive electrical stimulation have proven that the properties of the neuron electrical response are higly dependent on the intrinsic cytoarchitecture of the stimulated area, in both animals (ref) and humans (ref). Especially, it has been recently showed that the high frequency signatures could reveal different modes of afferents (ref). In the EEG field, cytoarchitecure and parcellation informations mainly served as priors in order to improve source reconstructions (ref).

We believe that combining TMS and EEG would be a possible way to assess functional parcellation, by looking at the differences in dynamic properties of the stimulated areas. They directly rely on local anatomical differences, since different proportion and organization of inhibitory, excitatory and other neuronal microcircuits lead to different patterns of current shape and orientation when being stimulated. For example, our results would support the fact that the primary motor cortex has a very specific anatomical organization, that react in a unique manner to the stimulation. On the other hand, it appears that the superior occipital lobe share common anatomical properties with the inferior and superior parietal lobes, able to generate sustained inhibitory alpha oscillations. However, the spatial resolution of the parcellation presented here is rather coarse, and further studies are needed in order to know the spatial scale limit in segregation that could achieve such a method.

...and a new way to assess resting state networks

Finally, it appears that the networks emerging from this study higly correlate with RSN already found in previous findings involving functional MRI (fMRI) (ref) and more recently magneto-encephalography (MEG) (ref). RSN can be revealed by studying the functionnal connectivity between cortical areas based on the spontaneous blood oxygen level dependant (BOLD) signal fluctuations (in fMRI) or on phase-amplitude coupling (PAC) synchronizations between low (theta - alpha) and high (gamma) frequencies (in MEG), supposed to support large-scale neural communication. Both techniques reveal that the spontaneous brain activity can be segregated into different RSN, ranging from local sensory-motor networks to large scale ones involving associated areas (ref). This findings higlhy correlate with our results, regarding the spatial clusterization of LSA (see for example comp # 4 for local motor network, or comp # 2 and 3 for distributed networks). Furthermore, our maps overlap significantly with several RSN found in the MEG study (ref), including in particular a network mainly driven by the bilateral SPL (as for comp # 1), or a right fronto-parietal network (as for comp # 2 and 3). Interestingly, we showed that those networks share some common properties regarding frequency signatures, mainly composed of alpha and low gamma bands. Since RSN segregation in the MEG study is based on PAC between alpha and high gamma bands, our results could reveal the basic oscillatory properties of the local network nodes needed for the large-scale neural communication to occur within the networks. Further studies investigating the ability of TMS to induce high gamma oscillations are however needed to fully support this idea.

4.3. Limitations

Several limitations regarding our work have to be addressed here.

EEG processing

First, there is still a lack of fully data-driven and automatic pipelines for processing EEG data recorded during TMS. In this study, we used the latest methodology described in the literature. Rogasch and al recommends the use of two rounds of ICA in order to filter out artifactual signals. Even if we developed some functions for automatically choosing the components to be rejected, there is still a need for a visual inspection of each of the remaining components. This human factor has to be eliminated as i. it could obviously lies to some induced variability, ii. it requires time and a good experience in EEG signal processing. Auditory and somatosensory evoked potentials due to the sensory feedback of the scalp muscle contractions might also influence the recorded EEG activity. The component found on TEPs at 100 and 200ms could reflect the presence of such remaining artifacts, regarding their overall latency and topography. However, several clues give strong arguments in favor of a real stimulation effect

on the neuronal activity. First, the precise spatial organization of these patterns greatly varies across stimulated areas, and their amplitude are three to four times smaller than those recorded on sham condition. Second, this component has already been found and discussed in numerous studies in TMS-EEG [48, 49]. It has been shown to reflect a neuronal activation generated by the stimulation rather than to a pure auditory artifact. Finally, these components have also been found in intracranial cortico-cortical evoked potentials (CCEPs) after direct electrical stimulation of various areas. These latter components (100, 200 and 280ms) could thus reflect, at least in part, the activation of remote cortical areas connected to the stimulation site. The last limitation lies in the ROIs definition step. ROIs were defined here in a straightforward manner, based on the targets used by the neuronavigation system. New fine modelization of the electrical field induced by TMS (ref) could be used in the future to directly define ROI in a more precise way.

Cortical excitability

We have to stay careful in our conclusion regarding CE homogeneity as we are still blind to the very first components of the evoked neuronal response, due to the signal interpolation of the TMS artifact period (0-15ms). This issue might however be difficult to overcome due to the extremely low SNR generally observed in this time window. Furthermore, the local EEG activity measured within 15-50ms might already contain feedbacks from other intrahemispheric connections [50], and differences could be due to the connectivity pattern of the stimulated area, rather than to the pure reactivity of its local neuronal population.

We also believe that the definition of cortical excitability, and our way of measuring it, as to be debated. If the definition of motor CE is quite straightforward, i.e. being the stimulation intensity required to activate directly and indirectly pyramidal neurons connected to the spinal track, and easy to observe via the study of MEP, this is (still) not true for other brain areas. As already said earlier, the first reason is based on the difference of their intrinsic cytoarchitecture. Our definition of CE based on the power of the earliest components of the scalp EEG signal could be unable to detect such complex differences, since the EEG signal is the summation of both excitatory and inhibitory post-synaptic potentials [51]. As a matter of fact, two different brain areas could be equally "activated" whereas showing great differences in the power and/or latency of their components, due to their differences in local neuronal population. Secondly, the expected effect of TMS depends on the stimulated area. Again, if the activation of the cortico-spinal track is the expected outcome for M1, we still have to define it for other brain areas. The aim of stimulating frontal or temporal areas may be for example to disturb the process of higher cognitive function sustained on complex network (inhibitory processes, association processes, etc.). The stimulated cortical targets may "only" be entry points for these particular networks. As a matter of fact, CE level could be defined in that case as the amount of stimulation intensity needed to disturb remote networks. Our data suggest that temporal and frontal areas show their greatest local activity around 130ms. At such latencies, this activity might be the feedback of neuronal communication with distant brain areas activity, as already said before. This may be the expected effect, and the CE level of these stimulated areas might in fact be already reached.

4.4. Future work

Future researches regarding this work first include the mapping of excitatory and inhibitory circuits independently, by using paired-pulse stimulations. The comparison between LSA maps obtained with intra-cortical inhibition and facilitation paired-pulse TMS protocols could help us to overcome the previous limitations regarding the precise nature of the neuronal circuits recorded by EEG during the mapping. Building maps using more points, or different sets of points, and using different coil angles is also one of the future aim, in order to better understand the influence of these parameters on these maps. The spatial resolution of this method used as a functional parcellation technique has also to be tested, regarding the size of the electrical field induced by TMS. Finally, although this work was mainly focused on the neuronal properties of the stimulated local circuits, the recorded data could also gave precious information regarding the connectivity of the stimulated areas. Building maps based on the global mean field potential (GMFP) generated by each cortical targets, or based on connectivity analysis made for each target separately, could give new insights regarding the spatial organization of the human brain connectivity.

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