

Influence de la connectivité anatomique sur la modulation de la perception visuelle induite par une activité frontale.

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Université Pierre et Marie Curie
Ecole Doctorale Cerveau Cognition Comportement
Institut du Cerveau et de la Moelle Epinière

INFLUENCE DE LA CONNECTIVITE ANATOMIQUE SUR LA MODULATION DE LA PERCEPTION VISUELLE INDUITE PAR UNE ACTIVITE FRONTALE

Thèse de Doctorat de Neurosciences Cognitives

Par Romain QUENTIN

Dirigée par Antoni VALERO-CABRE

Soutenue le 30 Septembre 2014, devant le jury composé de :

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Antoni VALERO-CABRE	Université Pierre & Marie Curie	Directeur

RESUME

Nous ne pouvons tout voir ou ressentir et par conséquent ce que nous observons n'est jamais une réplique exacte de notre environnement extérieur. L'attention, notre capacité à filtrer, sélectionner et moduler les informations, nous permet d'interagir de façon efficace avec le monde. L'attention visuo-spatiale en particulier est capable de moduler les performances visuelles, en les améliorant à l'endroit ou elle s'oriente et en les réduisant dans le reste de l'environnement visuel. Dans les travaux de cette thèse, nous avons utilisé une technique non invasive de modulation de l'activité cérébrale, la Stimulation Magnétique Transcrânienne (SMT, *en anglais Transcranial Magnetic Stimulation, TMS*) pour manipuler l'activité d'une région clé du réseau de l'attention spatiale, le champs oculomoteur frontal (en *anglais Frontal Eye Field, FEF*) droit, qui se situe dans le lobe frontal à la jonction du sillon précentral et frontal supérieur. Cette manipulation a pour but d'établir un lien causal entre l'activité de cette région, le réseau auquel elle appartient, et la modulation des performances visuelles. L'accent sera mis sur les connexions anatomiques sous-tendant ces changements perceptifs.

Après avoir présenté nos connaissances tirées de données comportementales, physiologiques et anatomiques sur l'attention visuo-spatiale (*Chapitre 1-3)* ainsi que les techniques utilisées au cours de cette thèse (*Chapitre 4)*, nous montrons dans la *Partie 1* du *Chapitre 6* que des impulsions simples de SMT délivrées sur le FEF de l'hémisphère droit juste avant l'apparition d'une cible améliore la détection consciente de celle-ci. Dans la *Partie 2* du *Chapitres 6* et dans le *Chapitre 8*, nous utilisons cette fois des trains de 4 impulsions à des fréquences particulières afin de moduler l'activité oscillatoire des régions frontales de l'hémisphère droit. Nous observons qu'une stimulation du FEF droit à la fréquence spécifique de 30 Hz juste avant l'apparition de la cible permet également d'améliorer la sensibilité visuelle, contrairement à une fréquence plus élevée de 50 Hz ou à une stimulation contenant le même nombre d'impulsions dans la même fenêtre temporelle mais sans fréquence spécifique.

Ces méthodes de stimulation ont majoritairement été décrites comme le résultat d'une modulation focale de l'activité au niveau de la région stimulée, ici le FEF droit. Mais le cerveau qui peut contenir jusqu'à 200 000 km de fibres myélinisées fonctionne avant tout en réseau. Nous avons étudié par Imagerie par Résonnance Magnétique de diffusion (IRMd) la connectivité anatomique de nos participants afin d'évaluer si des différences de connexion au sein de ces réseaux pouvaient influencer la modulation perceptive exercée par le FEF droit. La *Partie 1* du *Chapitre 7* décrit le faisceau fronto-tectal reliant les FEFs avec les colliculi supérieurs et montre que la probabilité de connexion anatomique reliant ces deux aires dans l'hémisphère droit influence l'effet de la SMT sur la détection visuelle. La *Partie 2* du *Chapitres 7* et le *Chapitre 8* décrivent les trois branches du faisceau longitudinal supérieur qui relient le lobe frontal et pariétal et démontrent une influence de la première branche dans l'hémisphère droit stimulé sur la modulation visuelle induite par les rafales de SMT. Des caractéristiques physiologiques de la substance blanche dépendent le temps de conduction des signaux électriques. Les résultats de cette thèse suggèrent un rôle important de la connectivité anatomique dans la possibilité de synchroniser les aires d'un réseau à une fréquence spécifique.

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Sigle	Anglais	Français
EEG	ElectroEncephaloGraphy	ElectroEncephaloGraphie
FEF	Frontal Eye Field	Champ Oculomoteur Frontal
IFG	Inferior Frontal Gyrus	Gyrus Frontal Inférieur
IPL	Inferior Parietal Lobule	Lobe Pariétal Inférieur
IPS	IntraParietal Sulcus	Sillon IntraPariétal
IRM	Magnetic Resonnance Imaging	Imagerie par Résonnance Magnétique
LIP	Lateral IntraParietal cortex	Cortex IntraPariétal
MEG	MagnetoEncephaloGraphy	MagnetoEncéphaloGraphie
MST	Medial Superior Temporeal area	Aire Temporale Supérieure Médiane
PEF	Parietal Eye Field	Champ Oculomoteur Pariétal
SEF	Supplementary Eye Field	Champ Oculomoteur Supplémentaire
SLF	Superior Longitudinal Fasciculus	Faisceau Longitudinal Supérieur
SMT	Transcranial Magnetic Stimulation	Stimulation Magnétique Transcrânienne
SPL	Superior Parietal Lobule	Lobe Pariétal Supérieur
STG	Superior Temporal Gyrus	Gyrus Temporal Supérieur
TPJ	Temporo-Parietal Junction	Jonction Temporo-Pariétale
VIP	Ventral IntraParietal area	Aire IntraPariétale Ventrale

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ARTICLES INCLUS DANS LA THESE

Chapitre 6, Partie 1. Chanes L., Chica AB., **Quentin R.**, Valero-Cabré A. 2012. Manipulation of Pre-Target Activity on the Right Frontal Eye Field Enhances Conscious Visual Perception in Humans. *PlosOne* 7(5).

Chapitre 6, Partie 2. Chanes L., **Quentin R**., Tallon-Baudry C., Valero-Cabré A. 2013. Causal Frequency-Specific Contribution of Frontal Spatiotemporal Patterns Induced by Non-Invasive Neurostimulation to Human Visual Performance. *Journal of Neuroscience.* 33(11). 5000-5.

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Chapitre 8 **Quentin R.,** Elkin Frankson S., Vernet M., Toba M., Bartolomeo P., Chanes L., Valero-Cabré A. Causal Contributions and White Matter Correlates of Right Frontal Rhythmic Activity to Visual Contrast Sensitivity Modulation in Humans. *(in prep).*

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Vernet M., **Quentin R.,** Chanes L., Mitsumasu MA., Valero-Cabre A. In revision. Frontal Eye Field, Where Art Thou ? Anatomy, Function and Non-Invasive Manipulation of Frontal Regions Involved in Eye Movements and Associated Cognitive Operations. *Frontiers in integrative neurosciences.*

CHAPITRE 1. L'ATTENTION

1.1. PETITE HISTOIRE DE L'ATTENTION

L'attention est un terme générique recoupant souvent plusieurs concepts et fréquemment utilisé de façon ambiguë. Une compréhension intuitive est possible en observant l'usage populaire de cette notion au travers d'expressions courantes telles que : « faire attention à » ou « porter son attention quelque part ». Par ces formules, nous comprenons que l'attention permet de sélectionner, de façon volontaire ou non, une certaine partie de notre réalité sensorielle ou psychique, souvent au détriment du reste du monde. A cet instant, en lisant ces mots – et en portant attention à ceux-ci – vous ne percevez que très peu de l'environnement autour de vous, depuis les bruits environnants parvenant à vos oreilles jusqu'aux sensations tactiles de vos orteils. Cependant, les stimuli sensoriels qui vous entourent pourront à tout moment prendre la place de la lecture de ce texte dans votre esprit, que ce soit une sirène d'alarme ou une douce odeur de cuisson remontant d'une cuisine. Le déplacement de votre attention se fera donc de façon volontaire ou non vers ce nouveau stimulus qui récupèrera, pour un nouvel instant, l'ensemble de vos ressources attentionnelles.

Cette capacité cognitive peut se percevoir comme une limite, car découlant directement de nos ressources finies. Elle provient de notre incapacité à traiter le déluge de signaux qui nous atteint de manière continue. Imaginons un instant un être aux capacités attentionnelles infinies, pouvant traiter et analyser l'ensemble des informations sensorielles tout en développant dans le même temps une multitude de pensées et réflexions. Chez cette personne fictive, la sélection de certaines informations au détriment d'autres ne serait d'aucune utilité et l'idée même de l'attention n'existerait pas car son cerveau serait capable de traiter l'infinité du monde qui l'entoure à tout moment. Il est difficile de concevoir que cette personne soit capable de penser, tant la sélection des informations est importante dans notre façon de construire notre réflexion, de raisonner et de donner du sens à ce qui nous entoure. Si l'on accepte pourtant cette idée, l'attention pourrait apparaitre non pas comme une capacité cognitive mais plutôt comme une incapacité cognitive. L'attention serait perçue comme une simple faiblesse de traitement.

Un tel cerveau n'existe pas et l'attention est davantage perçue comme un ensemble de mécanismes qui vient s'ajouter au traitement sensoriel et remédier à notre impossibilité de tout traiter. Elle nous permet d'interagir avec le monde extérieur sans nous laisser déborder par le flot incessant et gigantesque d'informations parvenant à nos sens. Cette interaction dépend de notre habilité à correctement filtrer et sélectionner l'information, ce qui n'est pas toujours une tâche aisée et peut prendre du temps, que ce soit dans la vie de tous les jours ou lors d'expériences au laboratoire (Treisman et Gelade 1980).

Il n'est pas toujours facile de séparer proprement l'attention d'autres processus et des ambiguïtés se retrouvent déjà dans la définition classique de l'attention par William James (James 1890).

« Tout le monde sait ce qu'est l'attention. C'est la prise de possession par l'esprit, sous une forme claire et vive, de l'un de ce qui semble être plusieurs objets ou suites de pensées simultanément possibles. Focalisation, concentration de la conscience en sont son essence. Elle implique le retrait de certains objets afin de traiter efficacement les autres, et est une condition qui a son contraire dans les états confus et étourdis qui en Français s'appelle distraction, et Zerstreutheit en Allemand. »

Ici sont confondus deux concepts aujourd'hui considérés distincts : l'attention et la prise de conscience. Ce lien complexe entre attention et conscience fait l'objet de nombreux travaux et sera développé dans la *Partie 1.3.1* de ce *Chapitre*.

La pensée fondatrice et nécessaire à l'émergence du concept d'attention est l'idée que nous ne pouvons tout voir et ressentir et que par conséquent notre perception du monde n'est pas une réplique parfaite du monde physique. Nicolas Malebranche au XVIIe siècle parlait déjà de perceptions imparfaites pour expliquer les causes de nos erreurs, et proposait l'attention comme solution.

« Il est donc nécessaire de chercher les moyens d'empêcher que nos perceptions ne soient confuses et imparfaites. Et parce qu'il n'y a rien qui les rende plus claires et plus distinctes que l'attention, comme tout le monde en est convaincu, il faut tâcher de trouver des moyens dont nous puissions nous servir pour devenir plus attentifs que nous sommes » (Malebranche 1675).

Peu de temps plus tard, Leibniz développe sa théorie des petites perceptions dans laquelle il fait la distinction entre perception et aperception (Leibniz 1714). Selon lui, les perceptions, reçues directement par nos sens sont en majorité tellement infimes et continues que nous ne pouvons pas les « apercevoir », c'est à dire en prendre conscience. Nous devons les moyenner ou les simplifier pour créer des représentations plus larges et confuses mais accessibles à cette conscience. Hermann von Helmholtz au XIXe siècle considérait lui que l'œil est trop pauvre pour percevoir correctement notre environnement et qu'il faut donc avoir recours à d'autres processus mentaux pour nous représenter le monde. Il proposa sa théorie des inférences inconscientes qui permettait, par le contexte et notre expérience, de parfaire notre perception (Helmholtz 1867). Même s'il parle ici de processus plus larges que l'attention, on retrouve l'idée fondatrice du concept de l'attention qu'il existe une perception de notre monde par deux niveaux, l'un provenant des sens et l'autre de processus plus élaborés correspondant à nos connaissances et attentes sur le monde. Les illusions d'optiques et l'étude de patients lésés sont venues démontrer la force de ces inférences sur notre perception.

Dans les années 1950, Colin Cherry, préoccupé par le problème du « *cocktail party* » qui demande de traiter une conversation en ignorant les autres, étudia ce phénomène par l'écoute dichotique. Il montra, en présentant simultanément des messages vocaux différents dans chaque oreille d'un participant, qu'il est extrêmement difficile de rapporter le message de l'oreille gauche si le participant a comme instruction de restituer le contenu du message de l'oreille droite, et inversement. En revanche, le participant est capable de restituer des aspects non sémantiques du message (le sexe ou la langue du locuteur par exemple) ou des mots si ceux-ci ont un sens particulier pour le participant (son prénom ou nom de famille par exemple). Ce traitement préférentiel d'une stimulation sensorielle au détriment d'une seconde qui, sous certaines conditions, peut malgré tout être perçue amena Donald Broadbent à proposer sa théorie du filtre attentionnel. Dans celle-ci, l'attention joue le rôle d'un filtre qui sélectionne une partie de l'information. Cependant, le reste de l'information est stocké pendant un court instant et peut être utilisé si jamais, contre la volonté attentionnelle première, l'information est finalement d'intérêt. L'autre notion importante de cette époque est que les stimuli sont en compétition au sein des ressources limitées de notre espace neuronal (Broadbent 1958). Lorsque l'on porte attention à un stimulus visuel qui doit apparaître à un endroit défini, cette compétition est en faveur des neurones qui codent l'information dans cette région spatiale et leur permet d'inhiber la réponse des neurones codant pour les régions voisines (Deco et Rolls 2005). Cette hypothèse a été extensivement démontrée grâce à l'électrophysiologie (Luck et al. 1997; Recanzone et al. 1997; Reynolds et al. 1999) et l'imagerie cérébrale (Kastner et al. 1998; Beck et Kastner 2005, 2007). Nous reviendrons sur ces démonstrations dans la *Partie 1.3.2* de ce *Chapitre*. Ces résultats ont

permis une nouvelle conception de l'attention, cohérente sur le plan psychologique et physiologique. Au niveau psychologique, l'attention impliquerait une allocation préférentielle des ressources de traitement et des canaux de réponse aux évènements pertinents pour la personne. Au niveau physiologique, l'attention suppose des modifications de la sélectivité, de l'intensité et de la durée des réponses neuronales en fonction des mêmes évènements saillants (Mesulam 2000).

En calculant le coût énergétique d'un potentiel d'action et la consommation totale du cortex, Lennie (Lennie 2003) arriva à la conclusion que seulement 1% de nos neurones pouvaient s'activer simultanément. Le cerveau est donc dans l'obligation d'allouer de façon extrêmement flexible les ressources énergétiques dans notre cerveau et cela pourrait représenter l'une de nos limites majeures et donc mener à la nécessité absolue d'avoir recours à des mécanismes de sélection attentionnelle.

1.2. L'ATTENTION SPATIALE VISUELLE

L'attention est présente de manière continue dans nos comportements, influence les représentations provenant de chacun de nos cinq sens et peut se définir dans plusieurs dimensions. Elle peut être soutenue dans le temps et correspondre à un niveau de concentration permettant d'effectuer une tâche sans se laisser distraire ou bien partagée lorsque plusieurs catégories d'information sont pertinentes ou que plusieurs tâches doivent être effectuées simultanément. Nous entamons dès maintenant le mouvement obligatoire de réductionnisme méthodologique pour s'orienter vers la réalité expérimentale de nos études et allons parler d'attention sélective visuelle, cette fonction cognitive capable de modifier la perception et l'activité des aires visuelles en l'absence totale de changement rétinien, c'est-à-dire avec des entrées visuelles parfaitement égales (Carrasco 2011).

Plusieurs divisions de l'attention visuelle sont possibles. La première distinction concerne l'attention visible et cachée (en anglais respectivement *overt* et *covert).* L'attention *overt* par définition implique le déplacement du regard vers un endroit d'intérêt pendant que l'attention *covert* décrit l'utilisation des ressources attentionnelles sans déplacement du regard. Rizzolatti et ses collègues proposèrent dans leur théorie pré-motrice de l'attention que l'orientation *covert* correspond à la programmation oculomotrice du mouvement des yeux sans son exécution, faisant d'un même mécanisme l'orientation de l'attention spatiale et la préparation des saccades oculaires (Rizzolatti et al. 1987). Il existe d'autres situations où l'attention sélective visuelle se pose non pas sur un endroit dans l'espace mais sur certaines caractéristiques des objets, comme leurs formes, leurs couleurs ou leurs déplacements dans l'espace. Nous nous intéresserons en particulier dans le reste de ce manuscrit à l'attention visuelle spatiale.

A la fin des années 1970, les études de chronométrie mentale (c'est-à-dire l'étude du temps qu'une personne met pour effectuer une tâche dans différentes conditions) posent les bases conceptuelles de l'attention (Posner et al. 1978). La seconde distinction importante se fait entre le déplacement endogène et volontaire de l'attention vers un endroit de l'espace et celui, exogène et involontaire, vers un changement brusque dans le champ visuel. En 1980, Posner décrit son célèbre paradigme et formule cette différence au début de son manuscrit (Posner 1980).

« Si l'orientation de mémoire ou liée à un stimulus externe vers un évènement ont une base commune, il est clair que nous devons être capable d'orienter notre attention en absence de stimulus externe. De même, les mouvements des yeux peuvent soit être entrainés par un stimulus externe, soit résulter d'un plan de recherche interne à l'organisme ».

Le paradigme de Posner a permis d'observer dans différentes conditions les effets comportementaux de l'orientation attentionnelle. Dans cette expérience pionnière, un participant face à un écran doit donner une réponse dès qu'une cible apparaît dans l'une des deux localisations spatiales possibles en laissant son regard fixe au centre de l'écran (*figure 1.1*). Avant l'apparition de la cible, un indice central (présenté au centre de l'écran à l'endroit où les participants ont la consigne de porter leur regard) peut être présent. Cet indice indique avec 80% de probabilité la bonne localisation de la cible (essai valide). Dans 20% des cas, l'indice indique la mauvaise localisation (essai invalide). En calculant le temps de réaction des différents essais, Posner observe que le temps moyen de réaction pour la détection de la cible dans les essais invalides et valides est respectivement plus long et plus court en comparaison à la condition neutre, c'est-à-dire sans indice. Il conclut que l'attention endogène déployée par le participant vers la cible grâce à l'indice lui permet de traiter celle-ci plus rapidement. A l'inverse, orienter son attention au mauvais endroit l'oblige à une réorientation attentionnelle et allonge son temps de réaction.

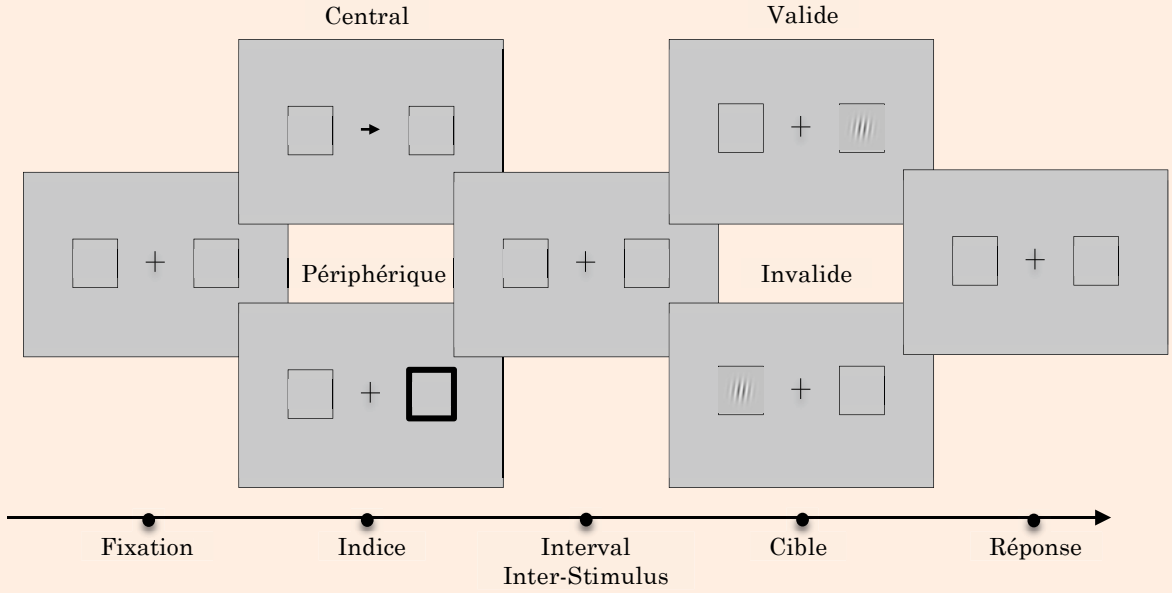


FIGURE 1.1 : PARADIGME DE POSNER.

Le participant doit fixer la croix centrale pendant l'ensemble de l'essai et répondre à l'apparition d'une cible. Un indice central ou périphérique prédisant avec un certain pourcentage l'apparition de la cible va apparaître peu de temps avant celle-ci. Suivant les différentes conditions et le temps entre l'indice et la cible, l'indice va diminuer ou augmenter les temps de réaction, reflétant l'orientation de l'attention.

L'utilisation d'indices périphériques (présentés hors de la région de fixation) et non-prédictifs (ne prédisant pas mieux que le hasard la position de la cible) permit d'observer l'effet comportemental du déplacement exogène de l'attention. Jonides et Irwin montrèrent que l'utilisation de tels indices capables de capturer l'attention de façon involontaire, en comparaison à un indice central, produit des temps de réaction plus rapides et une différence plus grande entre le bénéfice temporel des essais valides et le coût des essais invalides. Dans certaines conditions, les participants avaient pour consigne d'ignorer les indices centraux ou périphériques. Il s'avère qu'ils ont été incapables d'ignorer les indices périphériques, ce qui défend une vision automatique et non-volontaire de ce type d'engagement attentionnel (Jonides & Irwin 1981). Cependant,

plusieurs résultats démontrant la modulation des effets de l'attention exogène par une composante endogène ou par différentes tâches viennent suggérer que ce déploiement n'est pas complètement automatique (Yantis & Jonides 1990; Theeuwes 1991). De nombreuses autres expériences ont vu le jour afin de définir les liens et les différences entre attention endogène et exogène (pour une revue, voir Chica et al. 2013). Lorsque les indices sont non-prédictifs et périphériques, ce qui implique l'engagement de l'attention exogène seulement, et que le temps entre l'indice et la cible dépasse une certaine durée (de 300 à 700 ms suivant la tâche (Lupiáñez et al. 1997)), l'effet inverse se produit et les temps de réaction sont plus courts pour les essais invalides que pour les essais valides. Ce processus connu sous le nom d'inhibition de retour (Posner et al. 1985; Klein 2000; Lupianez et al. 2006) servirait à inhiber l'exploration d'une localisation spatiale déjà parcourue au profit du reste du champ visuel, et donc à favoriser des comportements de recherche visuelle dans des régions non explorées.

Les deux types d'attention, endogène et exogène, montrent parfois des effets perceptuels communs, par exemple une amélioration de la sensibilité au contraste (Ling & Carrasco 2006a). Mais de nombreuses différences ont également été observées dans la mise en place et les effets de ces deux types d'attention. Alors que l'attention endogène nécessite un temps de déploiement plus long d'environ 300 ms et peut se maintenir sur une longue période, l'attention exogène est transitoire et décroit rapidement après un pic autour de 120 ms après l'engagement de celle-ci, pour être ensuite suivie du phénoméne d'inhibition de retour (Müller & Rabbitt 1989). Ces différences d'automaticité et de déploiement temporel suggèrent des rôles et des fonctions différentes. L'attention exogène, qui permet une réaction rapide et automatique à un changement dans l'environnement, pourrait être phylogénétiquement plus ancienne (Carrasco 2011). Finalement, contre les théories fondatrices de l'attention dans les années 1980 qui ont postulé que l'attention est un mécanisme unique qui peut se déployer de façon endogène ou exogène, plusieurs études récentes observent des dissociations dans les effets obtenus par ces deux types d'attention (Klein & Shore 2000; Funes et al. 2007) et proposent une approche séparée de ces deux processus attentionnels (Chica et al. 2013).

1.3. L'ATTENTION AGIT TOUT LE TEMPS, MAIS SUR QUOI ?

Quoi que disent les professeurs de tout temps, un élève éveillé et en bonne santé n'est jamais dépourvu d'attention au sens cognitif du terme. Que ce soit de façon volontaire ou non, son cerveau est constamment en train de sélectionner certains sons et voix, certaines idées ou pensées, et finalement lui fera préférer écouter la leçon du jour ou observer ses amis jouer dans la cour. Il en va de même chez tous les individus. L'attention est présente dans tous nos comportements et influe à chaque seconde, et à une échelle de temps plus courte, l'ensemble de nos processus cognitifs et donc nos actions et perceptions.

Les effets de l'attention, exogène ou endogène, sur les performances visuelles ont été extensivement étudiés. L'amélioration du temps de détection de cibles visuelles lors d'une orientation attentionnelle est d'ailleurs souvent la preuve expérimentale de la présence de celle-ci. Elle conduit également à l'endroit où elle est orientée à une augmentation des capacités de localisation, de détection ou de discrimination de cibles visuelles (Yeshurun & Carrasco 1998; Carrasco et al. 2000). Cependant, il est difficile de savoir par quel mécanisme cette modulation se fait. L'augmentation de ces performances visuelles peut provenir d'une amélioration perceptive de bas niveau, ou d'une augmentation de la perception subjective (consciente) de la cible, ou encore d'une plus grande efficacité dans la prise de décision. De plus, chacune de ces possibilités n'est pas exclusive. L'influence de l'attention sur l'un de ces niveaux peut entrainer des effets sur l'un

ou plusieurs des autres niveaux. S'il est donc bien établi que l'attention augmente les performances visuelles dans des tâches variées, la nature de ces processus et les niveaux sur lesquels l'attention s'exerce ne sont pas bien connus.

1.3.1. APPORT COMPORTEMENTAL

Au niveau visuel, deux mécanismes principaux ont été décrits pour expliquer l'amélioration des performances par l'attention. Le premier repose sur l'amplification du signal du stimulus, permettant donc un meilleur traitement de celui-ci. C'est la théorie d'augmentation du signal. Le deuxième mécanisme est la réduction du bruit extérieur en filtrant les entrées visuelles de non-intérêt. Diminuer le bruit autour du stimulus cible permet également d'améliorer le traitement de la cible. Ces deux mécanismes conduisent à de meilleures performances visuelles mais dans des situations différentes. En l'absence de bruit externe, le mécanisme basé sur la réduction de celui-ci n'a évidemment pas d'effet et seul le premier mécanisme peut permettre d'améliorer le traitement de la cible. En présence de ce bruit en revanche, l'augmentation du signal dans la région spatiale ou l'attention s'est posée n'a que peu d'effet car le stimulus et le bruit sont également amplifié. En revanche, le deuxième mécanisme permet d'atténuer ce bruit externe et donc les performances visuelles sur la cible (Carrasco 2011).

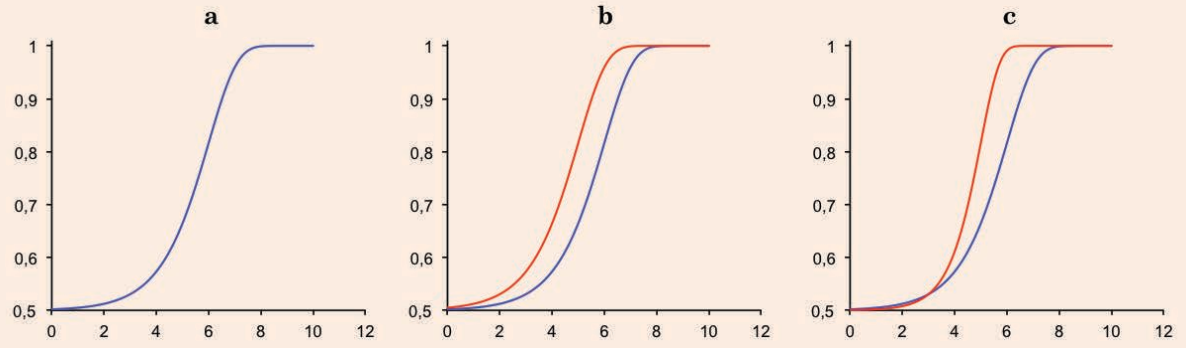


FIGURE 1.2 : COURBE DE SENSIBILITE AUX CONTRASTES ET MECANISMES DE MODULATION ATTENTIONNELLE

***a** Performances visuelles représentées par une sigmoïde (fonction Gumbel) avec le contraste en abscisse et le pourcentage de réponses correctes en ordonnée. **b.** Modulation attentionnelle par mécanisme de gain en contraste représenté par la courbe rouge. Le déplacement vers la gauche de la courbe signifie une amélioration des performances. Dans ce modèle, l'amélioration ne dépend pas de la valeur du contraste. **c.** Modulation attentionnelle par un mécanisme de gain en réponse représenté par la courbe rouge. Il y a toujours une amélioration des performances mais qui, cette fois, augmente avec la valeur du contraste.*

Deux mécanismes d'augmentation du signal ont été proposés. Les performances visuelles sont fréquemment représentées par une courbe en forme de sigmoïde qui exprime les performances du participant en fonction d'un paramètre physique du stimulus (souvent de façon logarithmique), par exemple le contraste (*figure 1.2.a*). Les deux mécanismes possibles n'ont pas le même effet sur la courbe de performance. Le premier, le gain en contraste, est une amplification du signal qui ne dépend pas de l'intensité du contraste. La courbe subit donc un déplacement général vers la gauche synonyme d'une amélioration constante quel que soit

l'intensité du contraste (*Figure 1.2.b*). Le deuxième, le gain en réponse, est une amplification proportionnelle à l'intensité du contraste. Il prédit une modulation par l'attention plus grande à haute qu'à basse performance (*Figure 1.2.c*). Il est possible de trouver des résultats d'expériences donnant raison soit au premier mécanisme (Reynolds et al. 2000; Reynolds & Chelazzi 2004; Ling & Carrasco 2006b) soit au deuxième (McAdams & Maunsell 1999; Ling & Carrasco 2006b; Barbot et al. 2011). Certaines données suggèrent que l'attention endogène opère par gain de contraste alors que l'attention exogène agit par gain en réponse (Pestilli et al. 2007; Carrasco 2009).

Cette augmentation des performances visuelles s'accompagne-t-elle d'une expérience subjective différente ? Autrement dit, est-ce que l'attention altère notre perception consciente ? L'attention spatiale a longtemps été considérée comme une condition préalable importante à la perception consciente (Posner 1994) et reste une porte d'accès privilégiée à notre conscience perceptive, que ce soit grâce à une augmentation du signal perceptif ou un accès facilité à une représentation consciente. Carrasco et al. ont étudié ces changements subjectifs par un ingénieux paradigme permettant d'estimer les corrélats phénoménologiques de l'attention. En présentant simultanément deux cibles et en demandant au participant d'indiquer l'orientation des lignes de la cible qui a le contraste le plus fort, ils ont observé que l'attention exogène augmentait le contraste apparent d'une cible, autrement dit sa perception subjective (Carrasco et al. 2004). Les paradigmes de cécité attentionnelle ont également montré que des changements saillants dans un environnement visuel ne sont pas toujours détectés lorsqu'ils sont inattendus, même s'ils sont présentés dans la région fovéale (Mack & Rock, 1998). Enfin, un argument soutenant un lien causal entre attention et conscience provient également des patients atteints d'une héminégligence visuo-spatiale qui, à la suite d'une lésion, plus fréquemment dans l'hémisphère droit, sont dans l'incapacité d'orienter leur attention dans l'hémichamp controlatéral à leur hémisphère lésé, ce qui les rend inconscients à des stimuli présentés dans cet espace (Bartolomeo 2007). Ces données suggèrent que l'attention est nécessaire pour la perception consciente d'un objet (Mack et al. 2002).

Cependant, des dissociations entre certaines formes d'attention et la perception consciente ont été mises en évidence. Par exemple, Kentridge et al. (Kentridge et al. 1999) ont démontré de façon très intéressante chez un patient avec des lésions au niveau du cortex visuel primaire que l'attention pouvait être déployée et pouvait améliorer les temps de réponse, même en l'absence de perception consciente de l'indice ou de la cible. Les études de Chica et al. montrent des effets différents des deux types d'attention sur l'accès à la conscience. Si l'attention endogène peut être dissociée facilement de la perception consciente, l'attention exogène apparait jouer un rôle important dans la sélection de l'information pour l'accès à la conscience (Chica et al. 2011).

Schneider et al. ont cependant suggéré qu'il y avait un biais dans les résultats de modulation de la perception subjective par l'attention observés par l'équipe de Carrasco (Carrasco et al. 2004; Anton-Erxleben et al. 2010). En changeant le type de questions posées aux participants (« Les deux cibles ont-elles le même contraste ? » *vs.* « Quel contraste est le plus élevé ? »), ils ont proposé que le phénomène observé était lié à une modulation des mécanismes de décision (Schneider 2011).

1.3.2. Apport neurophysiologique

Comment l'attention sélective permet-elle la sélection d'un stimulus plutôt qu'un autre au niveau neuronal ? Les champs récepteurs augmentent en taille lorsque l'on part de V1 et que l'on progresse vers la voie visuelle ventrale à travers V2, V4 puis jusqu'au cortex temporal inférieur. Il y a donc apparemment plus d'informations spatiales traitées par un neurone au fur à mesure que

le signal avance dans cette route. Moran et Desimone posent donc la question de savoir comment le système visuel limite le traitement des stimuli non pertinents (Moran & Desimone 1985). Ils ont répondu à cette question en enregistrant individuellement l'activité de plusieurs neurones visuels spécifiques à un paramètre du stimulus, par exemple une couleur ou une orientation, dans les aires V4 et le cortex temporal inférieur chez le singe. Les résultats montrent une modulation de la réponse des neurones en fonction de l'orientation attentionnelle du singe. En particulier, la réponse d'un neurone répondant à un stimuli particulier dans son champ récepteur est fortement atténuée si ce stimulus est ignoré, c'est-à-dire si l'attention est dirigée vers un stimulus différent présenté dans le même champ récepteur. Une modulation de l'activité neuronale par l'attention spatiale dans les régions visuelles V1, V2 et V4 a également été montrée (Motter 1993) en utilisant plusieurs stimuli dans des champs récepteurs différents. Les études suivantes ont cependant appuyé le fait que les effets attentionnels dans l'aire V4 étaient plus importants lorsque la cible et le distracteur étaient en compétition dans le même champ récepteur (Desimone & Duncan 1995; Luck et al. 1997; Maunsell & Treue 2006). Cette compétition cellulaire au niveau des aires visuelles des singes met en lumière un mécanisme attentionnel neuronal capable de sélectionner et de filtrer des informations. Cohen et Maunsell ont également montré en enregistrant plusieurs dizaines de neurones simultanément dans la région V4 de deux macaques que l'attention augmente les performances en réduisant les corrélations inter-neuronales, suggérant un impact de l'attention sur la communication entre les neurones (Cohen & Maunsell 2009).

Chez l'Homme aussi, les preuves d'une activité visuelle ne dépendant pas seulement des entrées rétiniennes a été démontré. Plusieurs études en IRMf ont enregistré une activité dépendante de l'orientation attentionnelle dans le système visuel (Gandhi et al. 1999; Somers et al. 1999) et ceci même en l'absence de stimuli (Kastner et al. 1999). Brefczynski et DeYoe ont montré que le déplacement de l'attention active des régions du cortex visuel primaire en préservant son organisation rétinotopique (Brefczynski & DeYoe 1999). La compétition attentionnelle pour la sélection d'un stimulus parmi d'autres, observée au niveau cellulaire chez le singe, a également été observée le long de la voie visuelle ventrale chez l'Homme. Lorsque plusieurs stimuli visuels sont présentés simultanément, les représentations corticales dans la voie de la reconnaissance des objets interagissent en s'inhibant mutuellement. L'attention permet de préserver la représentation d'un stimulus contre l'influence inhibitrice des représentations voisines (Kastner et al. 1998). Une modulation attentionnelle de l'activité neuronale a également été observée dans des structures sous-corticales comme le noyau géniculé latéral (O'Connor et al. 2002) ou le colliculus supérieur (Gattass & Desimone 1996; Schneider & Kastner 2009).

Les techniques d'électrophysiologie comme l'Electroencéphalographie (EEG) ou la Magnétoencéphalographie (MEG) ont également été en mesure d'enregistrer des signatures physiologiques de l'attention visuo-spatiale. L'activité dans la bande alpha (8-12 Hz) dans les régions visuelles ou motrices a longtemps été considérée comme une activité de repos. Fermer les yeux augmente la puissance spectrale de l'activité occipitale dans cette bande de fréquence (Berger 1929; Hari et al. 1997). Plusieurs études ont démontré une corrélation négative entre la puissance du signal dans cette même bande de fréquence dans les régions postérieures du cerveau et les performances de détection visuelle. Plus l'activité cérébrale à la fréquence alpha est faible, plus les performances de détection sont élevées (Ergenoglu et al. 2004; van Dijk et al. 2008). De façon intéressante, lorsque l'on oriente l'attention du participant avant l'apparition de la cible, on observe une modulation de l'activité cérébrale à cette fréquence dans les régions occipitales ou pariéto-occipitales. Cette activité oscillatoire diminue dans l'hémisphère controlatéral à l'orientation attentionnelle et augmente ou diminue moins fortement dans l'hémisphère ipsilatéral (Worden et al. 2000; Thut et al. 2006; Wyart & Tallon-Baudry 2008). De plus, une relation a été observée entre la phase de ces oscillations dans les régions visuelles et la

probabilité de détecter une cible (Busch et al. 2009; Mathewson et al. 2009). Les chances qu'un stimulus visuel soit perçu sont maximales lors d'une courte fenêtre temporelle revenant de façon cyclique avec une période correspondant au rythme alpha. Enfin, Womelsdorf et al. ont observé que le degré de synchronisation dans la bande gamma (40-70 Hz) évoquée par le stimulus dans les aires V4 du singe pouvait prédire le temps de réponse à cette cible (Womelsdorf & Fries 2006).

Ces études proposent un mécanisme attentionnel oscillatoire qui module la puissance et la synchronisation des neurones à des fréquences spécifiques et influence notre perception. Cependant, nous ne connaissons pas comment et à quel niveau précis l'attention spatiale module les processus de synchronisation entre les aires frontales, pariétales et occipitales. Nous reviendrons sur ces phénomènes dans le *Chapitre 3* dédié aux rythmes cérébraux.

1.4. RESEAU DORSAL ET VENTRAL DE L'ATTENTION

De nombreuses études de neuroimagerie ont mis en évidence chez l'Homme un réseau dorsal de l'attention. Etonnamment, ce réseau est commun à l'engagement attentionnel *covert,* c'est à dire sans déplacement du regard, et aux saccades oculaires (Corbetta et al. 1998). Ce réseau dorsal est présent dans les deux hémisphères, bien qu'il présente des asymétries fonctionnelles locales (Petit et al. 2009), et se compose des champs oculomoteurs frontaux (FEFs) situés au niveau du sillon précentral à la jonction avec le sillon frontal supérieur, des champs oculomoteurs supplémentaires (en anglais *Supplementary Eye Fields*, SEFs) situés le long de la scissure inter-hémisphérique à hauteur du FEF et enfin des sillons intra-pariétaux (en anglais *IntraParietal Sulcus*, IPS). A la fin des années 90, deux hypothèses quant au rôle du cortex pariétal dans les processus attentionnels sont présentes. La première postule que le cortex pariétal, et en particulier l'IPS est engagé lors de l'orientation volontaire de l'attention. Cette hypothèse est soutenue par des données chez le singe qui montrent une augmentation de la fréquence de décharge des neurones dans cette région lorsque ces singes attendent un stimulus dans une localisation spatiale définie (Colby et al. 1996; Snyder et al. 1997). Chez l'Homme, le lobule pariétal supérieur, comprenant IPS, s'active également lorsque les participants portent volontairement leur attention dans un endroit de l'espace, avec ou sans mouvements oculaires (Corbetta 1993; Gitelman et al. 1996; Nobre et al. 1997; Corbetta et al. 1998). Le deuxième rôle proposé du cortex pariétal dans l'attention provient des données de neuropsychologie sur des patients atteints d'une héminégligence visuo-spatiale. Les études de groupes de ces patients ont conclu que les lésions à l'origine de ce déficit, à priori attentionnel, se rencontraient fréquemment au niveau du cortex pariétal inférieur et de la jonction temporo-pariétale (TPJ) (Vallar 2001; Mort et al. 2003), suggérant pour ces régions cérébrales un rôle important dans la mise en place de l'attention, et en particulier dans la réorientation de celle-ci. D'autres études ont conclu à un rôle du lobe temporal supérieur (Karnath et al. 2001) ou une implication des fibres de matière blanche fronto-pariétale dans le syndrome de négligence visuo-spatiale (Bartolomeo et al. 2007; Doricchi et al. 2008; Urbanski et al. 2008). Cette double dissociation proposée entre orientation et maintien volontaire de l'attention et la partie supérieure du lobe pariétal d'un coté, et la réorientation de l'attention et la partie inférieure du cortex pariétal de l'autre, fut testée dans un paradigme d'IRM fonctionnelle en évènementiel permettant de séparer dans un même essai différents évènements (Corbetta et al. 2000; Hopfinger et al. 2000). Les données de Corbetta et al. montrèrent que l'IPS est actif pendant la période précédant la cible (orientation attentionnelle volontaire) alors que la jonction temporo-pariétale (TPJ) droite est plus fortement activée lors de l'apparition de la cible à un endroit inattendu (réorientation attentionnelle). Ces premières données de neuroimagerie lancèrent l'observation d'un réseau ventral latéralisé à droite activé spécifiquement lors de la réorientation de l'attention, composé de la partie inférieure du cortex

pariétal (en anglais *Inferior Parietal Lobule*, IPL et *Temporo-Parietal Junction*, TPJ) et du gyrus frontal inférieur (en anglais, *Inferior Frontal Gyrus*, IFG) (Corbetta & Shulman 2002) (*Figure 1.3)*. Un rôle plus général de commutateur a été proposé pour ce réseau ventral qui permettrait la bascule de l'activité entre différents réseaux (Corbetta et al. 2008).

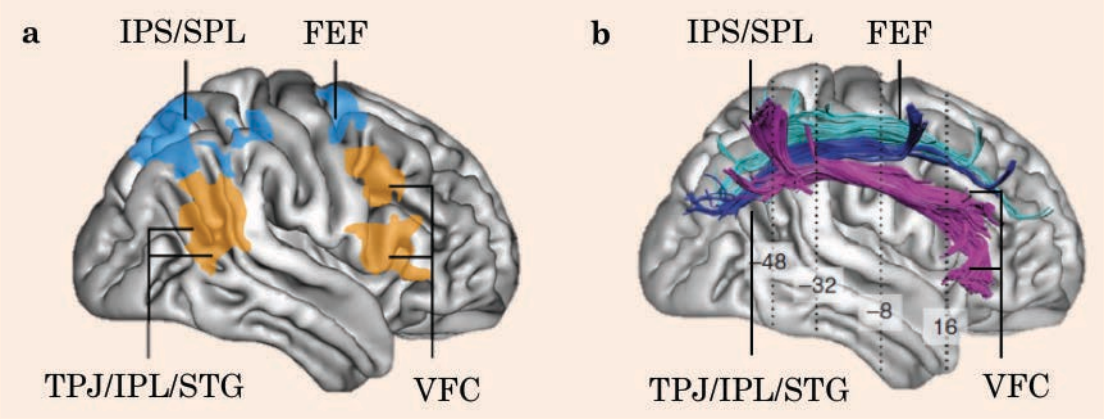


FIGURE 1.3 : RESEAUX DORSAL ET VENTRAL DE L'ATTENTION SPATIALE

***a.** Localisation topographique des deux réseaux de l'attention visuelle spatiale. Le réseau dorsal est en bleu et le réseau ventral est en orange. **b.** Connections anatomiques des 3 branches du faisceau longitudinal supérieur (SLF) qui connecte les lobes pariétaux et frontaux. Les terminaisons corticales de la branche 1 (turquoise) correspondent au réseau dorsal de l'attention, celles de la branche 3 (violet) au réseau ventral et la branche 2 (bleue) pourrait connecter ces deux réseaux ensemble. Adaptée de Corbetta et Shulman (2002) et Thiebaut de Schotten et al. (2011).*

CHAPITRE 2. ANATOMIE, CONNECTIVITE ET STIMULATION DES CHAMPS OCULOMOTEURS FRONTAUX

Le cerveau fonctionnel, qui nous permet de marcher, parler, prendre conscience ou ressentir apparaît comme relativement opaque. Malgré les avancées neuroscientifiques récentes, nous connaissons encore peu des processus qui permettent au cerveau de réaliser ces opérations extrêmement complexes. En revanche, nous connaissons relativement bien le cerveau anatomique. Nous allons nous intéresser ici aux connexions anatomiques existantes entre la région des champs oculomoteurs frontaux (FEFs) et le reste du cerveau, en particulier les régions et structures appartenant au système visuel et visuo-attentionnel. Cette région que nous avons stimulée, au centre du système visuo-attentionnel, est localisée dans le lobe frontal. La liste des fonctions cognitives dans lesquelles son implication a été proposée peut être longue : vision, mémoire spatiale, accès à la conscience, recherche visuelle et carte de saillance spatiale, processus de prise de décision, etc. Le point de vue anatomique ici adopté permet de s'affranchir provisoirement des hypothèses sur les compartiments cognitifs qui permettent de modéliser le fonctionnement de nos capacités cognitives. Cette approche ne suffit évidemment pas pour une explication complète de nos processus mentaux mais permet une description définie exclusivement par une réalité physique et non soumise aux entrelacements de modules fonctionnels spécifiques.

2.1. LE SYSTEME VISUEL

Chez les primates, la vision est l'un des sens les plus développés et ceci explique pourquoi les aires visuelles chez le macaque représentent plus de la moitié du cortex (Knierim and Van Essen 1992) et environ 20% chez l'Homme (Wandell et al. 2007). Le cortex visuel contient un grand nombre de régions distinctes, organisées de façon hiérarchique et correspondant à différents niveaux de traitement. Felleman et Van Essen ont décrit chez le macaque un total de 305 connections, pour la majorité bidirectionnelles, entre 32 régions visuelles primaires ou associatives (Felleman & Van Essen 1991)(*Figure 2.1*). La description du système visuel ici n'a pas comme objectif de dépeindre un tableau complet de l'architecture de ce réseau cérébral mais simplement de donner un aperçu pour comprendre comment une région frontale peut venir influencer le traitement perceptif visuel. L'entrée de la lumière dans notre cerveau se fait par la rétine, mince membrane couvrant la face interne du globe oculaire. Elle est équipée de photorécepteurs qui, par transduction, codent l'information portée par les photons qui atteignent la rétine en signaux électrochimiques. Ces signaux vont être intégrés à ce stade par des neurones présents dans la rétine, les cellules ganglionnaires, qui conduisent cette information visuelle le long de leur axone jusqu'aux différents centres sous corticaux de la vision. Ces faisceaux d'axones issus des cellules ganglionnaires de la rétine sont appelés nerfs optiques. Ils se rejoignent au niveau du chiasma optique pour permettre la décussation d'une partie des axones. Après ce passage, l'information visuelle du champ visuel gauche sera traitée par l'hémisphère droit et inversement. Le faisceau d'axones après le chiasma optique contenant l'information de chaque hémichamp visuel dans son hémisphère opposée est appelé tractus optique. Les signaux neuronaux de ce faisceau voyage vers un noyau du thalamus, le corps géniculé latéral, principal

relais entre la rétine et le cortex visuel. Après ce premier traitement, les radiations optiques quittent le thalamus pour rejoindre le cortex strié, également appelé V1, première étape corticale du traitement visuel. L'information visuelle est traitée ici de façon rétinotopique pour ensuite suivre différentes voies neuronales. Le cortex occipital se compose d'une succession de régions fonctionnelles à partir de V1 qui procèdent à un traitement de l'information de plus en plus intégré. Mishkin et Ungerleider (Mishkin & Ungerleider 1982) ont proposé une distinction entre une voie dorsale liée à la vision dans l'espace et une voie ventrale liée à la vision des objets. La voie dorsale se compose entre autre de l'aire temporale médiane (MT) qui contribue de façon importante à la perception du mouvement et des aires intra-pariétales ventrales (an anglais *Ventral IntraParietal*, VIP) et latérales (en anglais *Lateral IntraParietal*, LIP). La voie ventrale qui se dirige vers le cortex temporal se compose de l'aire V4 puis du cortex inféro-temporal. Une partie des fibres rétiniennes cependant ne passe par le corps géniculé latéral. Environ 10% projettent d'abord sur le colliculus supérieur pour ensuite rejoindre le cortex. Cette voie rétinotectale serait à l'origine de la vision aveugle détectée chez certains patients lésés au niveau du cortex visuel primaire. Malgré l'impossibilité de détecter consciemment l'environnement visuel, ces patients sont capables de répondre en partie à des stimuli non détectés consciemment (Poppel et al. 1973). Enfin, une partie de l'information rétinienne rejoint d'autres centres sous-corticaux comme le noyau supra-chiasmatique, qui joue un rôle important dans le contrôle des rythmes circadiens, ou le pretectum.

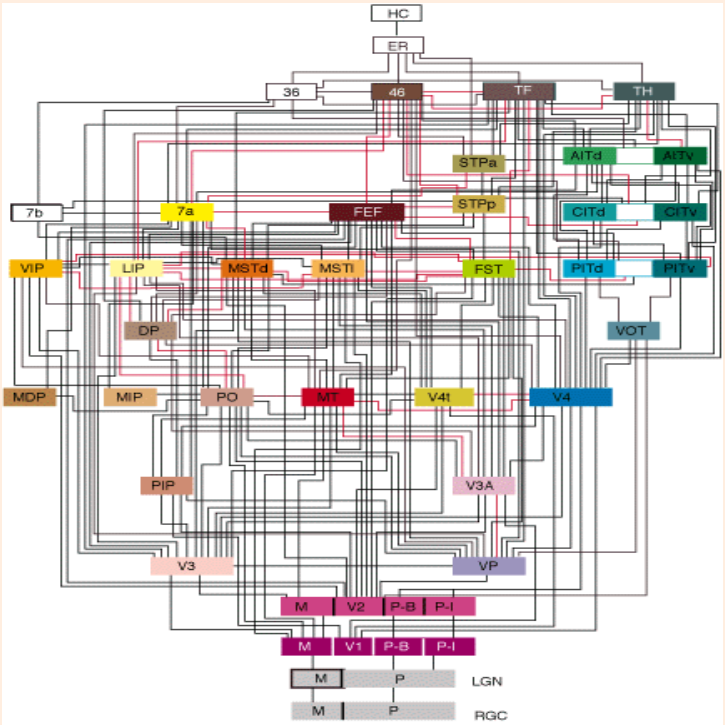


FIGURE 2.1 : CONNEXIONS ANATOMIQUES ENTRE LES REGIONS DU SYSTEME VISUEL.

305 connexions anatomiques reliant 32 aires visuelles distribuées en 10 niveaux hiérarchiques chez le macaque. Ce réseau pourrait constituer plus de la moitié du cortex chez cet animal. Adaptée de Felleman et Van Essen (1991).

Les FEFs, bien que plus antérieurs que l'ensemble des aires visuelles, font aussi partie de ce système. D'après Schmolesky et al. qui ont conduit des enregistrements cellulaires chez des macaques anesthésiés, les neurones des FEFs répondent à une information visuelle en moyenne en même temps que les aires V3 et MT et avant V2 et V4 (Schmolesky et al. 1998).

2.2. LES CHAMPS OCULOMOTEURS FRONTAUX

L'histoire des champs oculomoteurs frontaux commence avant le début du XXe siècle. A cette époque, et afin de montrer que le cerveau contient des régions capables d'opérer une fonction spécifique, plusieurs études de stimulation directe du cortex par courant électrique ont lieu chez l'animal. En 1874, lors d'expériences sur le singe, Ferrier observe après stimulation du gyrus frontal moyen un mouvement de la tête et des yeux et une dilatation des pupilles (Ferrier 1873). Dans son livre *The Functions of the Brain* publié en 1886, il nous propose une homologie des régions fonctionnelles entre le singe et l'Homme (Ferrier 1886). On y retrouve cette région frontale impliquée dans le mouvement du regard (*Figure 2.2*). Cinquante ans plus tard, les travaux de Penfield, par une approche électrophysiologique et cytoarchitectonique, ont défini la région FEF dans l'aire 8 de Brodmann au niveau de la partie postérieure du gyrus frontal moyen (Penfield & Boldrey 1937; Penfield & Erickson 1941). Depuis, et grâce aux techniques récentes d'imagerie cérébrale, la localisation des champs oculomoteurs frontaux chez l'Homme s'est précisée et se définit comme la jonction entre le sillon frontal supérieur et le sillon précentral. La bordure postérieure du sillon précentral au niveau de la partie supérieure du gyrus précentral contient une large proportion de neurones pyramidaux dans la couche V, spécificité retrouvée chez le singe dans la région FEF (Rosano et al. 2003).

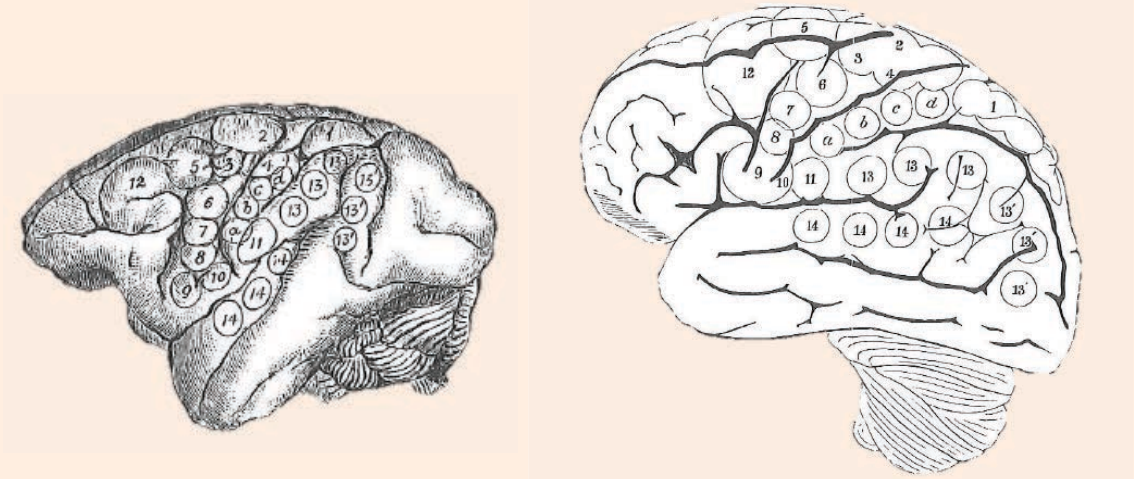


FIGURE 2.2 : HOMOLOGIE ENTRE LE CERVEAU D'UN SINGE ET D'UN HOMME EN 1886 PAR FERRIER

La région 12 représente la région produisant des mouvements latéraux des yeux et de la tête avec une dilatation des pupilles après stimulation électrique. Adaptée de Ferrier 1886.

La connectivité anatomique de cette région avec le reste du cerveau a largement été étudiée chez le singe par l'utilisation de traceurs neuronaux. Stanton et al. ont ainsi montré chez le macaque que des connexions partent des FEFs pour rejoindre un grand nombre de régions cérébrales postérieures. On y retrouve la partie latérale et ventrale du sillon, différentes régions visuelles du cortex temporal et les régions V2, V3 et V4 au niveau occipital (Stanton et al. 1995). Au niveau du lobe frontal, des connexions avec cing régions sont détectées, dont une aire contenant les champs oculomoteurs supplémentaires (SEF) (Stanton et al. 1993). Enfin au niveau sous-cortical, la même équipe décrit cinq fibres descendantes ; vers le striatum qui rejoint le noyau caudé au niveau rostral du genou de la capsule interne, vers le claustrum ainsi que des fibres trans-thalamiques, sous-thalamique et pédonculopontine (Stanton et al. 1988). Huerta et al. (Huerta et al. 1987) ont également mis en évidence des connexions réciproques très denses entre les FEFs et la partie caudale du sillon temporal supérieur et le cortex latéral et inférieur du sillon intra-pariétal. De la même façon, Tian et Lynch (Tian and Lynch 1996) concluent que les entrées neuronales principales des FEFs correspondent aux autres champs corticaux visuels, incluant les SEFs et les champs oculomoteurs pariétaux (en anglais *Parietal Eye Fields*, PEFs), et l'aire temporale supérieure moyenne (en anglais *Middle Superior Temporal*, MST). Des connexions par deux routes différentes avec le colliculus supérieur ont également été observées. La première rentre dans la partie postérieure de la capsule interne pour rejoindre le tegmentum puis les couches profondes du colliculus supérieur. La deuxième, plus directe, traverse le thalamus par la lame médulaire interne et les régions para-laminaires pour rejoindre le colliculus supérieur, en particulier sa couche intermédiaire (Leichnetz et al. 1981).

Chez l'Homme, nos connaissances en terme de connectivité anatomique se sont élargies depuis l'apparition de l'IRM de diffusion. Les connexions corticales des champs oculomoteurs frontaux avec les régions postérieures sont assurées par la branche I et II du faisceau longitudinal supérieur (en anglais *Superior Longitudinal Fasciculus,* SLF). Le SLF I connecte, parmi d'autres régions, les FEFs avec le lobule pariétal supérieur tandis que le SLF II connecte les FEFs avec la partie plus ventrale du lobe pariétal et TPJ (Thiebaut de Schotten et al. 2011).

2.3. STIMULATION DES CHAMPS OCULOMOTEURS FRONTAUX

Depuis leur découverte, les champs oculomoteurs frontaux, chez l'humain ou chez l'animal, ont été extensivement stimulés par micro-stimulation intra-corticale ou par stimulation non-invasive afin de déduire le rôle et le fonctionnement de cette région. Chez l'animal, les études ont confirmé le rôle oculomoteur des FEFs en provoquant des mouvements des yeux lors de la stimulation (Robinson & Fuchs 1969; MacAvoy et al. 1991) ou à l'inverse la suppression de saccades visuelles (Izawa et al. 2009) suggérant l'existence de neurone servant à la fixation. Différents types de neurones ont été observés au sein des FEFs dont des neurones moteurs actifs durant les mouvements oculaires, des neurones visuels actifs durant la présentation de stimuli visuels et enfin des neurones visuo-moteurs. Chez l'Homme, les micro-stimulations chez des patients implantés ont également démontré le rôle oculomoteur de cette région frontale (Blanke et al. 2000). La Stimulation Magnétique Transcrânienne (SMT) ne permet pas d'induire des mouvements oculaires (Müri et al. 1991; Wessel & Kömpf 1991) mais des modifications de la latence des saccades ont été observées en particulier pour des saccades volontaires (Thickbroom et al. 1996; Ro et al. 2002).

Au delà de son rôle oculomoteur, le rôle attentionnel des FEFs a été maintes fois démontré. La théorie pré-motrice de l'attention qui propose que l'orientation attentionnelle n'est autre que la préparation des mouvements des yeux place les FEFs au cœur du réseau cérébral

sous-tendant les capacités visuo-attentionnelles. Le rôle des FEFs dans la modulation de l'activité des aires et des performances visuelles, que le mécanisme soit appelé attention ou non, n'est plus à démontrer et est à rapprocher de la forte connectivité que cette aire possède avec l'ensemble du cortex visuel. Ainsi, Moore et Fallah ont observé chez des singes que la micro-stimulation à une intensité moindre que celle capable de déclencher une saccade oculaire permet de faire baisser le seuil de détection d'un stimulus lorsque celui-ci apparaît dans la région de l'espace représenté par le site cortical stimulé (Moore & Fallah 2001). Cette modulation opère donc seulement si la cible se trouve à l'endroit où la saccade se produirait si la stimulation était plus forte. Ces résultats ont été suivis par de ceux de Moore et Armstrong qui ont observé que les réponses visuelles dans l'aire V4 étaient augmentées par des micro-stimulations sous le seuil de déclenchement des saccades suivant la même règle rétinotopique (Moore & Armstrong 2003). De plus, cette stimulation supprime la réponse visuelle dans des régions de V4 qui ne correspondent pas aux champs récepteurs couvrant la région de l'espace où la saccade aurait lieu si la stimulation était assez forte pour l'évoquer. La modulation à la fois de l'activité des régions cérébrales et des performances visuelles par la stimulation des FEFs a également été démontrée chez l'Homme par une expérience combinant l'Imagerie par Résonnance Magnétique fonctionnelle (IRMf) et la SMT. Un train de 5 impulsions à 9 Hz appliqué sur le FEF droit module l'activité des régions visuelles de V1 à V4 avec une augmentation pour la représentation périphérique du champ visuel et une diminution pour la partie centrale (Ruff et al. 2006). Cette stimulation conduit à une modification comportementale cohérente avec la modulation de l'activité visuelle, c'est-à-dire une augmentation des contrastes perçus pour les stimuli périphériques en comparaison aux stimuli centraux. Lors d'une expérience avec deux bobines de SMT, Silvanto et al. ont établi, en calculant l'intensité nécessaire pour laquelle la stimulation de MT/V5 provoque un phosphène, que l'excitabilité de cette région était plus importante 20 à 40 ms après une impulsion de SMT sur le FEF (Silvanto et al. 2006). Enfin, Grosbras et Paus ont montré que la stimulation du FEF droit pouvait faire baisser le temps de réaction à la présentation de stimuli visuels périphériques (Grosbras & Paus 2002) ainsi qu'améliorer la détection consciente de stimuli masqués (Grosbras & Paus 2003).

Même si l'attention ne se limite surement pas à l'activité d'une seule aire à un moment donné, l'ensemble de ces études rapproche fortement les conséquences physiologiques et comportementales de la stimulation de la région FEF de celles de l'orientation attentionnelle.

CHAPITRE 3. RYTHMES CEREBRAUX

3.1. SYNCHRONISATION, ATTENTION ET PERCEPTION

La plupart de nos neurones reçoivent plusieurs milliers d'entrées synaptiques qui conduisent à chaque instant à la construction d'un certain pattern de sortie sous forme de potentiels d'actions. L'intégration synaptique (la transformation de plusieurs milliers de signaux électriques en un changement unique dans le potentiel de membrane) dépend de façon importante de la coordination temporelle des entrées synaptiques (Magee 2000). Ce fonctionnement requiert a priori une synchronisation entre plusieurs neurones et peut apparenter le neurone à un détecteur de coïncidence (König et al. 1996). Cette vision est cependant contestée par Shadlen et Newsome qui considèrent que le *timing* des décharges neuronales ne véhicule que peu ou pas d'information (Shadlen & Newsome 1994).

A un niveau plus intégré, comment différents compartiments cérébraux servant différentes fonctions s'associent pour créer une représentation globale d'une situation ? Il semble raisonnable qu'un mécanisme de coordination temporelle permette l'intégration de ces différents systèmes (Gray 1994). Des études chez le chat ont apporté les preuves d'une activité synchronisée de plusieurs neurones dans le cortex visuel au sein d'une même colonne corticale (Gray & Singer 1989) ou entre différentes colonnes (Gray et al. 1989). Peu de temps après, la même équipe a observé une synchronisation neuronale entre les deux hémisphères au niveau du cortex visuel du chat (Engel et al. 1991). Les auteurs suggèrent que cette synchronisation pourrait être une façon d'établir des relations entre différentes caractéristiques visuelles et permettre l'intégration de ces informations. Ils répondent de cette façon au problème d'intégration, c'est-à-dire à la question de savoir comment sont assemblées différentes caractéristiques d'une scène afin de former une expérience unique (Milner 1974; Singer 2007). A la même époque, Crick et Koch proposent que l'accès à la conscience est fortement lié à une activité neuronale synchronisée (Crick & Koch 1990). Une hypothèse similaire appliquée à des boucles thalamo-corticales sera également postulée (Llinás & Paré 1991). De façon globale, les théories des processus dit *top-down* ont largement utilisé le principe de synchronisation cérébrale. Dans le modèle des zones convergentes de Damasio, une synchronisation dans des aires corticales spécifiques permet la réactivation et l'intégration de différents contenus de niveaux moins intégrés, permettant le rappel de souvenir stockés (Damasio 1989).

Les mécanismes attentionnelles n'influencent pas la synchronisation cérébrale seulement dans les aires visuelles. Il a été proposé que l'attention sélectionne l'information sensorielle en modulant de façon dynamique la cohérence neuronale entre des régions corticales éloignées (Buzsáki and Draguhn 2004; Fries 2005). En accord avec cette hypothèse, différentes études chez le singe et l'Homme ont démontré une synchronisation cérébrale à des fréquences spécifiques entre les régions frontales et pariétales du réseau dorsal de l'attention (Buschman & Miller 2007; Siegel et al. 2008) ainsi qu'entre ces mêmes régions et les région visuelles (Saalmann et al. 2007; Doesburg et al. 2008; Siegel et al. 2008). Buschman et Miller ont observé en particulier chez le singe une synchronisation fronto-pariétal entre 22 et 34 Hz lors d'une recherche visuelle impliquant une orientation endogène de l'attention. En revanche, lors d'une tâche visuelle de type *pop-out*, c'est-à-dire lorsque la cible diffère des distracteurs par au moins deux dimensions – couleur et orientation – la synchronisation entre les mêmes régions s'opérait entre 35 et 55 Hz (Buschman & Miller 2007). De plus, ces résultats suggèrent qu'en condition de recherche visuelle, la sélection *top-down* survient d'abord dans les régions frontales tandis qu'en condition *pop-out*, le

signal apparaît d'abord en pariétal. Une synchronisation fronto-pariétale entre 22 et 34 Hz a également était observée lors de l'orientation endogène de l'attention chez l'Homme (Phillips & Takeda 2009).

De manière générale, des modifications de l'activité oscillatoire ont été reliées à des pathologies cérébrales. L'implication de rythmes anormaux et délétères ont été observé dans plusieurs troubles neurologiques comme l'hémiplégie et la maladie de Parkinson ou neuro-psychiatrique comme la dépression et la schizophrénie (Buzsaki & Watson 2012). Rastelli et al. ont également observé lors d'une étude en MEG avec des patients héminégligents qu'une activité synchronisée entre 13 et 17 Hz était présente dans les régions frontales gauches peu de temps avant l'apparition de cibles dans l'hémichamp droit lorsque celles-ci n'étaient pas perçues par les patients (Rastelli et al. 2013). L'apparition de cette activité rythmique semble prédire l'omission de la cible.

Cependant, et malgré un intérêt grandissant dans les neurosciences cognitives, l'activité oscillatoire cérébrale enregistrée pourrait selon certains auteurs n'être qu'un épiphénomène sans spécificité fonctionnelle (Pareti & De Palma 2004). L'utilisation de la stimulation non-invasive de façon rythmique afin de moduler l'activité oscillatoire pourrait nous permettre d'observer une relation causale entre un rythme cérébral particulier et une conséquence comportementale ou physiologique.

3.2. Synchronisation et connectivite anatomique

Les régions du cerveau s'activent donc à des fréquences spécifiques qui vont de quelques Hz à plus de 100 Hz, de façon parfois cohérente même à distance. Ces activités synchrones sont impliquées dans l'ensemble des processus cérébraux et dépendent de l'état de vigilance d'une personne, de son comportement, de la demande cognitive ainsi que de son état émotionnel. L'ensemble des études que nous avons décrites plus haut a permis d'observer des rythmes cérébraux spécifiques sur des groupes de participants lorsqu'ils sont engagés dans des tâches particulières. Cependant, à la manière des différences anatomiques entre les personnes, les fréquences de synchronisations varient entre les participants au sein d'une même bande de fréquence (Klimesch et al. 2003; Thut et al. 2011). Fründ et al. ont montré que les réponses évoquées dans la bande gamma peuvent fluctuer entre les participants mais est stable entre deux sessions différentes chez le même participant (Fründ et al. 2007).

La synchronisation entre deux entités dépend du temps que l'information met à parcourir la distance qui les sépare. Lorsque deux personnes discutent face à face, le temps que la parole passe de l'un à autre, qui dépend simplement de la distance entre eux et de la vitesse du son, est stable et court. Il peut donc y avoir une synchronisation rapide entre les deux interlocuteurs. Si ces deux personnes discutent à distance par internet avec une connexion hasardeuse, leur discours respectif met plus de temps à leur parvenir et leur fréquence de réponse dans le temps va baisser. Nous pouvons donc penser qu'avec un temps d'intégration synaptique constant et une boucle fermée et directe entre deux régions, la fréquence de synchronisation dépend du temps de communication entre celles-ci. Une autre possibilité est qu'une troisième aire, par exemple le thalamus (Uhlhaas 2009; Gollo et al. 2010), soit à l'origine d'un signal cohérent qui fasse osciller de façon synchrone deux aires distantes sans connexion directe entre elles. Dans tous les cas, une communication efficace et une coordination à travers les réseaux cérébraux demandent une précision temporelle des signaux neuronaux qui dépend des propriétés physiologiques des axones. La vitesse de conduction d'un potentiel d'action résulte directement du diamètre de l'axone et de

sa myélinisation. Il est donc envisageable que des propriétés structurelles de la substance blanche dépend la possibilité de synchroniser des réseaux cérébraux à des fréquences spécifiques. Basé sur cette hypothèse, Zaehle et Herrmann ont observé une corrélation positive entre la densité de matière blanche dans certaines régions du corps calleux et la fréquence des réponses visuelles évoquées dans la bande gamma (Zaehle & Herrmann 2011). L'importance du temps de conduction entre différentes aires dans les oscillations et synchronisations cérébrales a également été pris en compte dans des modèles computationnel (Pajevic et al. 2014). Bien qu'intuitif, le lien entre connectivité anatomique et connectivité fonctionnelle, c'est-à-dire la communication synchronisée entre des régions cérébrales, n'a été que très peu étudié.

CHAPITRE 4. METHODES ET TECHNIQUES

4.1. LA PSYCHOPHYSIQUE

La psychophysique permet d'observer le comportement humain, ses mécanismes et performances, à travers l'étude de la relation entre stimulations sensorielles et perception de ces stimuli. Gustav Fechner qui, en 1850, s'intéressait à la relation entre l'âme et le corps, fit le calcul que l'intensité de la sensation subjective évolue avec le logarithme de l'intensité du stimulus physique. Ces recherches, avec celles de son professeur Weber, sont considérées comme à l'origine de la psychophysique. Bien que ces concepts permettent d'étudier les cinq sens chez l'Homme, nous nous intéresserons en particulier aux principes psychophysiques appliqués au système visuel.

4.1.1. LA TACHE VISUELLE

Nous allons présenter ici un exemple de tâche visuelle permettant de calculer des performances visuelles objectives et subjectives. Cet exemple se base sur le paradigme typique utilisé ensuite au cours de cette thèse et permettra au lecteur de se familiariser avec lui. Il s'appuie sur le paradigme de Posner dont les variantes sont très fréquemment utilisées en neurosciences cognitives (*Figure 1.1)*. Le participant est assis face à un écran d'ordinateur. Après lui avoir présenté des stimuli visuels, il doit répondre à l'aide du clavier à un grand nombre d'essais afin de pouvoir moyenner les réponses et augmenter le pouvoir statistique des mesures. Chaque essai débute par un écran gris pendant quelques secondes, suivi d'une croix de fixation au centre de l'écran et deux carrés placés à droite et à gauche de la croix. Le participant doit laisser son regard fixe sur cette croix durant le temps de l'essai. Après un intervalle de temps qui varie entre 1000 et 1500 ms, la croix de fixation devient légèrement plus large pendant 66 ms afin de prévenir le participant de l'apparition imminente du stimulus d'intérêt. Un stimulus à faible contraste construit de lignes légèrement inclinées (un *gabor*) apparait 233 ms plus tard à droite ou à gauche de façon très brève (33 ms). Après chaque essai, des questions sont posées au participant pour analyser la perception qu'il a eu du stimulus. Ces questions portent sur des caractéristiques de la cible, sa localisation ou la perception subjective que le sujet a eu de celle-ci. Ce type de tâche permet donc d'étudier les performances de discrimination et de détection visuelle. Sur la base de cette expérience type, nous allons ajouter un ou plusieurs évènements et observer si ces éléments modifient les performances des participants. Ces ajouts peuvent être un indice visuo-spatial qui indique avec une certaine probabilité où la cible va apparaître ou encore une impulsion de SMT sur une région corticale peu de temps avant l'apparition de la cible. Dans les études du *Chapitre 6*, nous avons utilisé un contraste au seuil de perception. En faisant varier dans un premier temps ce contraste, nous cherchons la valeur pour laquelle le participant ne détecte consciemment qu'une cible sur deux. Ce niveau de performance est conservé tout au long de l'expérience grâce a des ajustements de contraste si nécessaire. Dans le *Chapitre 8*, nous avons voulu observer l'effet d'une stimulation à différents niveaux de performance. Nous avons donc utilisé des cibles à différents contrastes afin de reconstruire l'ensemble de la courbe de sensibilité visuelle. Cette fonction psychométrique représentée par une sigmoïde se définit par son seuil (point d'inflexion de la courbe, c'est-à-dire l'endroit ou la dérivée seconde est nulle) et sa pente, calculée au seuil. Nous avons utilisé une procédure adaptative basée sur une estimation bayésienne de ces deux paramètres. Les détails des études sont présentés dans les parties *méthodes* de chaque article.

4.1.2. LA THEORIE DE DETECTION DU SIGNAL

La théorie de détection du signal (Green & Swets 1966; Macmillan & Creelman 1991) permet de quantifier la capacité à différencier un stimulus du bruit – ou par extension à différencier deux stimuli. Elle offre donc un modèle de calcul des performances comportementales lors d'expériences de psychophysique. Cette méthode calcule au-delà d'un pourcentage de réponses correctes, une sensibilité perceptuelle (*d'*) et un critère de réponse (β ou *c*) à partir des réponses données. Elle sépare donc les capacités visuelles à proprement parler de la stratégie de réponse utilisée par le participant. Ce modèle prend en compte un bruit interne, ou une incertitude, qui conduit à une représentation du stimulus non pas unitaire le long d'un continuum sensoriel mais comme un échantillon aléatoire tiré d'une certaine distribution. Prenons l'exemple d'une tâche simple de détection visuelle dans laquelle une cible à faible contraste peut, ou non, apparaître sur un écran. Le participant doit dire à chaque essai s'il a vu ou non la cible. Il est possible de séparer les essais où il dit avoir perçu la cible en deux parties (*Figure 4.1.a*). Les essais où la cible est présente (détections correctes) et les essais où la cible n'est pas présente (fausse alarme). A partir de la proportion de ces deux types d'essais il est possible de calculer la *d'* suivant la formule d' = z(Pdc) – z(Pfa), où Pdc représente la proportion de détections correctes et Pfa la proportion de fausses alarmes. Cette grandeur reflète la facilité avec laquelle le participant fait la différence entre le stimulus et son absence. Le critère de réponse qui traduit la stratégie du participant se calcule par la formule c = (z(Pdc)+z(Pfa))/2 ou β = e(((z(Pdc)²)-((z(Pfa)²)/2) (*Figure 4.1.b*).

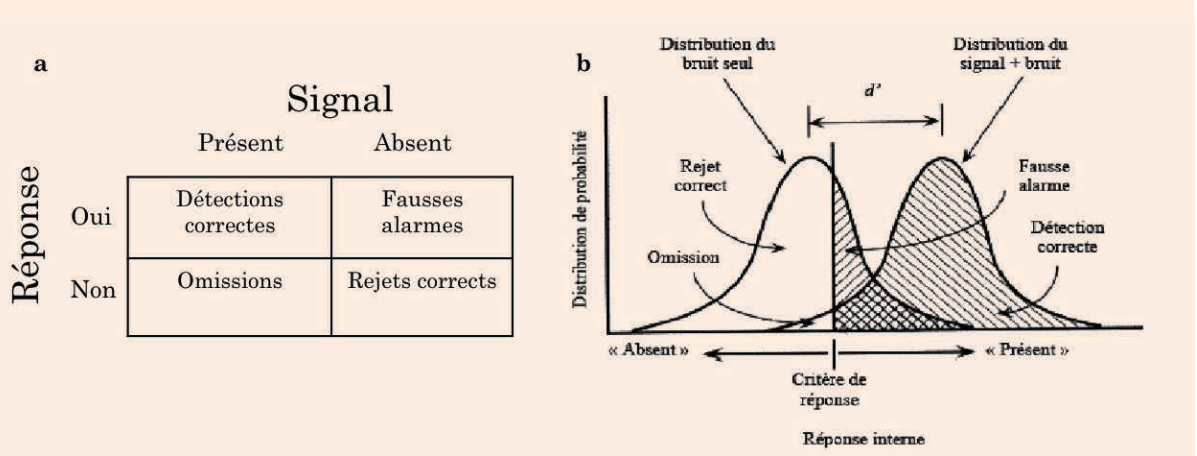


FIGURE 4.1 : ILLUSTRATION DE LA THEORIE DE DETECTION DU SIGNAL.

a. *Tableau regroupant les quatre types de réponses possibles.* ***b.*** *Distribution normale du bruit et du signal+bruit. La sensibilité (d') et le critère de réponse (c) sont représentés en fonction de ces deux courbes. Adaptée de Devinck 2003.*

Si le participant s'assure que la cible est présente pour répondre qu'il a perçu quelque chose en limitant au maximum les fausses alarmes, son comportement est de type conservateur. A l'inverse, s'il répond souvent avoir vu quelque chose même en l'absence du stimulus, alors son comportement est de type libéral. La théorie de detection du signal permet de savoir si un changement de performance est lié à un changement de la sensibilité perceptuelle ou du critère de réponse. L'utilisation de la *d'* permet également de linéariser la courbe psychométrique, ce qui est utile lorsque l'on veut corréler les performances psychophysiques avec une autre dimension

4.2. LA STIMULATION MAGNETIQUE TRANSCRANIENNE

Au cours de cette thèse, nous avons manipulé l'activité cérébrale chez l'Homme à l'aide de la SMT afin d'étudier les processus de modulation visuelle, et en particulier la possibilité d'améliorer la perception visuelle.

L'utilisation de courants électriques pour interagir avec le corps humain n'est pas nouvelle. Certains médecins de l'Empire Romain utilisaient le poisson torpille, animal de fond ayant la capacité de produire de l'électricité, appliqué sur la tête ou le pied pour soigner respectivement les migraines ou la goutte. Cependant, la connaissance des lois de l'électromagnétisme et la maitrise du courant électrique n'étant apparue qu'au XVIIIe siècle, le fonctionnement de ce poisson ainsi que l'idée de ce traitement par décharge devait s'avérer bien éloignés de notre conception moderne de l'électromagnétisme. Galvani et Volta ont montré pendant les années 1790 que l'on pouvait stimuler les nerfs ou les muscles grâce à des courants éléctriques. Ces découvertes sont les prémices de l'ensemble des techniques électromagnétiques qui permettent aujourd'hui de moduler l'activité cérébrale. En alternative au courant électrique direct, qui peut être douloureux et limité par la haute résistance électrique du crâne, l'idée basée sur la découverte récente de l'induction magnétique d'utiliser les courants électriques induit par un champ magnétique a vu le jour à la fin du XIXe siècle (Wagner et al. 2007). Arsonval rapporta voir des phosphènes en plaçant sa tête entre deux bobines alimentées par un courant alternatif. Il s'avéra plus tard que les phosphènes étaient dus à la stimulation directe de la rétine (Rossini et al. 1994). D'autres scientifiques tentèrent l'expérience de stimuler le cerveau par des champs magnétiques (*Figure 4.2*).



FIGURE 4.2 : SYLVANUS P. THOMPSON (A GAUCHE) ET MAGNUSSON OU STEVENS (A DROITE) EN TRAIN DE TESTER UN STIMULATEUR MAGNETIQUE AU DEBUT DU XXE SIECLE.

Adaptée de Walsh & Pascual Leone. 2003.

Il fallut attendre 1985 pour que l'équipe dirigé par Anthony Barker à Sheffield réussisse à développer la technologie nécessaire pour faire traverser le crâne par un champ magnétique assez bref et intense, permettant d'induire de façon indolore un champ électrique à l'intérieur du cerveau capable de dépolariser les neurones, marquant ainsi le début de la Stimulation Magnétique Trancrânienne (Barker et al. 1985). L'induction électromagnétique est un phénomène

physique où une différence de potentiel électrique est créée dans un conducteur électrique soumis à un champ magnétique variable. En neurostimulation, un courant bref et intense (entre 4 et 8 kA déchargé pendant 100 à 200 microsecondes) circule dans une bobine et crée un champ magnétique. Si l'on cible une région particulière du cerveau avec ce champ magnétique, celui-ci traverse le crâne et les méninges pour atteindre le cortex. Le champ magnétique variable induit un champ électrique, dont l'intensité dépend de la variation dans le temps du champ magnétique, qui provoque la dépolarisation des neurones.

Cette technique permet d'agir directement sur l'activité de certaines régions cérébrales et d'établir des relations causales entre des régions anatomiques et leur rôle fonctionnel. La première démonstration de cette technique par Barker et al. en 1985 a consisté à stimuler les aires motrices d'un participant et à observer le mouvement consécutif des muscles correspondant à la région stimulée (Barker et al. 1985). La preuve était faite qu'il est possible d'activer grâce à un champ magnétique une région corticale particulière. Quatre ans plus tard, Amassian et al. utilisent la stimulation magnétique au niveau du cortex visuel primaire et montrent une suppression de la perception visuelle lorsque l'impulsion est appliquée entre 80 et 100 ms après l'apparition d'une cible visuelle (Amassian et al. 1989). Cette première façon d'utiliser la SMT est dite à impulsion unique. Elle permet de stimuler une région du cortex afin de dépolariser les neurones et d'induire un effet comportemental. Sur des régions primaires comme les aires motrices ou les aires visuelles, l'activation de la région par stimulation est directement perceptible grâce au mouvement induit des muscles ou l'apparition de phosphènes. Appliqués au niveau d'aires associatives, le résultat comportemental est moins directe et sera mesuré lors de tâches psychophysiques. L'effet de la stimulation sera comparé à une condition sans stimulation réelle. Ainsi, remarquer des différences comportementales entre la condition avec et la condition sans stimulation permet d'inférer une relation causale entre la modulation comportementale obtenue et le rôle de la région stimulée (Valero-Cabre et al. 2011). Le rayon d'action de la SMT à été estimé dans des études de marquage d'activité par 2-Deoxyglucose chez l'animal entre 10 et 15 mm^2 (Valero-Cabré et al. 2005, 2007). Cependant, la modélisation du champ magnétique sur la surface corticale suggère qu'au-delà de la petite aire corticale qui se trouve au niveau du pic du champ magnétique, des régions sur une surface de 1 à 2 cm^2 peuvent être affectée (Wagner et al. 2009). La résolution temporelle est de l'ordre de la milliseconde, ce qui permet une excellente précision pour l'étude de la dynamique temporelle des fonctions cognitives. La latence des enregistrements par l'espace péridural de l'activité des neurones dans la moelle épinière après stimulation du cortex moteur a suggéré que les neurones les plus sensibles à la SMT étaient les interneurones qui, après une connexion synaptique, permettaient l'activation des neurones moteurs cortico-spinaux (Di Lazzaro et al. 2012).

Au-delà de l'utilisation de la SMT par impulsion unique, il est également possible d'utiliser la SMT de façon répétée, c'est-à-dire pendant un temps plus long sans interruption, pour induire un changement relativement durable de l'excitabilité de la région. Les effets de ce type de stimulation, selon les paramètres de stimulation et notamment le temps de stimulation, la fréquence et l'organisation des rafales d'impulsions dans le temps, peuvent induire des effets excitateurs ou inhibiteurs de la région ciblée et de son réseau associé qui peuvent durer plusieurs minutes après la stimulation. Il est donc possible de provoquer un changement dans le temps de l'activité cérébrale. La SMT répétitive est utilisée dans certaines pathologies comme la dépression sévère ou la schizophrénie (Wagner et al. 2007). Nous n'avons pas utilisé cette dernière méthode de stimulation dans ce travail de thèse. Appliquée chez le chat, elle a permis d'observer des modulations de la consommation de glucose dans la région stimulée mais également dans des régions distantes connectées de façon anatomique à la région cible (Valero-Cabré et al. 2005).

Cette technique est utilisée dans un nombre croissant de laboratoire de neurosciences cognitives et de services hospitalier depuis bientôt 30 ans. Il existe plusieurs limites à l'utilisation de la SMT et il est important de suivre les recommandations d'utilisation pour éviter les effets indésirables (Rossi et al. 2009). Une contre-indication absolue est la présence de métal à proximité de la bobine (*pacemaker* ou implant cochléaire par exemple) et il existe également un risque épileptogène chez les personnes sensibles. Au niveau des expériences en laboratoire, la SMT fait du bruit et donne une légère sensation de tapotement sur le crâne. Elle peut donc avoir des effets non spécifiques de l'aire stimulée. Des conditions contrôles doivent donc reproduire au mieux le bruit et la sensation de tapotement.

Nous avons vu précédemment que l'activité oscillatoire du cerveau joue sans doute un rôle important dans nos fonctions cognitives. Récemment, l'idée d'utiliser des *patterns* rythmiques de SMT pour entrainer ou moduler cette activité oscillatoire a émergé. Romei et al. ont ainsi stimulé les cortex pariétaux et occipitaux à une fréquence de 10 Hz avec l'idée d'augmenter l'activité des régions postérieures du cerveau dans cette bande de fréquence. Les modulations comportementales observées sont parfaitement cohérentes avec les corrélations observées dans d'autres études entre l'activité alpha et les performances visuelles. La détection visuelle est améliorée dans l'hémichamp ipsilatéral à la stimulation et détériorée dans l'hémichamp controlatéral (Romei et al. 2010). Cette méthode de stimulation est appelée SMT rythmique est permet donc de moduler l'activité oscillatoire cérébrale. Cet entrainement d'oscillation a été démontré lors d'une expérience de SMT et d'EEG combinées. Des courtes rafales d'impulsions magnétiques à une fréquence spécifique provoquent un entrainement des oscillations naturelles de la région corticale stimulée (Thut et al. 2011). Cette façon récente d'utiliser la SMT dans le but de moduler et d'interférer avec les rythmes cérébraux a été utilisée lors de ce travail de thèse (*Chapitres 6 et 8*).

Les effets de la SMT ont longtemps été considérés comme focaux, agissant simplement sur la région stimulée, et moins comme impactant un réseau dont la région stimulée est une porte d'entrée. Chez le chat, il a été montré que la taille des effets métaboliques à distance de la région stimulée dépendait de la force des connexions anatomiques observées à l'aide d'un traceur neuronal (Valero-Cabré et al. 2005). Des expériences utilisant deux sondes de SMT ont montré qu'une première impulsion sur une région du cortex pouvait influencer l'excitabilité corticale d'une deuxième région. Par exemple, au repos, une première impulsion sur les régions pré-motrices ventrales va inhiber le potentiel moteur évoqué par une deuxième impulsion sur la région motrice primaire (Davare et al. 2008). Cependant, peu d'études chez l'Homme se sont intéressées au rôle de la substance blanche dans la propagation du signal neuronale induit par la stimulation et toutes proviennent de l'équipe de Matthew Rushworth à Oxford. L'équipe d'Oxford a observé que l'anisotropie fractionnelle, un marqueur de la densité et du diamètre axonal, corrélait dans certains faisceaux avec la modulation que la première impulsion crée sur l'effet comportemental de la deuxième (Boorman et al. 2007; Buch et al. 2010; Neubert et al. 2010). Autrement dit, l'influence d'une région cérébrale sur une autre dépend des faisceaux anatomiques qui les relient et ces différences dans la substance blanche sont mesurables par imagerie de diffusion.

4.3. L'IMAGERIE PAR RESONNANCE MAGNETIQUE DE DIFFUSION

L'imagerie de diffusion et les techniques de tractographie qui en découlent sont les premières méthodes permettant d'observer les connexions anatomiques du cerveau *in-vivo*.

La diffusion est un phénomène physique dont l'histoire s'est rappelée qu'il a été découvert par le botaniste Robert Brown en 1827 alors qu'il observait au microscope l'intérieur de grains de pollens. Il constata la présence de très petites particules animées d'un mouvement désordonné qu'il prit d'abord comme la manifestation d'un « fluide vital » (Brown 1828). La découverte du même phénomène dans la matière inorganique le fit changer d'avis. Il venait de faire la découverte du mouvement dit *brownien*, qui correspond aux mouvements aléatoires des molécules dans un fluide à une température supérieure à 0 Kelvin (*Figure 4.3.a)*. Ce sont les molécules d'eau présentes en très grand nombre dans notre cerveau qui, animées de ce mouvement, permettent l'imagerie de diffusion. Parce que le processus de diffusion est entravé par la géométrie structurelle de l'environnement, la visualisation de l'anatomie à travers la diffusion des molécules d'eau est possible (*Figure 4.3.b et c)*.

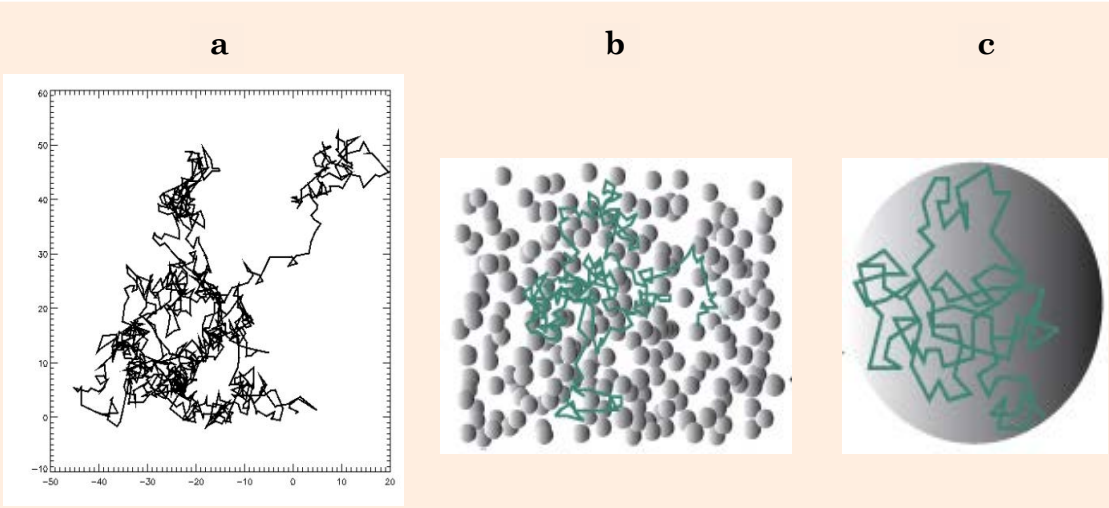


FIGURE 4.3 : LA DIFFUSION DES MOLECULES D'EAU

Simulation du déplacement d'une molécule d'eau soumise au mouvement brownien dans un environnement libre ***(a)****, dans le milieu extracellulaire* ***(b)*** *et dans le milieu intracellulaire* ***(c)****. Adaptée de Behrens 2009.*

4.1.2. PRINCIPE GENERAL DE L'IMAGERIE PAR RESONNANCE MAGNETIQUE

L'imagerie par résonnance magnétique repose sur le principe de résonnance magnétique nucléaire qui concerne certains atomes, dont l'hydrogène, possédant un spin nucléaire, lorsqu'ils sont placés dans un champ magnétique. Soumis à une onde radio dont la fréquence, constante pour un isotope donné, dépend de la valeur du champ magnétique et du rapport gyromagnétique, ils peuvent emmagasiner l'énergie du rayonnement puis la relâcher sous forme de relaxation. La vitesse de cette relaxation, autrement dit le temps par lequel le noyau va restituer l'énergie absorbée à son environnement proche, est enregistrée pour reconstruire l'image IRM. Cette relaxation dépend du type de tissus dans lequel se trouve le noyau et permet donc de

visualiser les structures anatomiques (*Figure 4.4.a*). Le noyau d'hydrogène est le noyau le plus présent dans le corps humain et permet donc de récupérer le plus de signal. Il est cependant possible d'imager à partir d'autres noyaux comme le Carbone (^{13}C), le Fluor (^{19}F), le Sodium (^{23}Na) ou le Phosphore (^{31}P). Les étapes importantes dans l'acquisition d'une image sont donc un fort champ magnétique qui permet l'aimantation des spins, une onde radiofréquence qui les fait entrer en résonnance et leur permet d'absorber de l'énergie et une phase de relaxation lorsque le noyau restitue l'énergie qui correspond à l'enregistrement de l'image proprement dite. En plus du champ statique élevé de l'IRM, des gradients magnétiques viennent modifier légèrement le champ magnétique de façon linéaire dans les trois directions orthogonales de l'espace. La fréquence choisie de l'onde radio ne faisant entrer en résonnance que les atomes plongés dans un champ magnétique d'une valeur précise, l'application des gradients permet de déterminer la localisation des noyaux qui ont été excités et donc, en faisant varier la fréquence de l'onde radio, de reconstruire une image en 3D.

4.1.3. L'IMAGERIE DE DIFFUSION

L'IRM de diffusion s'intéresse aux micromouvements liés au mouvement brownien des molécules d'eau dans le cerveau. Dans un liquide sans barrières physiques et au repos, au centre d'un verre d'eau par exemple, on peut considérer que la diffusion, le déplacement aléatoire des molécules du liquide sous l'agitation thermique, est isotrope, c'est-à-dire la même dans toutes les directions de l'espace. A l'inverse, dans l'organisme, ces mouvements rencontrent différentes barrières (membranes cellulaires, fibres, protéines, etc.). Le calcul de ce déplacement dans plusieurs directions permet de façon indirecte d'inférer la forme et la structure des organes et tissus. Cette technique d'imagerie développée par Le Bihan et Breton (Le Bihan & Breton 1985), Merboldt et al. (Merboldt et al. 1985) et Taylor et Bushell (Taylor & Bushell 1985) s'est rapidement révélée très utile au niveau clinique pour la détection précoce des accidents vasculaires cérébraux ischémiques et la localisation des tumeurs cérébrales. De très nombreuses avancées techniques et informatiques sont venues augmenter le pouvoir de ce type d'imagerie rendant possible en particulier la visualisation des fibres de matière blanche.

Les séquences de diffusion utilisent une séquence IRM classique dite SE-EPI (Spin Echo – Echo Planar Imaging) pondérée en T2. L'ajout de gradients supplémentaires à cette séquence va permettre d'obtenir des images dont les contrastes sont influencés par le mouvement des atomes d'hydrogène excités. Deux gradients intenses sont appliqués dans une direction donnée. Le premier va déphaser les spins des atomes d'hydrogène et le deuxième va les remettre en phase. Seulement, si certaines molécules d'eau se sont déplacées dans la direction des gradients entre leurs applications, les noyaux d'hydrogène qui les constitue ne seront pas sensibles au second gradient et ne seront pas remis en phase. Il y aura alors une perte de signal liée au déphasage des spins dont les algorithmes se servent pour reconstruire les images de diffusion (*Figure 4.4.c et d*). L'imagerie de diffusion est donc par nature une imagerie de perte du signal. Plus la pondération en diffusion de la séquence est forte, moins le signal est important, ce qui limite la possibilité de rendre la séquence IRM de plus en plus sensible à la diffusion. La pondération en diffusion est exprimée par la valeur b en s/mm^2 qui dépend de l'amplitude des gradients de diffusion, de leur temps d'application et du délai entre les deux. Pour reconstruire les images de diffusion, un volume de référence avec une pondération en diffusion nulle (b=0) est nécessaire (*Figure 4.4.b*). Enfin, une seule direction de diffusion est enregistrée pour chaque volume acquis, il est donc obligatoire de répéter ces mesures plusieurs fois pour rendre compte de la diffusion dans plusieurs directions. En pratique, il faut au minimum 6 directions pour modéliser le tenseur de diffusion et plus de 60 directions pour utiliser des techniques à haute résolution angulaire.

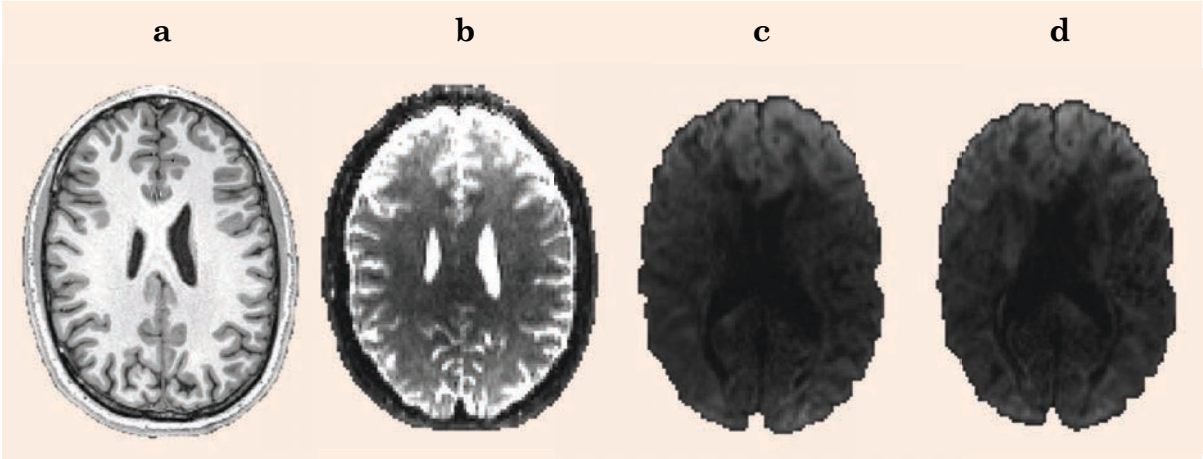


FIGURE 4.4 : IMAGES IRM.

a. *Image anatomique pondérée en T1. La substance grise, la substance blanche et le liquide cérébro-spinal peuvent être différenciés en différents niveaux de gris.* ***b.*** *Image T2 avec une pondération nulle en diffusion (b=0 s/mm²).* ***c et d.*** *Images pondérées en diffusion avec une valeur de b = 1500 s/mm². La perte de signal est visible et n'est pas identique entre* ***c*** *et* ***d*** *car les directions des gradients de diffusion sont différentes.*

C'est en 1990 que Moseley et al. reporta que la diffusion était anisotrope dans la matière blanche (Moseley et al. 1990). Rapidement, l'idée de pouvoir visualiser grâce à ce principe le cheminement des faisceaux de fibres se répandit et le modèle du tenseur de diffusion fut proposé (Basser & LeBihan 1992; Basser et al. 1994). Ce tenseur, calculé pour chaque voxel, est une matrice symétrique 3*3 qui décrit dans les 3 dimensions la nature de l'anisotropie de la diffusion (*Figure 4.5.a*). Ce modèle permet de calculer la direction principale de diffusion, la diffusivité moyenne ou perpendiculaire ainsi que l'anisotropie fractionnelle, indice rendant compte de l'anisotropie de la diffusion. Bien que ce modèle soit encore le plus utilisé pour sa rapidité de calcul, surtout en clinique, beaucoup de modèles rendant mieux compte de la réalité de la diffusion ont fait leur apparition. En effet, le défaut majeur du tenseur est son hypothèse de gaussianité. Assomption adéquat dans un voxel où une seule population de fibres est présente, ce modèle représente très mal les voxels avec une structure plus complexe, des croisements de fibres en particulier. Il est admis qu'environ 2/3 des voxels de la substance blanche contiennent plusieurs populations de fibres (Jeurissen et al. 2012). Pour pallier à ce problème, de nouvelles façons de modéliser la diffusion sont apparues, qui nécessitent des séquences avec une pondération plus forte en diffusion et au minimum 60 directions de diffusion. La distribution de l'orientation des fibres peut être exprimée par exemple à l'aide de déconvolutions sphériques (*Figure 4.5.b*). Cette technique qui permet la visualisation de plusieurs populations de fibres au sein d'un voxel permet de pallier aux problèmes du tenseur de diffusion et améliore donc les algorithmes de reconstruction de fibres.

La techniques de reconstruction de fibres ou de suivi de fibres (tractographie) à partir d'images IRM de diffusion est le seul outil non-invasif qui permet d'obtenir de l'information sur la connectivité anatomique de la substance blanche. Actuellement, les algorithmes de tractographie sont majoritairement basés sur l'utilisation de la direction principale de diffusion du tenseur (Mori et al. 1999). Contrairement aux techniques de traceur axonal qui permettent de suivre un axone sur toute sa longueur, la tractographie reconstruit une trajectoire fictive en suivant la direction principale de diffusion de voxel en voxel. Cette trajectoire ne représente pas directement

un axone et peut se tromper de direction ou s'arrêter lorsque l'anisotropie est trop faible ou le signal trop bruité. Des techniques plus complexes de suivi de fibres ont également été proposées (Mori & van Zijl 2002). L'information de la distribution de l'orientation des fibres obtenue avec les techniques de déconvolution sphérique a également été utilisée pour reconstruire les faisceaux de matière blanche (Tuch 2004; Descoteaux et al. 2009). Ces techniques récentes de tractographie permettent de reconstruire les faisceaux même lorsque plusieurs populations de fibres sont présentes au sein d'un même voxel (*Figure 4.6*). Il faut en effet rappeler que la résolution des images de diffusion est de l'ordre de 8 mm^3 pendant que le diamètre d'un axone est de l'ordre du micromètre.

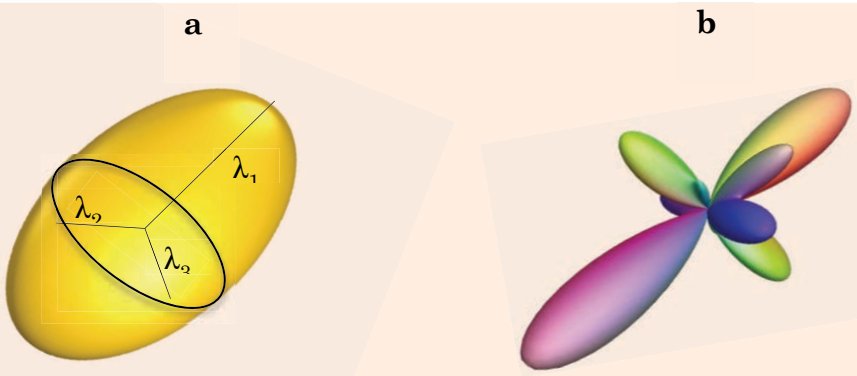


FIGURE 4.5 : MODELISATION DU SIGNAL DE DIFFUSION

a. *Tenseur de diffusion. Le signal de diffusion est exprimé par 3 vecteurs dont λ_1 représente la direction de plus grande diffusion. Cette modélisation ne représente pas les croisements de fibres au sein du même voxel.* ***b.*** *Déconvolution sphérique. Plusieurs pics de diffusion peuvent être observés et permettent une estimation de la distribution de l'orientation des fibres.*

Deux familles d'algorithmes de tractographie existent : les déterministes et les probabilistes. Le suivi de fibres déterministe consiste à passer de voxel en voxel en suivant les directions de diffusion afin de reconstruire les trajectoires des fibres. Cette méthode peut se révéler trop conservatrice car elle ne pourra pas reconstruire certaines fibres qui passent par des voxels dont le signal de diffusion n'est pas assez anisotrope dans une direction (bruit, croisement de fibres, matière grise, etc.). La méthode probabiliste utilise la même logique mais propose de lancer un grand nombre de trajectoires (plusieurs milliers) pour chaque voxel en modifiant légèrement la direction de la diffusion dans chaque voxel dans lequel cette trajectoire va passer. Il faut ensuite fixer un seuil de probabilité (nombre de trajectoires minimal) à partir duquel on considère que le résultat correspond à un faisceau réel. Cette méthode qui permet de pallier au problème des techniques déterministes par le grand nombre d'essais lancés peut à l'inverse créer des faux positifs (Johansen-Berg & Behrens 2009).

Il est possible à partir des données de diffusion de calculer différents paramètres permettant de décrire les propriétés micro-structurelles de la substance blanche. L'anisotropie fractionnelle dans chaque voxel permet d'observer la distribution de la diffusion dans l'espace. Elle dépend de la densité axonale, du diamètre et de la myélinisation des axones (Beaulieu 2002). Une baisse de la diffusivité moyenne dans le cerveau au cours du développement est par exemple interprétée comme une augmentation de la myéline (Dubois et al. 2008). Des paramètres de tractographie comme la probabilité de connexion ou le volume d'un faisceau, bien que plus sensibles au bruit, permettent également d'observer des différences en terme de connexions anatomiques (Thiebaut de Schotten et al. 2011).

a **b**

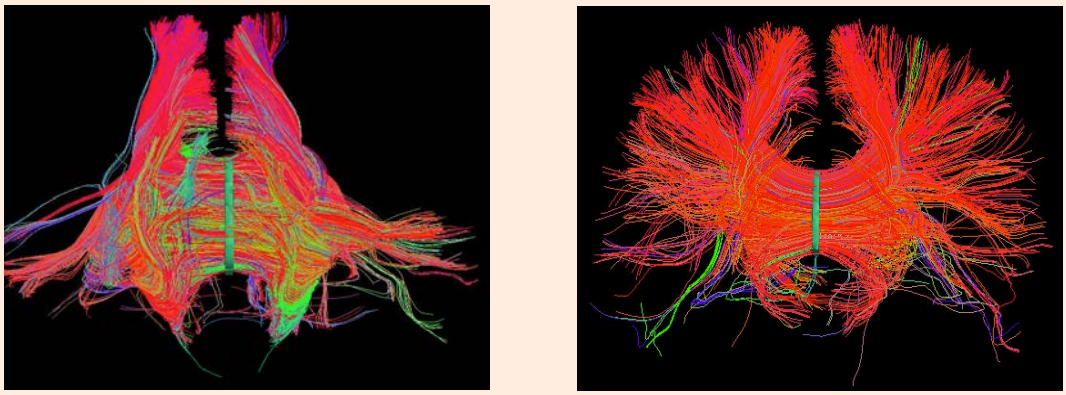


FIGURE 4.6 : DISSECTION DU CORPS CALLEUX. TENSEUR VS. DECONVOLUTION SPHERIQUE

a. *Modèle du tenseur de diffusion.* ***b.*** *Modèle de déconvolution sphérique.*
Les fibres latérales du corps calleux ne sont pas reconstruites avec le tenseur de diffusion car elles croisent avec le faisceau pyramidal et le faisceau longitudinal supérieur. Les déconvolutions sphériques permettent la reconstruction de ces fibres.

CHAPITRE 5. OBJECTIFS DE LA THESE

Les processus de modulation perceptive modifient notre perception du monde. Ces modifications peuvent être observées grâce aux performances, objectives et subjectives, des participants. De nombreuses études ont décrit ces mécanismes dans lesquels le réseau fronto-pariétal joue un rôle primordial. Nous avons choisi ici de nous intéresser à la contribution de la région frontale clé de ce réseau visuo-attentionnel, le FEF, et en particulier à la dynamique temporelle de son activité, dans ces processus de modulation perceptive.

Le *Chapitre 6* comportent deux études qui explorent les effets perceptifs de la SMT à impulsion unique (*Partie 1*) et de la SMT rythmique (*Partie 2*). Le *Chapitre 7* s'intéresse aux substrats anatomiques de la variabilité individuelle observée lors des études de SMT et le *Chapitre 8* explore les effets de la SMT rythmique sur l'ensemble de la courbe de sensibilité visuelle et s'interesse également au rôle de la connectivité anatomique dans cette modulation. Nous décrivons ici brièvement comment chaque étude répond aux deux objectifs principaux.

Le premier objectif consiste à comprendre la contribution d'une activité frontale sur la discrimination visuelle et la détection consciente.

Nous avons utilisé dans la *Partie 1* du *Chapitre 6* des impulsions uniques sur la région FEF droite à différents moments juste avant l'apparition d'une cible visuelle. Dans une des expériences, un indice visuel pouvait orienter l'attention du sujet, ce qui nous a permis d'étudier l'impact d'une activité frontale dans différentes conditions d'orientation attentionnelle.

La dynamique temporelle de l'activité cérébrale a été extensivement étudiée de façon corrélationnelle grâce aux méthodes d'électrophysiologie, mais rarement de manière causale en observant l'impact comportemental d'une activité rythmique. Dans la *Partie 2* du *Chapitre 6* et le *Chapitre 8*, nous avons exploré la contribution de l'activité rythmique de la région FEF droite grâce à la SMT rythmique. Nous avons d'abord utilisé le même paradigme que dans l'expérience de SMT à impulsion unique qui nous a permis d'observer les effets potentiels de la SMT rythmique sur la discrimination et la détection consciente. Dans le *Chapitre 8*, nous avons fait varier les contrastes présentés aux participants grâce à un algorithme qui estime la courbe psychométrique représentant les performances de détection en fonction du contraste. Cette dernière approche nous a permis d'observer une potentielle modulation perceptive sur l'ensemble de la courbe, c'est-à-dire à différents niveaux de contraste.

L'hypothèse générale de ces trois expériences est que l'activité de la région FEF droite, et par extension du réseau fronto-pariétal, avant l'apparition d'une cible, peut moduler la perception et en particulier améliorer les performances visuelles.

Le deuxième objectif de cette thèse a été d'étudier le rôle de la connectivité anatomique dans les processus de modulation perceptive. Cette deuxième approche peut se résumer à cette question : les connexions efférentes d'une région stimulée influencent-elles la modulation perceptive visuelle induite par la stimulation non-invasive de cette région ?

Dans la *Partie 1* du *Chapitre 7*, nous avons utilisé une méthode de tractographie probabiliste pour reconstruire quatre faisceaux connectés au FEF et potentiellement impliqués dans les processus de modulation visuelle. En récupérant les données individuelles de l'expérience de stimulation à impulsion unique (Chapitre 6, *Partie 1)*, nous avons observé si des

différences de connectivité anatomique pouvaient influencer l'effet comportemental de la stimulation.

Dans la *Partie 2* du *Chapitre 7* et dans le *Chapitre 8*, nous avons utilisé une méthode de tractographie déterministe basée sur les déconvolutions sphériques. De par l'utilisation de la SMT rythmique et l'hypothèse de synchronisation cérébrale au sein du réseau fronto-pariétal, nous avons reconstruit les trois branches du SLF afin d'observer si des paramètres de ces faisceaux influencaient la modulation perceptive induite par la SMT rythmique.

L'hypothèse générale de cette deuxième approche est que les données de diffusion permettent l'observation de différences en terme de connectivité anatomique qui influencent l'effet perceptif d'une stimulation frontale et l'identification des faisceaux impliqués dans cette modulation visuelle.

CHAPITRE 6. MODULATION DE LA PERCEPTION VISUELLE PAR STIMULATION NON-INVASIVE

6.1. AMELIORATION DE LA PERCEPTION VISUELLE PAR SMT A IMPULSION UNIQUE DES FEFS

Dans cette première étude, nous avons testé si l'activation des champs oculomoteurs frontaux par SMT permettait de moduler la perception visuelle. Plusieurs études chez le singe ont montré une relation entre l'activité des FEFs et la perception visuelle. Moore et Fallah ont observé que la micro-stimulation du FEF permettait de faire baisser le seuil de détection d'un changement de luminance (Moore & Fallah 2001) et Thompson et Schall ont observé que l'activité de la région FEF permettait de prédire si un stimulus caché par un masque était detecté ou non (Thompson & Schall 1999). Chez l'Homme, Grosbras et Paus ont montré que la stimulation des FEFs pouvait faire baisser le temps de réaction de stimuli visuels périphériques (Grosbras & Paus 2002) ainsi qu'améliorer la détection consciente de stimuli masqués (Grosbras & Paus 2003). Dans notre expérience, nous avons utilisé des stimuli à très faible contraste présenté en périphérie. Notre paradigme comportemental comporte deux questions sur un même stimulus. La première question est un choix forcé qui porte sur l'orientation droite ou gauche des lignes du *gabor* (tâche de discrimination). Le participant doit répondre le plus rapidement possible et à chaque essai. Il répond à cette question même s'il n'a pas perçu consciemment la cible. Ensuite vient une deuxième question où le sujet doit dire s'il a perçu la cible dans le carré de droite ou de gauche, ou s'il n'a rien vu (tâche de détection). Deux expériences ont été effectuées. Dans la première, aucun indice attentionnel n'a été utilisé et la SMT a été appliquée sur le FEF droit 80, 100 et 140 ms avant l'apparition de la cible. Dans la deuxième expérience, nous avons utilisé des indices prédictifs et périphériques pour orienter l'attention du participant. L'indice indiquait dans 75% des essais le côté où la cible allait effectivement apparaître. Dans l'ensemble des expériences, la SMT n'a pas eu d'effet sur la tâche de discrimination à choix forcé. En revanche, dans la première expérience, un effet d'amélioration de la détection visuelle consciente a été observé de façon bilatérale. Cette amélioration s'avère plus importante lorsque la SMT est appliquée 80 ms avant la cible. Dans la deuxième expérience, nous avons observé que cet effet d'amélioration n'était présent que pour les essais valides, c'est-à-dire lorsque le participant orientait son attention du côté où allait apparaître la cible. La stimulation des champs oculomoteurs frontaux avant l'apparition d'une cible à faible contraste est donc capable d'augmenter les performances de détection consciente. Cet effet est dépendant de l'orientation attentionnelle du sujet.

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Manipulation of Pre-Target Activity on the Right Frontal Eye Field Enhances Conscious Visual Perception in Humans

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Abstract

The right Frontal Eye Field (FEF) is a region of the human brain, which has been consistently involved in visuo-spatial attention and access to consciousness. Nonetheless, the extent of this cortical site's ability to influence specific aspects of visual performance remains debated. We hereby manipulated pre-target activity on the right FEF and explored its influence on the detection and categorization of low-contrast near-threshold visual stimuli. Our data show that pre-target frontal neurostimulation has the potential when used alone to induce enhancements of conscious visual detection. More interestingly, when FEF stimulation was combined with visuo-spatial cues, improvements remained present only for trials in which the cue correctly predicted the location of the subsequent target. Our data provide evidence for the causal role of the right FEF pre-target activity in the modulation of human conscious vision and reveal the dependence of such neurostimulatory effects on the state of activity set up by cue validity in the dorsal attentional orienting network.

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Introduction

Since the pioneering studies by Posner and collaborators [1], the ability of visuo-spatial attentional orienting to influence visual performance has been widely demonstrated. More recent work has specifically reported enhancements in several aspects of visual perception such as spatial resolution, contrast sensitivity and orientation discrimination in those regions of the visual field where attention is willfully focused or involuntarily captured [2,3,4]. Such facilitatory phenomena are thought to be mediated by the ability of long-range connectivity from non-visual regions to reduce background noise, sharpen the tuning, boost the gain, or reduce the variance in firing activity of neuronal populations located within primary visual areas [5,6].

Solid neuroimaging evidence of the human brain has so far helped identify a dorsal network involved in visuo-spatial attentional orienting, with the participation among others, of key cortical sites such as the right Intraparietal Sulcus (IPS) and the Frontal Eye Fields (FEF) [7]. This dorsal system would be supplemented by a ventral network, which would act as a "circuit breaker", allowing the re-orientation of attention to unexpected and task-relevant events [7,8]. Interestingly, some of these sites appear to co-localize with the nodes of a distributed long-range connectivity network, which, according to theoretical models and neuroimaging data, might play an essential role in access to consciousness [9,10,11,12,13].

Some understanding of FEF interactions with other brain locations has been provided by non-human primate studies revealing that the microstimulation of this area yields selective perceptual modulations for stimuli presented within locations corresponding to the receptive fields of the stimulated neurons, but not outside [14,15]. Likewise, the non-invasive manipulation of the right FEF activity in the human brain by Transcranial Magnetic Stimulation (TMS) has also shown its ability to modulate neural activity in early visual areas [16,17] and visual performance on the detection of high-contrast and masked targets [18,19]. All together those studies suggest that frontal activity has the potential to modulate the processing of visual stimuli, particularly under challenging perceptual conditions. Nonetheless, the processes underlying the ability of this specific cortical frontal site to influence and eventually ameliorate visual perception, particularly when manipulated during the time period preceding the onset of a visual target remain debated.

In the current study, we used single TMS pulses to modulate FEF pre-target activity and studied its impact on the conscious perception of low-contrast near-threshold targets (Experiment 1). Given that neurostimulatory effects have been shown to depend on the pre-existing patterns of activity within the targeted region [20,21], we then made use of visuo-spatial cues, likely to modulate neural activity along the dorsal attentional orienting network, to study whether the effects of pre-target FEF TMS interacted or not

with the state of activity within that network (Experiment 2). The topic holds the potential to provide novel insights on the role of right FEF activity on conscious visual perception and could also help settle the bases in an upcoming near future, for new strategies to manipulate such region with the goal of enhancing human perceptual capabilities.

Materials and Methods

A group of thirteen participants (8 women and 5 men) aged between 18 and 28 years (average: 24 years old) took part in the study. All participants reported no history of neurological or psychiatric disorders and normal or corrected-to-normal visual acuity. They were all naïve as to TMS and the purpose of the experiments and participated voluntarily. The research protocol and inform consent was reviewed and sponsored by the Inserm (*Institut National de la Santé et la Recherche Scientifique*) ethical committee and approved by an Institutional Review Board (CPP *Ile de France 1, Hôpital de la Pitié-Salpêtrière*). Written informed consent was received from all participants in the study prior to participation. Participants took part in two experiments (Experiment 1 and 2), the order of which was counterbalanced across subjects.

Apparatus, Visual Stimuli, and Tasks

Visual stimuli were displayed on an eye tracker screen (Tobii T50, Technology AB, Danderyd, Sweden, 17'' wide, 1024×768, 16.67 ms refresh rate) using a laptop computer (Dell Latitude E6400, Round Rock, Texas, USA) and standard stimulus presentation software (E-prime, Sharpsburg PA, USA). All stimuli were presented against a grey background (RGB: 194, 194, 194) (Figure 1) and eye movements were controlled throughout each trial. The fixation point (a black "+" sign of 0.5×0.5°) was displayed in the center of the screen, along with three black squared boxes (6.0° width×5.5° height), one central and two lateral ones (centered 8.5° to the left and right of the fixation point). The target consisted of a *Gabor* stimulus (2 cycles/deg. spatial frequency, 3.0° diameter, 0.3° of SD, minimum and maximum Michelson contrast of 0.062 and 0.551, respectively), which could appear at the center of one of two lateral boxes for a brief period of time (33 ms). The lines of the *Gabor* were tilted 1° to 10° to the left or to the right (corresponding 0° to their vertical orientation). Participants were requested to keep fixation on the central cross throughout the trial and to execute two consecutive tasks after the presentation of the target. They were first asked to determine line orientation (*categorization* task), as fast and as accurately as possible, by pressing the corresponding button on a computer keyboard with the index and middle finger of their right hand ("1" for left and "2" for right). In this task, we encouraged them to respond to every trial within a window of 2000 ms, and to guess a response even when the target was not presented or they did not consciously perceive it. Performance was assessed through accuracy and reaction time measures. Secondly, participants were required to report whether they had consciously seen the target or not (*detection* task). To do so, two arrow-like stimuli, one below and one above the fixation cross (>>> and <<<), pointing to the left and to the right side of the screen were presented. Participants were provided with three keys, which they had to operate with their left hand: an upper key ("d"), a lower key ("c") and the space bar. The upper key signaled the side of the screen pointed by the arrow presented in the upper part of the fixation point, while the lower key was associated to the side of the screen pointed by the lower arrow. Participants had to respond by pressing the space bar if they did not see the stimulus, or, if they did see it, with the corresponding key ("d" or "c") to indicate the location where the target had been consciously perceived (left or right). The position of the arrows pointing left or right was randomized across trials. Perceptual sensitivity (d') and response bias (beta) used in Signal Detection Theory [22,23] served to assess performance in this task. The former (d') is a bias-free statistic that provides a measure of observers' ability to detect weak signals, while the latter (beta) describes their relative preference for one response over the other. To compute those two parameters, trials in which the location of a target presented in the screen was correctly determined by participants, were considered as correct detections or "hits"; trials in which the presence of a present target was not acknowledged by participants were considered as "misses"; trials in which participants reported the location for targets that were not presented on the screen were treated as "false alarms"; trials in which the target was absent and participants correctly reported not to have seen it were considered "correct rejections"; and finally, trials in which the location of a present target was incorrectly reported by participants (4% of the 'seen' targets in both experiments) were excluded from the analyses as errors.

A titration procedure performed prior to the experimental trials allowed to determine, in each experiment and for each participant, the stimulus contrast at which ~62% of the displayed targets were consciously reported in the *detection* task and the degree of line tilting for which performance in the *categorization* task remained between 65 and 85% correct. Participants started the titration trials with a high contrast stimulus and, every 20 trials, target contrast and line tilting were adjusted in order to converge to the above-mentioned criteria. Experimental trials started once such performance levels were attained and during the experiment, this whole set of stimulus parameters was also automatically adjusted every 20 trials to avoid behavioral fluctuations caused by task practice or fatigue.

In Experiment 1, every trial started with a fixation screen lasting randomly from 1000 to 1500 ms in order to achieve an inter-trial interval of at least two seconds. The fixation cross became then slightly bigger (0.7×0.7°) for 66 ms to signal the upcoming event. After an Inter Stimulus Interval (ISI) of 233 ms, the target could appear at the center of one of the two lateral boxes. The experiment consisted of 600 trials, including 120 trials in which the target was absent. In half of the trials, chosen randomly, a single TMS pulse was delivered on the right FEF either at 80, 100 or 140 ms prior to the target onset (active TMS trials). In the other half (sham TMS trials), a single pulse was delivered, at those same timings, by a second TMS coil placed next to the stimulation site, with the coil surface perpendicular to the head surface, preventing the magnetic field from reaching the skull and stimulating the brain.

In Experiment 2, everything was kept the same as in Experiment 1 except for the following. The fixation sign did not increase its size but, instead, a visuo-spatial cue, consisting of a black circle (1.5° diameter), was presented in the upper external corner of one of the two lateral boxes and displayed for 66 ms. After the same ISI (233 ms), the target could appear at the center of the cued (valid trial) or uncued (invalid trial) lateral box. The cue was predictive about the location of the upcoming target (75% valid and 25% invalid trials). A cue was considered valid when it correctly signaled the location of the upcoming target (left or right), and invalid when it incorrectly signals target location. A valid trial was the one including a valid cue whereas the opposite applied to invalid trials. Similarly, validly cued targets were those preceded by a valid cue, whereas invalidly cued targets were preceded by an invalid cue. The experiment consisted of 800 trials, including 160 target-absent trials. Active or sham TMS pulses were only delivered 80 ms pre-target onset, given the inability to test all three timings and keep the session within a reasonable duration. Prior experiments suggested that short pre-target timings had the highest potential to induce behavioral effects [19].

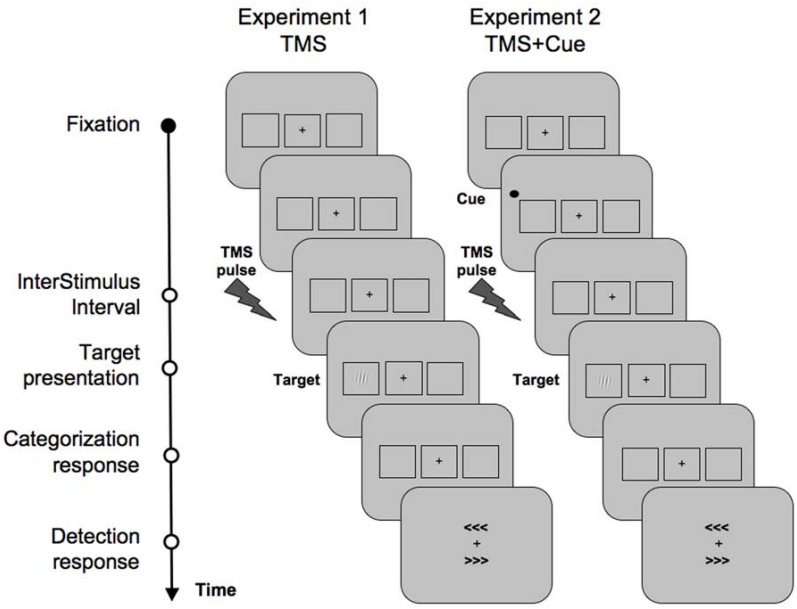


Figure 1. Sequence of events during a representative trial of Experiment 1 (left) and Experiment 2 (right). In both experiments, participants were requested to fixate at a central cross for a randomly variable period of time between 1000 to 1500 ms. In Experiment 1, the fixation cross became slightly bigger for 66 ms and was followed by an active or a sham single TMS pulse delivered on the right FEF, 80,100 or 140 ms prior to target onset. In Experiment 2, a peripheral visuo-spatial cue, consisting in a black circle was displayed for 66 ms to the right or the left of the fixation cross. The cue was predictive about the location of the subsequent target (75% valid and 25% invalid trials), and was followed by a TMS pulse delivered 80 ms pre-target onset. In both experiments active or sham TMS pulses were interleaved in a randomized order. Then, after an interstimulus interval (ISI) of 233 ms, a *Gabor* with the lines tilted to the left or the right appeared for 33 ms at the center of one of the two lateral boxes. Participants were then requested to perform two sequential tasks; first a visual line *categorization* task to indicate the orientation of the *Gabor* lines (left/right) and second, a conscious visual *detection* task in which they had to report if they did see the target, and where they saw it (left/right). A cue is considered valid when it correctly signals the location of the upcoming target (left or right), and invalid when it incorrectly signals target location. A valid trial is the one including a valid cue and the opposite applies to invalid trials. The figure shows for Experiment 2 an example of a valid trial (see Material and Methods for full details on the behavioral paradigms).
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Transcranial Magnetic Stimulation (TMS)

TMS pulses were delivered using a biphasic repetitive stimulator (Superapid^2, Magstim, Withland, UK) with a 70 mm diameter figure-eight air-cooled coil (Figure 2). Pulses were triggered through E-prime software (E-prime, Sharpsburg PA, USA) running on a laptop computer (Dell, Latitude 6410). Prior to the experimental tasks, a structural T1-weighted MRI scan was acquired for every participant at the CENIR MRI center (*Hôpital de la Pitié-Salpêtrière*, Paris). A 3T Siemens MPRAGE sequence, flipangle = 9, Repetition Time = 2300 ms, Echo Time = 4.18 ms, slice thickness = 1 mm, was used. For the TMS experiments, the right FEF region was localized using previously identified Talairach coordinates x = 31, y = −2, z = 47 [24] and labeled with a 0.5 cm radius spherical Region of Interest (ROI) in the MNI space with the Marsbars toolbox (Sourceforge.net). Using SPM5 software (UCL, London, UK), each participant's structural MRI image was segmented into white and gray matter and the inverse segmentation matrix was used to individually de-normalize the ROI (spatial smooth isotropic Gaussian Kernel of 1-mm full-width half-maximum). The same software was used to co-register the de-normalized ROI with each participant structural MRI volume, obtaining a precise individual localization of the area. The final MRI was uploaded into a frameless stereotaxic system (eXimia NBS System, Nexstim, Helsinki, Finland) and reconstructed in 3D for online neuronavigation of the TMS coil. Given the small size of the region and the high inter-individual variability in FEF location, a TMS-guided individual functional confirmation of the location of the right FEF was conducted by following a well-established protocol based on evidence that a single TMS pulse delivered on the FEF during the preparation time of a saccade has the ability to delay its onset [25].

At all times, the active TMS coil was held tangential to the skull, with its handle oriented ~45° in a rostral-to-caudal and lateral-to-medial orientation, i.e., parallel to the central sulcus. The TMS coil was kept steady within an area of ~2 mm radius from the targeted region by using online neuronavigation feedback on each participant's structural MRI. For all interventions, stimulation intensity was initially set up for every subject at 67% of the TMS machine maximum output. Nonetheless, in some participants, intensity had to be slightly decreased to abolish temporal involuntary muscle activation, involuntary blinks or other types of facial sensations. The average intensity at which participants were stimulated was 66±1% for both experiments (113±12% and 111±15% of the mean resting motor threshold in Experiments 1 and 2, respectively).

Data Analysis

Trials in which participants showed response anticipations, i.e. pressed the button before stimulus presentation (0.02% and 0.01% of all trials respectively), or broke fixation and performed eye movements to one of the lateral boxes (3% and 6% of all trials for Experiment 1 and 2, respectively) were eliminated from the analyses. The first three participants taking part in Experiment 1

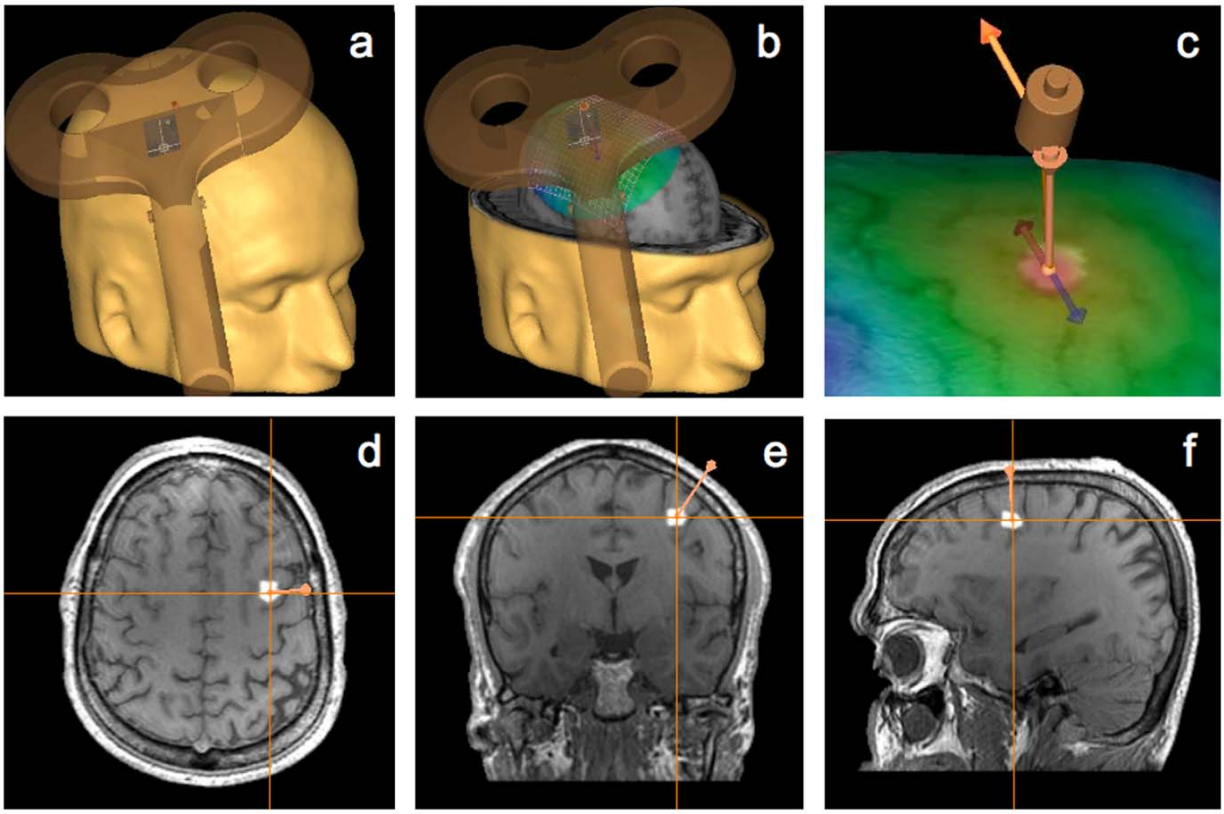


Figure 2. TMS targeted region, neuronavigation and coil placement. The specific location of the right FEF was identified and labeled in a three dimensional reconstruction of each participant's MRI. The area was targeted with a 70 mm figure-of-eight TMS coil guided by a frameless stereotaxic neuronavigation system (a and b). The active TMS coil was placed flat with its center tangential to the targeted site and oriented lateral to medial and rostral to caudal orientation (c), approximately parallel to the medial portion of the central sulcus, i.e., ~ a 45° angle with respect to the interhemispheric fissure. See axial (d), coronal (e) and sagittal (d) MRI views of the location for the TMS targeted right FEF (see Material and Methods for full details on the targeting strategy).
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could not be included in the analyses due to a software programming error.

As accuracy in the *categorization* task was high when participants correctly reported to have seen the target (74% in both experiments) and remained at chance levels when they reported not to have seen it (51% and 49% in Experiment 1 and 2, respectively), only correctly seen target trials were considered for reaction time and accuracy analyses. For each timing (80, 100 and 140 ms), TMS condition (active or sham TMS) and validity (valid and invalid), trials with reaction time faster than 150 ms and outside 4 standard deviations of the mean (0.1% and 0.4% in Experiment 1 and 2, respectively) were eliminated from the analyses as outliers.

All behavioral outcomes (accuracy and reaction time for the *categorization* task and perceptual sensitivity and response bias for the *detection* task) were subjected to a repeated measures ANOVA with timing (80, 100 and 140 ms), target location (left and right) and TMS condition (active and sham TMS) as within-participant factors in Experiment 1 and with validity (valid and invalid), target location and TMS condition as within-participant factors in Experiment 2. Such analysis was also performed for detection errors (i.e. target-present trials in which participants incorrectly indicated target location) to rule out any potential TMS effects on these specific types of events. In Experiment 1, no significant main effects or interactions were observed in such trials. In Experiment 2, only a main effect of validity was observed, indicating that participants made fewer errors in valid than invalid trials ($F(1, 12) = 13.64$, $p = 0.003$).

Results

In Experiment 1, we used single TMS pulses on the right FEF to test the ability of pre-target activity on this region to modulate conscious visual perception of low-contrast near-threshold targets. Participants correctly reported to have seen the target in 56% of the present-target trials and the mean rate of false alarms was 2%. All measures (accuracy and reaction time for the *categorization* task and perceptual sensitivity and response bias for the *detection* task) were subjected to a repeated measures ANOVA with timing (80, 100 and 140 ms), target location (left and right) and TMS condition (active and sham TMS) as within-participant factors. In the *categorization* task, no significant effects of TMS condition were observed. Only a main effect of target location in reaction time reached significance ($F(1,9 = 7.88$, $p = 0.020$), participants being faster for targets displayed on the right than on the left visual hemifield. Responses also proved to be more accurate when responding to right than left targets ($F(1,9) = 6.68$, $p = 0.030$). In contrast, in the *detection* task, a main effect of TMS condition

reached significance, with overall higher perceptual sensitivity (d') under active than sham TMS pulses ($F(1,9) = 8.31$, $p = 0.018$). On the basis of the a *priori* hypothesis that stimulation should depend on pulse delivery time, we performed three separate repeated measures ANOVA for the three TMS timings, with side and TMS condition as within-participant factors. The TMS effect only reached significance when pulses were delivered 80 ms pre-target onset ($F(1, 9) = 9.77$, $p = 0.012$), but not when applied 100 ms ($F = 5.09$, $p = 0.051$) or 140 ms ($F = 3.95$, $p = 0.078$) pre-target onset (Figure 3 and Table 1). No main effects or interactions reached statistical significance for the response bias (beta).

In Experiment 2, FEF TMS was delivered after the engagement of the dorsal attentional orienting network by a peripheral visuo-spatial cue, which was predictive about the location of the subsequent target. Given our purpose of studying the combined effects of a single TMS pulse and a cue-driven engagement of attentional orienting, only participants effectively orienting their attention according to the cue, and thus exhibiting cueing effects under sham TMS trials, were considered for further analyses. An assessment of the perceptual effects induced by visuo-spatial attentional orienting using the exact same paradigm (see Experiment 4 in [26] for details) demonstrated that, for this very same *categorization* task, effective visuo-spatial attentional orienting entailed significant reaction time reductions in valid as compared to invalidly cued targets. Accordingly, the presence of a significant cueing effect was statistically assessed in our participants by comparing the mean reaction time of valid vs. invalid sham TMS trials. Seven out of the thirteen participants showed statistically significant reductions of reaction time for valid vs. invalid sham TMS trials (unpaired 1 tailed t-test, $p<0.05$) and thus were considered as exhibiting cueing effects.

Those participants reported to have seen the target in 58% of the present-target trials and the mean rate of false alarms was 6%. All measures (accuracy and reaction time for the *categorization* task and perceptual sensitivity (d') and response bias (beta) for the *detection* task) were subjected to a repeated measures ANOVA with validity (valid and invalid), target location (left and right) and TMS condition (active and sham TMS) as within-participant factors. In the *categorization* task, only a main effect of validity in reaction time reached significance ($F(1, 6) = 60.22$, $p<0.001$), with faster responses for valid than invalid trials. In the *detection* task, a significant interaction between validity and TMS condition was observed on perceptual sensitivity ($F(1, 6) = 6.54$, $p = 0.043$), indicating the dependency of TMS effects on the validity of the cue. More specifically, active stimulation improved perceptual sensitivity (d') only when the cue correctly predicted the location of the target (valid trials), as compared to sham TMS ($F = 19.26$, $p = 0.005$). Interestingly, no differences between active and sham TMS were observed for invalid trials, in which the cue incorrectly predicted the location of the target ($F<1$) (Figure 4, Table 2). No

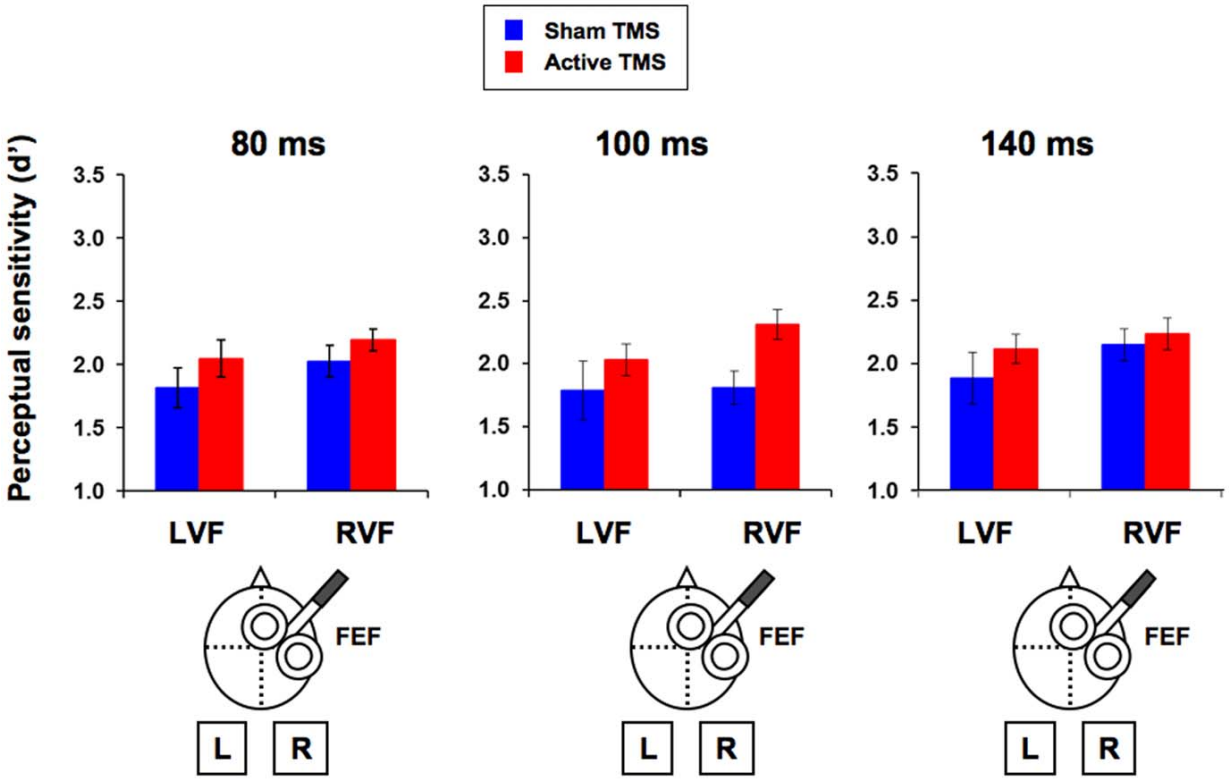


Figure 3. TMS-induced modulations of right FEF pre-target activity on conscious detection (Experiment 1). Perceptual sensitivity (mean ± SE) for the three different timings (80, 100 and 140 ms pre-target onset) used in Experiment 1. Data is presented separately for targets displayed in the visual field contralateral (left visual field, LVF) or ipsilateral (right visual field, RVF) with respect to the targeted right FEF under active (red) or sham (blue) TMS stimulation. A main effect of TMS condition was observed, with higher perceptual sensitivity scores under active than sham TMS pulses ($F(1,9) = 8.31$, $p = 0.018$). Based on the a priori hypothesis that such effect depended on timing, we performed three separate repeated measures ANOVA for the three timings. The TMS effect only reached significance when pulses were delivered 80 ms pre-target onset ($F(1, 9) = 9.77$, $p = 0.012$), but not when applied 100 ms ($F = 5.09$, $p = 0.051$) nor 140 ms ($F = 3.95$, $p = 0.078$) pre-target onset.
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Table 1. Data from TMS-induced modulations of right FEF pre-target activity on visual performance (Experiment 1).

Task	Mean values±SE	TMS condition	80 ms		100 ms		140 ms	
			LVF	RVF	LVF	RVF	LVF	RVF
Detection	**d' score**	**Sham**	1.82±0.16	2.03±0.13	1.79±0.23	1.81±0.13	1.89±0.20	2.15±0.12
		Active	2.05±0.15	2.20±0.09	2.03±0.13	2.31±0.12	2.12±0.11	2.23±0.12
	Beta measure	**Sham**	5.69±0.45	5.66±0.29	4.66±0.56	4.93±0.53	5.38±0.45	5.42±0.35
		Active	5.60±0.37	6.84±0.34	5.91±0.33	5.50±0.37	5.90±0.31	5.32±0.43
Categorization	**RT (ms)**	**Sham**	849±55	778±51	805±38	767±49	814±49	779±58
		Active	840±52	792±53	833±52	776±41	834±50	789±40
	Accuracy	**Sham**	0.68±0.03	0.79±0.04	0.70±0.04	0.78±0.03	0.76±0.04	0.72±0.03
		Active	0.77±0.02	0.79±0.02	0.69±0.03	0.76±0.02	0.69±0.04	0.75±0.02

Perceptual sensitivity (d' scores, mean ± SE) and response criterion (beta measures, mean ± SE), and reaction time (RT) (mean ± SE) and accuracy (mean ± SE), for the three different TMS delivery timings (80, 100 and 140 ms pre-target onset), obtained respectively for the conscious visual *detection* and visual *categorization* tasks explored in Experiment 1. Data are presented for targets displayed in the visual field contralateral (left visual field, LVF) and ipsilateral (right visual field, RVF) with respect to the stimulated right FEF under the effects of active or sham TMS pulses.

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significant main effects or interactions were observed for the response bias (beta).

Discussion

The potential of non-invasive brain neurostimulation to boost cognitive performance beyond the limits set up by individual skills and capabilities in healthy [27,28,29,30,31,32,33] and pathological states [34,35,36,37,38] has been postulated for more than a decade. Thanks to its ability to activate discrete cortical regions and associated networks [39], TMS, a focal magnetically-based non-invasive brain stimulation technique, has been shown to induce punctual or lasting changes in the firing patterns of restricted key cortical regions and, in virtue of such capabilities, influence normal or pathological human behavior [40,41]. We hereby assayed in healthy humans whether conscious visual

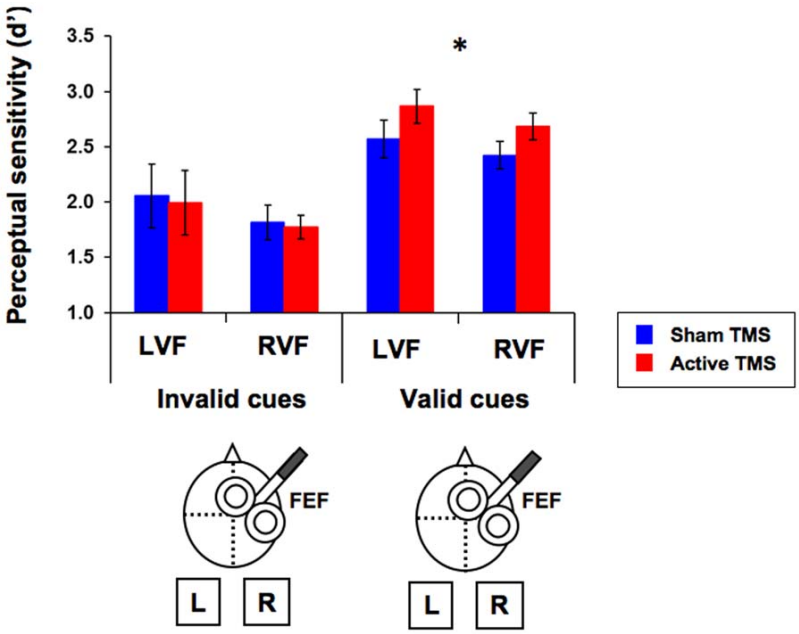


Figure 4. TMS-induced modulations of FEF pre-target activity on conscious detection after cue-driven attentional orienting (Experiment 2). Perceptual sensitivity (mean ± SE) for targets displayed in the visual field contralateral (left visual field, LVF) or ipsilateral (right visual field, RVF) with respect to the stimulated right FEF site under active TMS (red) or sham TMS (blue). An interaction between validity and TMS proved statistically significant ($F(1, 6) = 6.54$, $p = 0.043$) indicating that, when delivered after the presentation of a peripheral predictive visuo-spatial cue, TMS pulses yielded significant bilateral enhancements of conscious visual detection only when the cue correctly signaled the location of the subsequent target (valid trials, $F = 19.26$, $p = 0.005$, indicated by the asterisk), whereas no effects were observed when the cue incorrectly predicted it (invalid trials, $F<1$).

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Table 2. Data from TMS-induced modulations of FEF pre-target activity on visual performance after cue-driven attentional orienting (Experiment 2).

Task	Mean values±SE	TMS condition	Invalid		Valid	
			LVF	RVF	LVF	RVF
Detection	**d' score**	**Sham**	2.05±0.77	1.81±0.41	2.57±0.45	2.42±0.33
		Active	1.99±0.78	1.77±0.28	2.87±0.40	2.68±0.32
	Beta Measure	**Sham**	15.67±6.57	15.73±4.87	9.73±6.89	13.41±6.54
		Active	13.49±5.21	14.94±4.76	10.44±4.79	14.09±7.13
Categorization	**RT (ms)**	**Sham**	910±175	825±74	717±133	730±105
		Active	832±136	820±120	719±128	719±97
	Accuracy	**Sham**	0.73±0.18	0.79±0.03	0.73±0.05	0.79±0.04
		Active	0.79±0.14	0.83±0.10	0.74±0.05	0.74±0.06

Perceptual sensitivity (d' scores, mean ± SE) and response criterion (beta measures, mean ± SE), and reaction time (RT) (mean ± SE) and accuracy (mean ± SE), for the conscious visual *detection* and visual *categorization* tasks explored in Experiment 2. Data are presented for valid and invalid trials, in which targets were displayed in the visual field contralateral (left visual field, LVF) and ipsilateral (right visual field, RVF) to the stimulation site (right FEF), under the effects of active or sham TMS pulses.
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perception of low-contrast near-threshold targets could be enhanced with non-invasive neurostimulation, by modulating the activity of the right FEF prior to the onset of a visual target. Such brain region has been shown to be involved in visuo-spatial attentional orienting [7] and also to have bearing on conscious access [9,10,11,12,13] for visual stimuli. In agreement with prior work [14,15,18,19,42], our data from Experiment 1 indicate that right FEF pre-target activity is indeed relevant for conscious perception and that its non-invasive manipulation with TMS can induce relevant visual perceptual sensitivity improvements. Interestingly, when the dorsal attentional orienting network was previously activated by means of peripheral predictive visuo-spatial cues (Experiment 2), the modulation of right FEF pre-target activity with TMS pulses brought visual perceptual sensitivity modulations, which were shaped according to cue validity. More specifically, only when the prior visuo-spatial cue correctly predicted the site (left or right) of the subsequent target (valid trials) but not when it incorrectly predicted it (invalid trials), TMS induced facilitatory effects on conscious detection. These results suggest that cue-driven neural activations related to attentional orienting interact with conscious perception and have the potential to sculpt the effects of time locked pre-target FEF stimulation and render such perceptual facilitatory outcomes more specific. In spite of the lack of an active control condition mimicking not only the TMS clicking noise but also the scalp tapping sensations, the lack of significant effects when TMS pulses were combined with invalid spatial cues became an internal control that rules out a hypothetical contribution of such phenomena to our results.

Prior studies have demonstrated that the impact of non-invasive neurostimulation can be highly influenced by the pre-existing patterns of activity within the stimulated region and its associated networks [20,21]. In our experiments, visuo-spatial cues could have differentially modulated the firing patterns of distinct neuronal subpopulations within the right FEF region, prior to the onset of neurostimulation, and hence have primed the effects of FEF TMS only for those under certain states of activation. In support of this hypothesis, non-human primate research has shown that peripheral predictive visuo-spatial cues increase (and maintain increased along the cue-to-target period) the firing patterns of the FEF neurons that specifically code for the signaled location, but not for those whose receptive fields lay outside the cued site [43]. On the basis of this observation, different activity levels or 'states' of activation across FEF neuronal subpopulations as driven by visuo-spatial cues could easily explain how, on a trial-by-trial basis, highly selective visual facilitation patterns could emerge from the stimulation of roughly the same cortical resources as a function of cue validity [44].

Our data indicate that the FEF TMS visual facilitatory effects interacted with the orienting of spatial attention engaged by means of predictive spatial cues. Nonetheless, given the frequently hypothesized role of the right FEF not only as a crucial node of the dorsal attentional network but also as relevant in providing access to consciousness, which of these two systems might have been ultimately responsible for the observed visual facilitatory effects remains unclear. Contributing to the discussion of this issue, our data reveal that FEF TMS neither when used in isolation (Experiment 1) nor when combined with visuo-spatial cues (Experiment 2) did modulate the reaction times or accuracy levels for the visual *categorization* task. A behavioral study performed and published separately by our group assessed the behavioral effects of visuo-spatial attentional orienting in the same exact paradigm, and showed significant shorter reaction times in response to stimuli presented at attended than unattended locations (see [26] Experiment 4 for details). The latter effects, which were accompanied by a modulation in perceptual sensitivity in the *detection* task only when the cue was predictive about target location, strongly suggest that cue-validity effects in such paradigm should be considered a solid signature of attentional orienting. On such basis, it is tempting to interpret the current lack of reaction time modulations for the *categorization* task, accompanying improvements in visual *detection* by FEF pre-target activity modulations, not as ultimately mediated by the manipulation of visuo-spatial orienting processes but reflecting a genuine effect of right FEF TMS on visual consciousness. In spite of obvious differences between intact and damaged systems, this interpretation could be in agreement with patient work showing a relevant role of the prefrontal cortex in access to consciousness of masked stimuli, not accountable either by attentional orienting processes [45]. Nonetheless, given that attention can alter appearance [3] and that in our paradigm composed of two serial tasks, subjects could have eventually sacrificed reaction time for accuracy, or categorization performance for detection performance, whether attention can modulate conscious visibility without affecting reaction time remains an open question.

Our data contribute further evidence in support of the notion that the right FEF and its associated systems may constitute according to monkey [14,15,42] and human [19,44] data, a key area facilitating access to consciousness for visual stimuli. Moreover, our combined modulation strategy based on an 'at will' stimulation of the FEF and the presentation of visuo-spatial cues, showed its ability to selectively enhance human visual awareness for low-contrast near-threshold stimuli and to shape the specificity of such effects, thus setting up the stage for the use of TMS on the direct manipulation of visual conscious perception in healthy and pathological states. Unfortunately, in absence of brain neuroimaging data, we cannot yet rule out if such facilitatory phenomena were driven locally at the stimulated right FEF and directly manipulated by the alleged ability of this area to contribute to visual awareness; emerged from connectivity-conveyed trans-synaptic effects on primary visual regions through fronto-parietal-occipital top-down projections [17,46]; or resulted from the modulation of other intermediate cortical or subcortical structures interconnected with the FEF. This remains a highly relevant question to be addressed in an immediate future through specific experiments which, as elegantly performed elsewhere [17,46] might require the combination of stimulation and neuroimaging. Moreover, in the current study, we manipulated activity patterns within the right FEF since this area is a key component of the dorsal network devoted to visuo-spatial attentional orienting; its anatomical location can be individually confirmed through a well-established mapping procedure; there is precedence on its ability to induce connectivity mediated functional modulation on visual regions, and in consideration of its hypothesized role in visual awareness. In agreement with findings suggesting the dominant role of the right hemisphere sites in attentional orienting and consciousness [18,19,27], our intervention in the right FEF proved similarly efficacious for right and left targets. Prior studies have also reported bilateral effects for right FEF activity modulations, whereas the manipulation of the left FEF stimulation would be restricted to an influence on targets presented in the right visual hemifield. Future venues will have to explore the role of left FEF pre-target activity in conscious visual perception and the extent of such effects throughout the visual field. Furthermore, functional MRI and TMS brain-function studies suggest that the modulation of non necessarily frontal regions, such as the right intraparietal sulcus or the angular gyrus [7] could potentially also interact with cue validity and result in visual facilitatory effects, and thus they would also deserve to be explored in similar paradigms in the future.

In sum, our findings show that FEF pre-target activity can be effectively manipulated to influence conscious visual perception using non-invasive neurostimulation methods, and that a combined strategy based on right hemisphere frontal stimulation and visual cues can be implemented not only to episodically enhance visual performance, but to shape the selectivity of those effects. The fact that a combination of TMS and attentional cues can indeed improve visual sensitivity should be considered a proof of concept that visual capabilities can be manipulated and improved through those approaches. On that basis, strategies operating on cerebral sites involved in attentional orienting and conscious access could become a reality to punctually increase visual capabilities in healthy participants. Similar principles could be also applied to clinical rehabilitation, aiming at containing visual acuity losses in patients with retinal defects, and allowing the emergence of episodic or lasting periods of conscious vision in cortically damaged patients. Nonetheless, it should also be strongly emphasized that the ameliorations demonstrated in our study operate trial-by-trial and remain extremely short lasting. Furthermore they have been demonstrated for lateralized right or left peripheral detections and thus might not equally occur for targets presented in other locations of the visual hemifield. Both aspects weaken the current applicability of the results for meaningful behavioral ameliorations in healthy individuals or therapeutic applications in patients. In order to overcome such limitations, however, longer rTMS patterns and multi-day rTMS regimes combined with spatial cuing paradigms remain to be studied and evaluated for their ability to generate lasting increases in visual sensitivity. Similarly, the differential ability of TMS based approaches to generate ameliorations for targets presented at different visual field locations than those tested in the current paper would need to be studied before our findings could be considered potentially interesting for clinical applications.

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Author Contributions

Conceived and designed the experiments: LC ABC AVC. Performed the experiments: LC AVC. Analyzed the data: LC ABC RQ AVC. Contributed reagents/materials/analysis tools: LC ABC AVC. Wrote the paper: LC AVC. RQ Contributed to data analysis and manuscript discussions leading to the written interpretations included in this PLoS ONE submission: RQ.

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6.2. AMELIORATION DE LA PERCEPTION VISUELLE PAR SMT RYTHMIQUE DES FEFS

Lors de leurs expériences chez le singe, Buschman et Miller ont montré grâce à l'enregistrement simultané de plusieurs neurones que le réseau fronto-pariétal se synchronise dans la partie supérieure des fréquences beta (22-34 Hz) lors de l'engagement endogène de l'attention. En revanche, lors de l'engagement exogène, le même réseau se synchronise à des fréquences plus hautes (35-55 Hz) (Buschman & Miller 2007). La synchronisation du réseau fronto-pariétal autour de 30 Hz lors de l'orientation endogène de l'attention a également été observée chez l'Homme (Phillips & Takeda 2009). Aussi, récemment, l'idée d'utiliser la SMT pour moduler l'activité oscillatoire au sein de régions corticales a émergé (Romei et al. 2010; Thut et al. 2011). Dans notre expérience, nous avons stimulé la région FEF droite à deux fréquences spécifiques, 30 Hz et 50 Hz. Le paradigme expérimental est similaire à l'étude précédente excepté qu'aucun indice attentionnel n'a été utilisé ici. Quatre impulsions de SMT toutes les 33 ms (30 Hz) ou 20 ms (50 Hz) ont été appliquées juste avant l'apparition de la cible. Afin de s'assurer de l'effet spécifique de la fréquence, nous avons comparé l'effet de cette rafale à quatre impulsions appliquées dans la même fenêtre temporelle mais ne présentant pas de fréquence spécifique. Comparée à leurs conditions *sham*, la stimulation à 30 Hz provoque une augmentation de la sensibilité visuelle (*d'*) alors que la stimulation à 50 Hz change le critère de réponse. Les résultats comportementaux, différents suivant la fréquence de stimulation, mettent en valeur l'importance de l'activité rythmique d'une région et sa capacité à coder des mécanismes différents en fonction de son activité oscillatoire.

Brief Communications

Causal Frequency-Specific Contributions of Frontal Spatiotemporal Patterns Induced by Non-Invasive Neurostimulation to Human Visual Performance

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Neural oscillatory activity is known to play a crucial role in brain function. In the particular domain of visual perception, specific frequency bands in different brain regions and networks, from sensory areas to large-scale frontoparietal systems, have been associated with distinct aspects of visual behavior. Nonetheless, their contributions to human visual cognition remain to be causally demonstrated. We hereby used non-uniform (and thus non-frequency-specific) and uniform (frequency-specific) high-beta and gamma patterns of noninvasive neurostimulation over the right frontal eye field (FEF) to isolate the behavioral effects of oscillation frequency and provide causal evidence that distinct visual behavioral outcomes could be modulated by frequency-specific activity emerging from a single cortical region. In a visual detection task using near-threshold targets, high-beta frequency enhanced perceptual sensitivity (d') without changing response criterion (beta), whereas gamma frequency shifted response criterion but showed no effects on perceptual sensitivity. The lack of behavioral modulations by non-frequency-specific patterns demonstrates that these behavioral effects were specifically driven by burst frequency. We hypothesize that such frequency-coded behavioral impact of oscillatory activity may reflect a general brain mechanism to multiplex functions within the same neural substrate. Furthermore, pathological conditions involving impaired cerebral oscillations could potentially benefit in the near future from the use of neurostimulation to restore the characteristic oscillatory patterns of healthy systems.

Introduction

Evidence in support of the fundamental role played by cerebral oscillations in cognitive processing has strongly emerged in the last decades. In the particular domain of visual perception, prior work has indicated that for different brain regions and systems, from sensory areas to large-scale frontoparietal networks exerting top-down influences on visual processing and behavioral performance, oscillatory activity at specific frequency bands might contribute to distinct aspects of behavior (Donner et al., 2007; Fries, 2009; Siegel et al., 2011). However, the specific role of neural oscillatory frequency remains to be causally isolated.

For nearly two decades, the ability of non-invasive neurostimulation to depolarize local neuronal clusters and interfere with neural processing has been used to establish, in several cognitive domains, causal associations between brain regions and behaviors (Wagner et al., 2007). Recently, by comparing the behavioral modulations obtained at different frequencies, transcranial alternate current stimulation and short-burst and repetitive transcranial magnetic stimulation (TMS) have been used in the investigation of the oscillatory basis of human cognition (Klimesch et al., 2003; Kanai et al., 2008; Romei et al., 2010, 2011; Feurra et al., 2011). More importantly, seminal work performed in this field has demonstrated that uniform TMS bursts can entrain rhythmic brain oscillation patterns tuned to the applied input frequency (Thut et al., 2011).

In the present study, we compared the behavioral impact of frequency-specific (or uniform) and non-frequency-specific (or non-uniform) TMS patterns delivered over a right frontal region to provide causal evidence in humans on the modulatory role of high-beta and gamma activity to distinct aspects of human visual performance. For both frequencies, these two types of TMS patterns had equal duration and number of pulses. Nonetheless, in frequency-specific patterns pulses were uniformly distributed across the duration of the burst, whereas in non-frequency-

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specific patterns, those were delivered at fixed unequal interpulse intervals. This approach warrants the delivery of an identical amount of activity during the same time interval in both types of bursts, isolating the specific impact of stimulation frequency to behavior.

We targeted the right frontal eye field (FEF), a site involved in visuospatial attentional orienting (Corbetta and Shulman, 2002; Corbetta et al., 2008) and conscious perception (Grosbras and Paus, 2003; Moore and Armstrong, 2003; Libedinsky and Livingstone, 2011; Chanes et al., 2012), holding rich interactions with parietal and occipital brain regions, that can engage in high-beta (30 Hz) and gamma (50 Hz) oscillatory activity (Fries et al., 2001; Buschman and Miller, 2007; Gregoriou et al., 2009). More specifically, Buschman and Miller (2007) reported a differential involvement of these two oscillation frequencies in a pop-out and a visual search task engaging, respectively, exogenous and endogenous attentional orienting processes, which are known to induce distinct behavioral influences on human visual performance (Chica et al., 2011). We hypothesized that uniform TMS bursts delivered over the right FEF at high-beta versus gamma frequency would yield frequency-specific effects on visual performance, compared with their equivalent non-uniform TMS patterns not tuned to any particular frequency.

Materials and Methods

Two groups of 14 participants (6 women and 8 men and 10 women and 4 men), aged between 19 and 39 years (average of 25 ± 3 and 25 ± 6 years old) reporting no history of neurological or psychiatric disorders and normal or corrected-to-normal vision, took part in the experiments. Twenty-three of them were naive as to TMS and to the purpose of the experiments, and they all participated voluntarily. The protocol was reviewed by the Inserm ethical committee and approved by an Institutional Review Board (CPP Ile de France 1).

Apparatus, stimuli, and procedure. Visual stimuli were displayed on an eye-tracker screen (Tobii Technology AB; 17 inches wide, 1024 × 768) using a laptop computer (Dell Latitude E6400) and standard stimulus presentation software (E-Prime Software). Each trial started with a gray resting screen (luminance: 75 cd/m^2, 2500 ms), followed by a fixation screen (randomly lasting between 1000 and 1500 ms) (Fig. 1*a*). The fixation cross (0.5 × 0.5°) was displayed in the center, along with three rectangular boxes (6.0 × 5.5°): one central and two lateral ones (centered 8.5° to the left and right of the fixation point). Then, the fixation cross became slightly larger (0.7 × 0.7°, 66 ms) to alert participants of an upcoming event. After an interstimulus interval (233 ms), a target appeared at the center of one of the two lateral boxes for a brief period of time (33 ms). The target consisted of a low-contrast Gabor stimulus (2 cycles/degree spatial frequency, 3.0° diameter, 0.3° of SD, minimum and maximum Michelson contrast of 0.031 and 0.283, respectively) with its lines tilted 1° to 10° clockwise or counterclockwise. The intertrial interval lasted at least 4 s.

Participants were asked to execute two tasks. The first task was to determine the orientation of the Gabor lines (discrimination task) by pressing the corresponding button on a computer keyboard ("1" for left and "2" for right) with the index and middle fingers of their right hand. Participants were forced to guess a response even when the target was not present or they did not consciously perceive it and accuracy was collected as outcome measure. The second task was to report whether they had consciously perceived the Gabor or not (conscious detection task). To do so, two arrow-like stimuli (<<< and >>>) pointing to the left and to the right were simultaneously presented below and above the fixation cross. Participants were provided with 3 keys, which they had to operate with their left hand: an upper key "d," a lower key "c," and the space bar. The upper and lower keys were associated to the arrows presented on the top and the bottom, respectively. Participants had to respond by pressing the space bar if they did not see the stimulus, or the key ("d" or "c") to select the arrow pointing to the visual hemifield (right/left) in which they perceived the target. The location of each arrow, above or below the fixation point, was randomized across trials. This task was assessed through perceptual sensitivity (d') and response criterion (beta), two measures used in Signal Detection Theory (Green and Swets, 1966; Macmillan and Creelman, 2005). Perceptual sensitivity is a bias-free measure that informs on participants' ability to detect weak signals in situations that might be strongly influenced by belief. Response bias (beta) describes the relative preference of participants for one response over the alternative one, independently on signal strength. When participants favor neither a "yes, I saw it" response nor a "no, I did not see it" response, beta is equal to 1. Values lower than 1 indicate a bias toward the affirmative response, whereas values >1 indicate a bias toward the negative response. To compute these measures, trials in which the location of a target was correctly determined by participants were considered as correct detections or "hits"; trials in which the presence of the target was not acknowledged were counted as "misses"; trials in which participants reported the location for targets that were not presented were considered "false alarms"; trials in which the target was absent and participants correctly reported not to have seen it were considered "correct rejections"; and, finally, trials in which the location of a present target was incorrectly reported were counted as "errors" and excluded from further analyses. Eye movements were monitored during each trial for fixation control purposes. Fixation was considered broken when participants' eyes position was recorded outside the central box (i.e., 3° away from the fixation cross horizontally and 2.75° vertically).

A titration procedure performed before the onset of the experiment allowed us to determine for each participant the stimulus contrast at which ~50% of the displayed targets were consciously reported. The degree of line tilting was also adjusted to maintain discrimination accuracy between 65 and 85% of correctly reported targets. Such titration levels ensured that in both tasks, performance was halfway between the worst (0% in the detection task and 50% in the forced-choice discrimination task) and the best possible performance (100% for both tasks).

Participants started the titration trials with a high contrast stimulus and, every 20 trials, target contrast and the degree of line tilting were adjusted (in steps of 0.07 Michelson contrast and 1° of tilting, respectively) to converge to the preestablished criteria. The experiment started once performance levels reached those criteria. Throughout the experiment, stimulus parameters were automatically adjusted every 20 trials to maintain these titration levels.

Each block consisted of 200 trials, including 40 trials in which the target was absent. In half of the trials, a short burst of 4 TMS pulses was applied to the right FEF (active TMS trials) so that the last pulse of each burst was always delivered 16 ms before target onset. In the other half (sham TMS trials) the same short burst was delivered by a second TMS coil placed next to the stimulation site, with the coil surface perpendicular to the head surface, preventing the magnetic field from reaching the skull and stimulating the brain. The order of active and sham TMS trials was randomized across trials. Participants were allowed to take a short break every 40 trials and at the end of each sub-block received feedback on the screen about their performance and eye movement rates.

In two groups of participants, we explored the effects of two different stimulation frequencies, high-beta (30 Hz) and gamma (50 Hz), on visual performance. Each group performed two blocks of trials: in the frequency-specific block, 4 TMS pulses were distributed uniformly, whereas in the non-frequency-specific block, pulses were unequally distributed over the same period of time (the first and last pulses occurred at timings identical to those in the frequency-specific block, whereas the second and third pulses were slightly anticipated and delayed respectively; Fig. 1*b*). The order in which participants performed the two blocks was counterbalanced across participants.

Transcranial magnetic stimulation (TMS). TMS pulses were delivered using a biphasic repetitive stimulator (Superapid 2, Magstim) with a 70-mm-diameter figure-of-eight coil (Fig. 1*c*). A structural T1-weighted MRI scan (3T Siemens MPRAGE, flip angle = 9, TR = 2300 ms, TE = 4.18 ms, slice thickness = 1 mm) was acquired for every participant at the CENIR (Centre de Neuro-Imagerie de Recherche) MRI center (Salpêtrière Hospital, Paris). The right FEF region was localized on each individual MRI using averaged Talairach coordinates $x = 31$, $y = -2$,

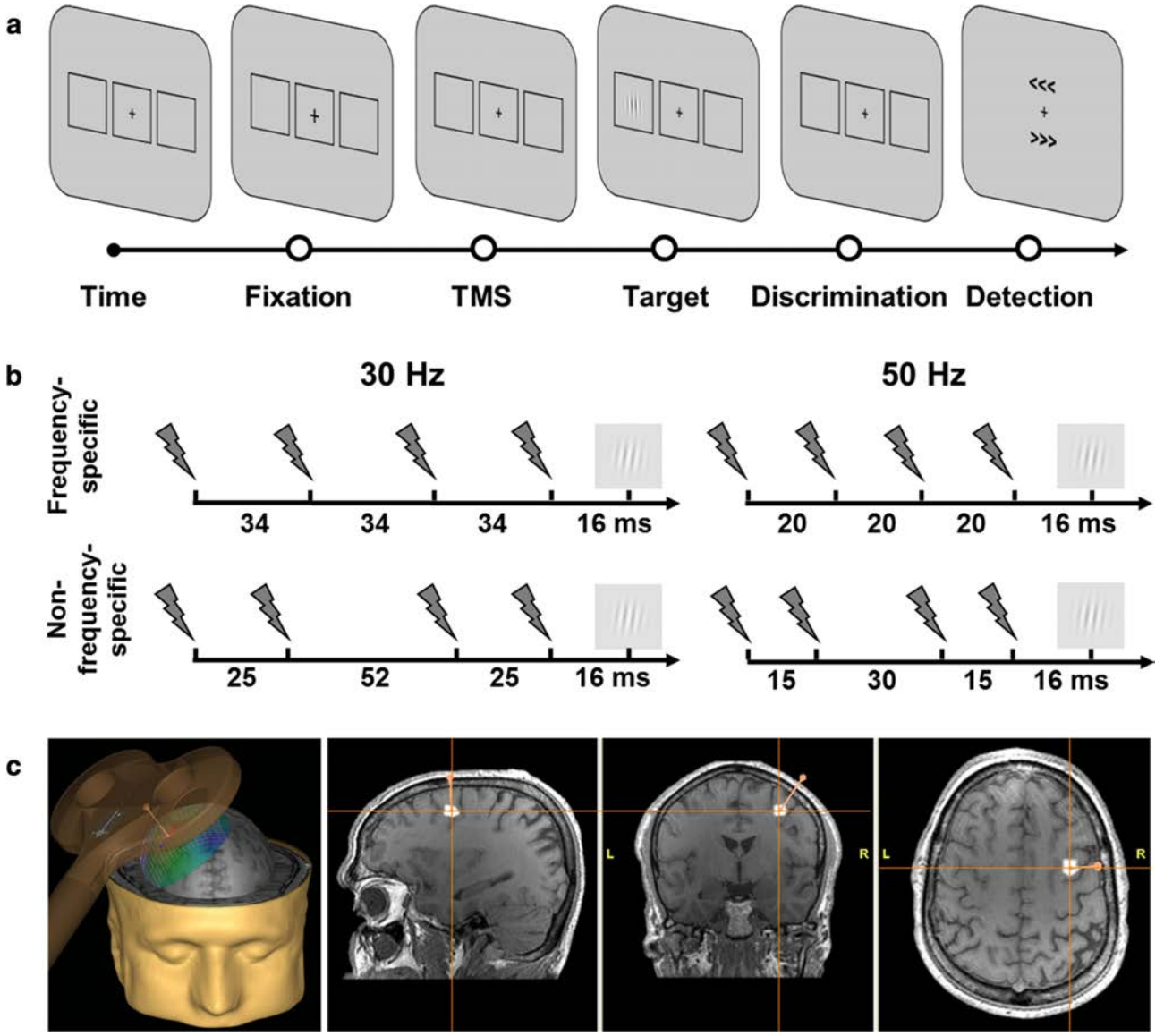


Figure 1. Experimental design. ***a***, Following a period of central fixation, a low-contrast near-threshold Gabor stimulus was briefly presented within a left or right peripheral box. Participants were requested to perform a discrimination task, indicating the orientation of the Gabor lines (left/right), followed by a conscious detection task in which they reported if they had seen or not a Gabor and where ("no" or if "yes," left/right). ***b***, Schematic drawing representing the temporal distribution of the 4 pulses of each TMS burst in frequency-specific (uniform) and non-frequency-specific (nonuniform) blocks. For each stimulation frequency (30 Hz and 50 Hz), bursts used in either block were equal in duration and number of pulses. ***c***, TMS coil positioning on the right FEF, displayed in a representative 3D reconstructed native MRI brain and its associated sagittal, axial and coronal brain sections.

$z = 47$ (Paus, 1996) and a 0.5 cm radius spherical region of interest (for details see Chanes et al., 2012). The final MRI was uploaded into a frameless stereotaxic system and reconstructed in 3D for its use in an online stereotaxic TMS neuronavigation system (eXimia NBS System, Nexstim).

At all times, the TMS coil was held tangentially to the skull, with its handle oriented ~45° in a rostral-to-caudal and lateral-to-medial orientation, i.e., approximately parallel to the central sulcus. Coil position was tracked online throughout the experiments and kept steady within an area of ~2 mm radius from the targeted site. The representation of the right primary motor cortex (M1) of the abductor pollicis brevis muscle was located and the left and right motor thresholds were determined as the TMS intensity yielding thumb twitching responses in ~50% of the attempts.

For all interventions, stimulation intensity was set up at 45% of the TMS machine maximal output. Nonetheless, in some participants such a level had to be slightly decreased to abolish temporal and facial muscle involuntary activations, blinks, or other types of facial sensations induced by magnetic field spread. Before the experiment, we verified on each participant that none of the TMS FEF patterns used induced contralateral motor activations on forearm or hand muscles. The average intensities at which participants were stimulated were 44.3% (SD 1.5%) and 44.9% (SD 0.5%) of the maximum machine output for the 30 and 50 Hz bursts groups, respectively (i.e., 72 ± 13% and 74 ± 14% of their individual motor thresholds).

Statistical analyses. Outcome measures (perceptual sensitivity and response criterion for the conscious detection task and accuracy for the discrimination task) of each group (30 and 50 Hz) were subjected to a 2 × 2 × 2 repeated-measures ANOVA with block (frequency- and non-frequency-specific), target location (left and right visual field), and TMS condition (active and sham) as within-participant factors. The same ANOVA was performed for trials in which participants reported to have seen the target but incorrectly determined its location (error trials), which were eliminated from the analyses, to exclude any potential effect

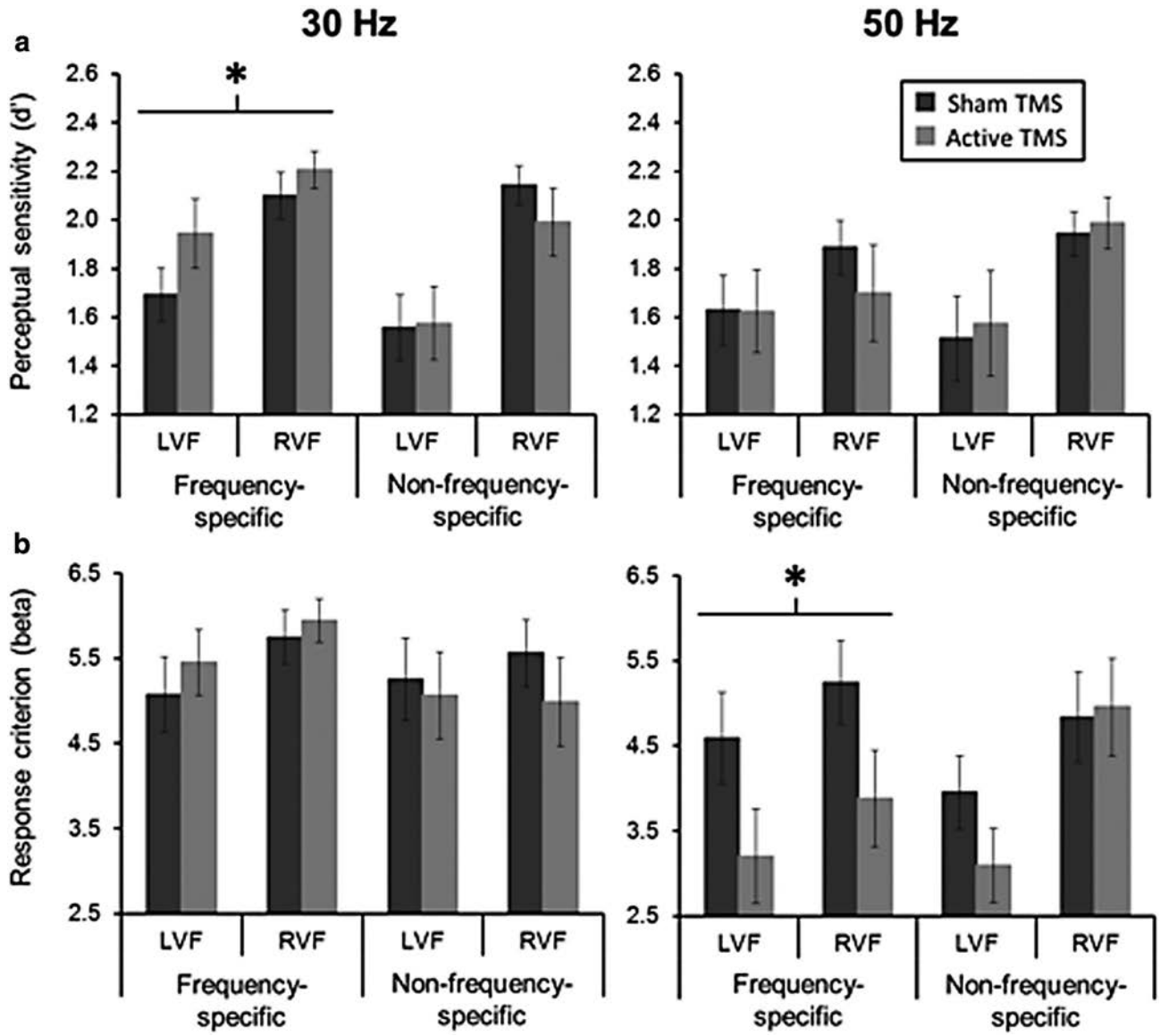


Figure 2. Impact of neurostimulation bursts at 30 and 50 Hz on conscious visual detection measures. ***a***, ***b***, Series of histograms displaying the effects of active (light gray) or sham (dark gray) frequency-specific and non-frequency-specific TMS bursts on perceptual sensitivity (***a***) and response criterion (***b***) values for each of the two TMS frequencies tested. Data are presented for targets displayed in the contralateral (left) and ipsilateral (right) visual fields (LVF and RVF, respectively) with regards to the stimulated right FEF region. Notice that active 30 Hz TMS bursts (but not their non-frequency-specific associated bursts) enhanced perceptual sensitivity (d') compared with sham TMS patterns. Neither uniform 50 Hz bursts nor their associated non-frequency-specific patterns modulated this outcome measure. In contrast, active 50 Hz TMS bursts (but not its associated non-frequency-specific burst) relaxed response criterion for active TMS bursts compared with sham. No significant criterion differences were observed either for 30 Hz TMS bursts or for their associated non-frequency specific patterns. Asterisks indicate statistically significant differences for active versus sham TMS conditions.

of TMS in such trials. Finally, the factor group (30 and 50 Hz) was implemented as between-participant factor in a general ANOVA with the same within-participant factors described above.

Results

One participant was excluded from the analyses in the 30 Hz group because broke fixation in >50% of the trials. Trials in which participants broke fixation were eliminated from the analyses (8% and 5% for the 30 and 50 Hz groups, respectively). Moreover, error trials were also eliminated (3% and 7% of seen targets for the 30 and 50 Hz groups, respectively). The repeated-measures ANOVA for errors did not yield any significant main effects or interactions, indicating that those were similar across conditions. The average number of trials per participant used in the analyses of each experimental condition ranged between 35 and 38 (mean ± SD: 36 ± 4). In the discrimination task, participants' general accuracy was 63% and 64% for the 30 Hz and 50 Hz groups, respectively. As expected, it was high when they reported to have seen the target (75% and 76%, respectively), and it remained at chance levels when they reported not to have seen it (50% for both groups).

Our data revealed frequency-specific contributions of FEF activity to visual performance (Fig. 2; Table 1). For the conscious detection task, active TMS bursts delivered at 30 Hz, but not at the matched non-frequency-specific patterns, improved participants' perceptual sensitivity (significant interaction between block and TMS condition, $F_{(1,12)} = 6.07$, $p = 0.030$). Scores were higher for

Table 1. Summary of main statistical effects and interactions of the different neurostimulation patterns on conscious visual detection

Group	Main effects and interactions	Perceptual sensitivity (d')		Response criterion (beta)	
		F	*p*	*F*	*p*
30 Hz	Block	6.328	0.027*	0.715	0.414
	Side	10.978	0.006*	1.770	0.208
	TMS	0.576	0.463	0.056	0.816
	Block × Side	1.219	0.291	1.584	0.232
	Block × TMS	6.072	0.030*	3.897	0.072
	Side × TMS	2.178	0.166	1.055	0.325
	Block × Side × TMS	0.013	0.911	0.045	0.836
50 Hz	Block	0.229	0.641	0.002	0.968
	Side	2.180	0.164	8.069	0.014*
	TMS	0.048	0.830	7.948	0.014*
	Block × Side	1.666	0.219	1.005	0.334
	Block × TMS	1.776	0.205	6.418	0.025*
	Side × TMS	0.866	0.369	0.486	0.498
	Block × Side × TMS	0.288	0.601	0.973	0.342

All statistically significant main effects and interactions (repeated-measures ANOVA) are indicated in the table by an asterisk (*$p < 0.05$). In addition to the significant interaction between block and TMS condition reported, for 30 Hz TMS patterns and its associated non-frequency-specific bursts: perceptual sensitivity was higher for targets displayed to the right than to the left visual field ($F_{(1,12)} = 10.98$, $p = 0.006$) and for frequency-specific (or uniform) blocks than for non-frequency-specific (or non-uniform) blocks ($F_{(1,12)} = 6.33$, $p = 0.027$). For the 50 Hz TMS pattern (and their corresponding non-frequency-specific or non-uniform bursts), in addition to the significant interaction between block and TMS condition reported, response criterion was more relaxed for targets displayed to the left than to the right visual field ($F_{(1,13)} = 8.07$, $p = 0.014$) and with active than sham TMS bursts ($F_{(1,13)} = 7.95$, $p = 0.014$).

active than for sham TMS only when pulses were uniformly delivered at 30 Hz (planned comparison active vs sham for the frequency-specific block: $F = 5.55$, $p = 0.036$), but not when non-uniform patterns were used (planned comparison active vs sham for the non-frequency-specific block: $F < 1$) (Fig. 2*a*, left). Moreover, no significant main effects or interactions were observed for the response criterion (Fig. 2*b*, left). In the discrimination task, no significant modulations of accuracy were observed in any of the blocks.

On the other hand, TMS bursts delivered at 50 Hz and their corresponding non-frequency-specific patterns proved unable to modulate perceptual sensitivity (d') in the conscious detection task (Fig. 2*a*, right). However, the uniform pattern shifted response criterion (significant interaction between block and TMS condition, $F_{(1,13)} = 6.42$, $p = 0.025$). Active 50 Hz TMS bursts decreased the strictness of participants' response criterion compared with sham TMS (planned comparison active vs sham for the frequency-specific block: $F = 13.37$, $p = 0.003$), whereas no significant differences in response criterion were observed when TMS bursts were delivered at their associated non-frequency-specific pattern (planned comparison active vs sham for the non-frequency-specific block: $F = 1.05$, $p = 0.325$) (Fig. 2*b*, right). In the discrimination task, no main effects or interactions were observed.

Finally, the significant interaction between group × block × TMS condition for both perceptual sensitivity ($F = 6.84$, $p = 0.015$) and response criterion ($F = 10.14$, $p < 0.01$) when group (30 and 50 Hz) was integrated as between-participant factor in a general ANOVA emphasizes the frequency specificity of the TMS impact.

Discussion

Our findings shed novel light on the oscillatory basis underlying visual detection behavior for near-threshold stimuli and suggest distinct modulatory roles for high-beta and gamma frontal activity in visual performance.

Frontal 30 Hz TMS bursts impacted perceptual sensitivity (d') in a conscious visual detection task, whereas 50 Hz TMS patterns yielded changes in response criterion. Beta oscillations from the FEF have been previously correlated with modulations of visual performance (Gross et al., 2004; Donner et al., 2007), and we thereby show here that such activity could be causally linked to these behavioral effects. These oscillations may reflect reverberant activity within and among visual, frontoparietal and frontal motor cortices (Engel and Fries, 2010), which might facilitate the accumulation and maintenance of sensory evidence for decision-making (Donner et al., 2007; Siegel et al., 2011). Importantly, our data provide direct proof that the processing of visual sensory evidence could be episodically enhanced by an extrinsic source of neural synchronization, such as TMS, tuned to a specific oscillation frequency.

Patterns at 50 Hz over the right FEF specifically decreased response criterion when detecting faint near-threshold stimuli. This finding is consistent with prior work showing a correlation between prestimulus gamma-band oscillations in occipital regions and decision biases (Wyart and Tallon-Baudry, 2009). We now extend this result to frontal regions, and, most importantly, we hypothesize a causal contribution of gamma-band oscillations to such processes. The modulation of these phenomena by stimulus features reported previously suggests that oscillatory activity at this frequency band is likely to reflect sensory evidence (Frien et al., 2000; Siegel and König, 2003; Kayser and König, 2004; Hall et al., 2005; Henrie and Shapley, 2005; Hoogenboom et al., 2006; Liu and Newsome, 2006; Vidal et al., 2006; Siegel et al., 2007; Berens et al., 2008; Wyart and Tallon-Baudry, 2008, 2009). Accordingly, we hypothesize that the induction of a brief low-gamma pretarget pattern on a higher cortical region, such as the right FEF, holding connections with the visual cortex, may have been encoded as sensory evidence, and thus favored a conscious affirmative detection response ("Yes I saw it") over a negative one ("No I did not see it") for near-threshold targets, independent of stimulus presence, hence decreasing the strictness of the response criterion.

The double dissociation observed between stimulation frequency (30 Hz vs 50 Hz bursts) and behavioral outcome measure (perceptual sensitivity vs response criterion), together with the lack of behavioral modulations when the same activity (equal number of TMS pulses delivered across the same interval at identical stimulation intensity) was induced by a slightly different TMS pattern indicate that the observed effects are a specific consequence of stimulation frequency, rather than depend on the total amount of activity induced within a critical time window. Furthermore, none of our interventions proved able to modulate the visual discrimination task, suggesting that the induced activity might not impact visual performance at a purely perceptual level but could rather operate on conscious access. Alternatively, the discrimination task could not have been modulated simply because it might require more refined processing and accumulation of more evidence.

In sum, our results provide causal evidence that characteristic spatiotemporal activity patterns induced by neurostimulation to the same cerebral region can yield exquisitely distinct behavioral outcomes such as increases of visual sensitivity and decreases of response criterion. Such evidence may reflect a general brain mechanism to multiplex functions within the same neural substrate (Thut et al., 2012). Findings coherent with this notion have been reported for parietal TMS bursts delivered at lower stimulation frequencies (Romei et al., 2010, 2011). Similarly, recordings in non-human primates have provided correlational evidence of enhanced gamma frequency synchrony between frontal and posterior parietal regions during exogenous attention in a pop-out visual detection task, and synchrony increases at the high-beta range between these

same areas during endogenous attentional orienting, as tested in a visual search paradigm (Buschman and Miller, 2007, 2009). Similar to the current data, such evidence in the field of attentional orienting supports the hypothesis that characteristic synchronization patterns emerging from the FEF may underlie different cognitive processes, leading to different behavioral outcomes.

Finally, our data show that perceptual sensitivity in healthy participants can be episodically enhanced by an extrinsic source of neural synchronization tuned to a specific frequency and support future uses of non-invasive neurostimulation to probe and manipulate oscillatory phenomena in the human brain from circumscribed cortical regions. Furthermore, pathological conditions involving specific alterations of cerebral oscillations (Thut et al., 2012) associated with impaired cognitive performance could potentially benefit from the use of frequency-tailored neurostimulation to locally manipulate activity and restore the characteristic oscillation frequencies of the healthy system.

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CHAPITRE 7. INFLUENCE DE LA CONNECTIVITE ANATOMIQUE DANS LA MODULATION PERCEPTIVE VISUELLE PAR SMT

7.1. IMPLICATION DU FAISCEAU FRONTO-TECTAL DANS LA MODULATION VISUELLE PAR SMT A IMPULSION UNIQUE

Le cerveau est un organe composé de 100 milliards de neurones chacun possédant jusqu'à 10 000 synapses permettant la communication avec les autres neurones. Les axones peuvent connecter des régions éloignées dans le cerveau et transmettre l'influx nerveux avec une vitesse de plusieurs dizaines de mètres par seconde. Le cerveau est l'organe de la communication par excellence et imaginer dans ce contexte que l'effet de la SMT est simplement focal et n'impacte que la région stimulée est un pari risqué et peu probable. Pourtant, peu d'études sur la neurostimulation se sont intéressées à ces effets en réseau. Valero-Cabre et al. ont montré des effets métaboliques à distance dans des régions corticales et sous-corticales qui reçoivent des projections de la région stimulée (Valero-Cabré et al. 2005, 2007). Nous avons testé s'il existait une relation entre des différences inter-individuelles de connectivité anatomique et les effets d'amélioration perceptive obtenus lors de notre première expérience de SMT à impulsion unique sur le FEF droit (*Chapitre 6, Partie 1)*. Une corrélation négative est apparue entre la modulation visuelle induite par SMT et la probabilité de connexion de la région stimulée avec le colliculus supérieur du même hémisphère. Des différences entre les sujets dans ce faisceau fronto-tectal semblent impacter la magnitude de l'effet visuel du à la SMT, suggérant un rôle important des connexions anatomiques dans la modulation perceptive par stimulation non-invasive.

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Fronto-tectal white matter connectivity mediates facilitatory effects of non-invasive neurostimulation on visual detection

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ABSTRACT

The causal ability of pre-target FEF activity to modulate visual detection for perithreshold stimuli has been recently demonstrated in humans by means of non-invasive neurostimulation. Yet in spite of the network-distributed effects of these type of techniques, the white matter (WM) tracts and distant visual nodes contributing to such behavioral impact remain unknown. We hereby used individual data from a group of healthy human subjects, who received time-locked pulses of active or sham Transcranial Magnetic Stimulation (TMS) to the right Frontal Eye Field (FEF) region, and experienced increases in visual detection sensitivity. We then studied the extent to which interindividual differences in visual modulation might be dependent on the WM patterns linking the targeted area to other regions relevant for visuo-attentional behaviors. We report a statistically significant correlation between the probability of connection in a right fronto-tectal pathway (FEF-Superior Colliculus) and the modulation of visual sensitivity during a detection task. Our findings support the potential contribution of this pathway and the superior colliculus in the mediation of visual performance from frontal regions in humans. Furthermore, we also show the ability of a TMS/DTI correlational approach to contribute to the disambiguation of the specific long-range pathways driving network-wide neurostimulatory effects on behavior, anticipating their future role in guiding a more efficient use of focal neurostimulation.

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Introduction

Visual systems translate information from the real world into sophisticated bioelectrical patterns, which can be used thereafter to build a neural representation of our environment. It is well known that such function is strongly modulated by bilaterally distributed fronto-parietal networks in charge of orienting attention to specific regions of the space, facilitating the detection and discrimination of visual stimuli (Cameron et al., 2002; Carrasco et al., 2000, 2001; Yeshurun and Carrasco, 1999). Such operations are essential for the selection of behaviorally crucial targets to be attended in a world rich in distractors, without being overwhelmed by numerous and diverse sources of information.

Fronto-parietal visuo-attentional networks are classically divided into a bilateral dorsal system, linking the Frontal Eye Fields (FEF) and the Intra-parietal Sulcus (IPS), involved in the orienting of attention in space (Beauchamp et al., 2001; Chica et al., 2011; Corbetta and Shulman, 2002; Shulman et al., 2010), and a ventral right-lateralized system between the middle and the Inferior Frontal Gyrus (MFG/IFG), and the Temporo-Parietal Junction (TPJ), responsible for the reorientation of attention during unexpected events (Chica et al., 2011; Corbetta and Shulman, 2002; Shulman et al., 2010). Importantly, neuroimaging data (Nobre et al., 1997; Petit et al., 2009), non-invasive neurostimulation evidence (Grosbras and Paus, 2003; Hilgetag et al., 2001; Thut et al., 2005), and clinical observations (Bartolomeo et al., 2012) strongly support a right hemisphere dominance in visuo-spatial attention, and demonstrate the ability of such right-hemisphere systems to influence visual perception for targets in both visual hemifields (Grosbras and Paus, 2003; Chanes et al., 2012).

White matter (WM) connections established between nodes of this network have been thoroughly studied and remain essential to understand its contributions to spatial attention and perception. Intracortical microstimulation and tracing studies carried out in the non-human primate brain have shown that the FEF is highly connected to the superior and ventral portions of the parietal lobe and to caudal regions of the superior temporal cortex (Huerta et al., 1987; Stanton et al., 1995). Similarly in humans, this network is underlain by a rich set of anatomical WM projections which in homology to non-human primates have

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been recently identified as the three branches of the Superior Longitudinal Fasciculus (Thiebaut de Schotten et al., 2012), linking key regions of the frontal and the posterior parietal lobes (Thiebaut de Schotten et al., 2011; Umarova et al., 2010). Finally, connections between fronto-parietal systems and subcortical structures such as the pulvinar nucleus of the thalamus and the superior colliculus (SC) in the midbrain are also important and contribute to both overt and covert attentional deployment (Shipp, 2004).

Engaged exogenously (i.e., by reflexively capturing attention) or guided endogenously (i.e., according to feature-based instructions), these circuits have the ability to modulate the gain of retinal incoming signals to cortical (Reynolds and Chelazzi, 2004; Reynolds and Desimone, 2003; Reynolds et al., 2000) and subcortical structures (Gattass and Desimone, 1996; O'Connor et al., 2002; Schneider and Kastner, 2009; Wurtz and Goldberg, 1972), and impact visual processing. Indeed, studies in non-human primates have proven the potential of FEF microstimulation, alone or in combination with bottom-up visual inputs to modulate activity in visual areas (Ekstrom et al., 2009; Reynolds and Chelazzi, 2004) and influence visual performance (Moore and Fallah, 2004). Similarly in humans, Transcranial Magnetic Stimulation (TMS), a tool which induces pattern-dependent local and transynaptic effects through long-range connectivity (Valero-Cabré et al., 2005, 2007) has shown the ability to elicit in the FEF and IPS regions brief (Grosbras and Paus, 2002, 2003; Ruff et al., 2006; Silvanto et al., 2006) and transient (Hilgetag et al., 2001; Thut et al., 2005) modulations of visual behaviors.

In a recent report, we demonstrated that single-pulse TMS stimulation delivered to the right FEF had the ability to improve the detection but not the discrimination of low-contrast near-threshold visual stimuli (Chanes et al., 2012). This result strongly supports the notion that vision can be non-invasively manipulated and enhanced in humans. However the underlying circuitry linking the targeted regions, the right FEF, and other brain locations contributing to such visual ameliorations are not easy to disambiguate on the basis of differences in the behavioral patterns recorded under the causal influence of neurostimulation. Using a hypothesis-driven approach, we correlated individual MRI diffusion data (Behrens et al., 2007) from a set of four anatomically plausible tracts emerging from the stimulated right FEF and known to be involved in the orienting of spatial attention, and visual performance outcomes modulated by TMS. A preceding Tract-Based Spatial Statistics (TBSS) data-driven analysis was employed in an attempt to identify WM voxel clusters with diffusion measures correlated to visual performance outcomes. Overall, we aimed to identify the WM pathways which would best explain individual effect differences in visual sensitivity for our population of right FEF neurostimulated participants (Chanes et al., 2012) that could be most likely associated with our patterns of behavioral effects. We hypothesized that the WM pathways significantly correlated with neurostimulation-driven outcomes would involve brain sites linked to the FEF, with processing features and abilities compatible with the characteristics of the modulated visual behaviors.

Material and methods

Participants

The TMS data used in the current manuscript were extracted from two experiments of a recently published behavioral-TMS data set (Chanes et al., 2012). This study included 13 human subjects (5 males and 8 females; mean age, 23.8 $\pm$ 3 years; range 18–28 years). All these participants provided informed written consent and were compensated for their participation. They all took part voluntarily in the study, and were naïve to both, the purpose of the experiment and the uses of TMS. The protocol was reviewed by the Inserm (*Institut National de la Santé et la Recherche Scientifique*) ethical committee and approved by an Institutional Review Board (CPP *Ile de France 1*).

Behavioral paradigm and TMS stimulation

The visual paradigm used in both experiments worked as follows. A fixation point was displayed in the center of the screen, along with three black square boxes, one central and two lateral ones. The target consisted of a *Gabor* stimulus, which could appear at the center of one of two lateral rectangular place holder for a brief period of time (33 ms). The *Gabor* bars were tilted 1° to 10° to the left or to the right (corresponding 0° to their vertical orientation). Single TMS pulses were delivered 80 ms prior to target onset on the right FEF. This region was individually labeled on each individual MRI volume using averaged Talairach coordinates $x = 31$, $y = -2$, $z = 47$ (Paus, 1996). This location was confirmed on each participant's MRI native space by a procedure based on the elicitation of saccade preparation delays under the impact of single TMS pulses on this site (Chanes et al., 2012; Grosbras and Paus, 2002, 2003; Ro et al., 2002; Thickbroom et al., 1996). In Experiment 1 (pre-target onset TMS pulses alone), after a variable fixation period of time (1000–1500 ms), the central fixation cross became slightly bigger for 66 ms and following an Interstimulus Interval (ISI) of 233 ms a target was displayed for 33 ms within one of the two lateral boxes. Single TMS pulses were delivered on the right FEF 80, 100 or 140 ms prior to the target onset. Active TMS pulses were randomly interleaved by an equal number of sham single pulses delivered by a second TMS coil with its surface located perpendicular to the head surface, next to the right FEF site. The experiment consisted of 600 trials, including 120 target-absent trials. In Experiment 2 (pre-target onset spatial cues combined with single TMS pulses), the paradigm was kept identical, except that a peripheral cue consisting in a black dot (1.5° diameter) was presented for 66 ms in the upper outer corner of one of the two lateral square place holder to orient the attention of the participant to that location (Fig. 1). After an identical ISI, a *Gabor* appeared at the center of the cued (valid trials) or uncued (invalid trials) lateral box. The cue was predictive about the location of the subsequent target (75% valid and 25% invalid trials). For this second experiment, single TMS pulses were delivered 80 ms prior to target onset and the session consisted in 800 trials, including 160 target-absent trials.

In both experiments, participants were first required to determine the orientation of the *Gabor* bars (*categorization* task) as fast and as accurately as possible. They were encouraged to respond to every trial within a window of 2000 ms, and forced to guess a response, even when the target was not present or they did not consciously perceive it. Secondly, they were requested to report whether they perceived the *Gabor* in the left, in the right, or they did not see it (*detection* task). Categorization performance was analyzed through accuracy (correct grating orientation categorization) and reaction time for correctly reported targets. Perceptual sensitivity (d') and response bias (beta) used in Signal Detection Theory (SDT) served to assess the modulation of visual detection in the second response. Subjects were requested to keep their gaze on the fixation cross throughout the trial. Correct fixation was controlled by an eye-tracker system. Target contrast was adjusted prior and throughout the task so that ~62% of the displayed targets were reported (*detection* task) and 65 to 85% of the correctly reported targets were also correctly discriminated (*categorization* task) (see Chanes et al., 2012 for details).

MRI acquisition

Prior to the TMS study, diffusion tensor MRI scans were obtained in all thirteen participants on a 3 Tesla MRI scanner (Tim Trio, Siemens Healthcare, Erlangen, Germany) located in the CENIR (Centre de Neuro-Imagerie de Recherche) at the Hôpital de la Pitié Salpêtrière, in Paris (France). Using a 12-channel array coil and a maximum gradient strength of 28 mT/m, diffusion weighting was isotropically distributed along 64 directions. Note that high angular resolution of the diffusion weighting directions yields robust probability density estimation by

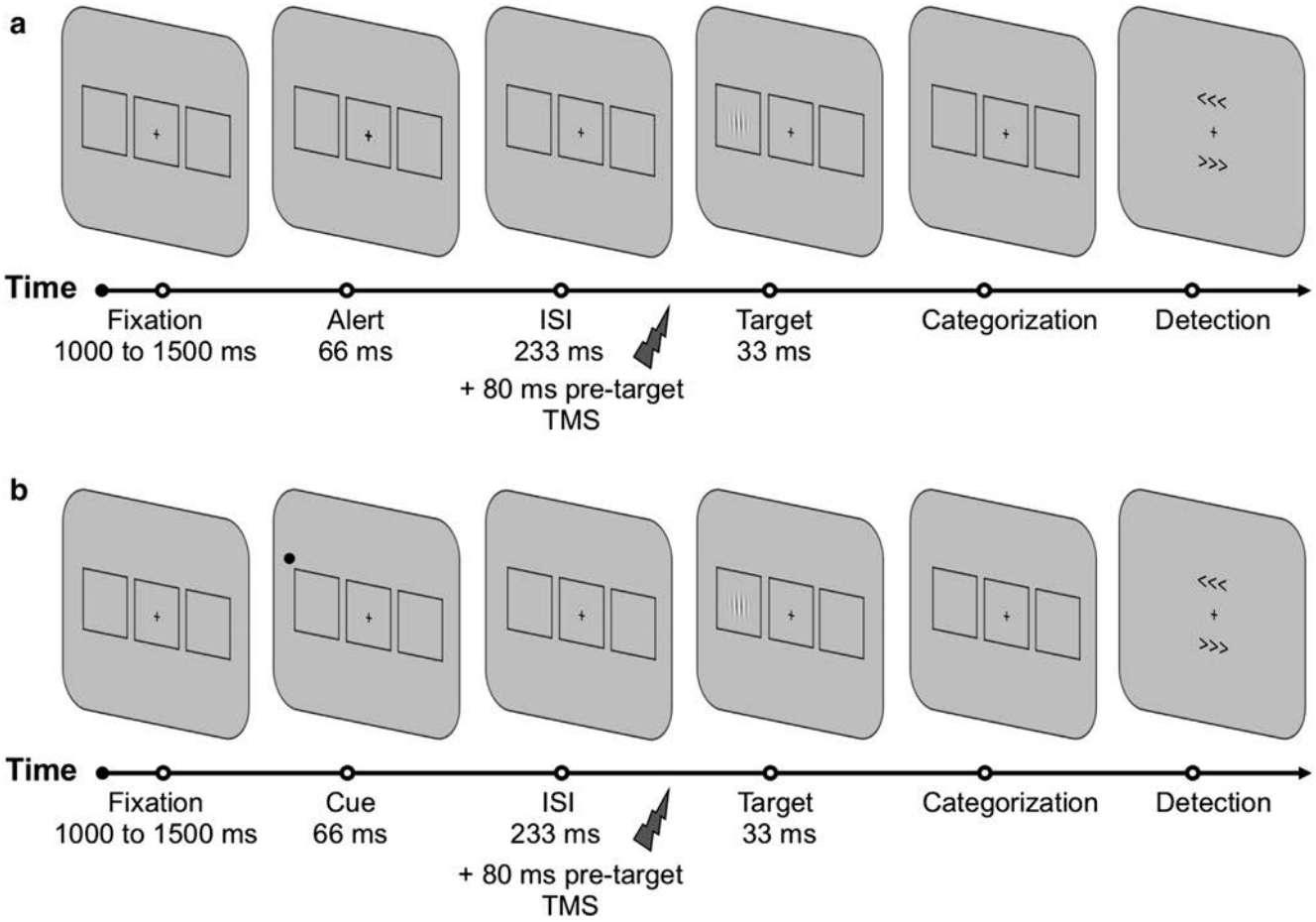


Fig. 1. Sequence of events during a representative trial for each of the TMS Experiments, whose data sets were used in our study. In both, participants were requested to fixate at a central cross for a randomly variable period of time between 1000 and 1500 ms. In Experiment 1 (a), there was no peripheral cue but the central cross became slightly bigger for 66 ms to alert participants of an upcoming event. The TMS pulse was delivered on the right FEF 80, 100 or 140 ms prior to target onset. In Experiment 2 (b), a peripheral visuo-spatial cue, consisting in a black circle was displayed for 66 ms to the right or the left of the fixation cross. The cue was predictive about the location of the subsequent target (75% valid and 25% invalid trials), and was followed by a TMS pulse delivered 80 ms pre-target onset. In both experiments, active or sham TMS pulses were interleaved in a randomized order. Then, after an interstimulus interval (ISI) of 233 ms, a Gabor with bars tilted to the left or the right appeared for 33 ms at the center of one of the two lateral place holders. Participants were then requested to perform two sequential tasks; first a visual categorization task to indicate the orientation of the Gabor bars (left/right) and second, a conscious visual detection task in which they had to report if they did see the target, and where they saw it (left/right). A cue was considered valid when it correctly signaled the location of the upcoming target (left or right), and invalid when it incorrectly signaled target location. A valid trial was the one including a valid cue whereas the opposite applies to invalid trials. The lower panel (b) shows for Experiment 2 an example of a valid trial (see Chanes et al., 2012 for further details on the behavioral paradigms).

increasing the signal-to-noise ratio and reducing directional bias. One image with no diffusion (b0) was acquired initially and served as an anatomical reference for eddy current corrections. The imaging parameters were repetition time (TR) = 11.000 ms, echo time (TE) = 88 ms, b = 1000 s/mm2 and matrix size = 128 × 128 × 60. Each set of images contained 60 contiguous slices with a 2 mm thickness. Total acquisition time was 12 min and 30 s. This resulted in a tensor for every voxel ($2 \times 2 \times 2$ mm^3) in a slice. The eigenvectors and eigenvalues were computed for every tensor, to constitute the raw data set for tractography analysis. A 3D structural T1-weighted MRI was also acquired for each subject (TR = 2300 ms, TE = 4.18 ms, FOV = 256 mm, matrix size = 256 × 256, 176 sagittal slices with thickness = 1 mm).

Data preprocessing, Tract-Based Spatial Statistics (TBSS) and tractography

Data preprocessing

Diffusion tensor imaging (DTI) pre-processing and analyses were performed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL 4.1.6 — www.fmrib.ox.ac.uk/fsl/). Head motion effect and image distortion caused by eddy currents were corrected using affine registration to the reference volume b0 and the Brain Extraction Tool (BET) was applied to remove non-brain tissues. The gradient direction for each volume was corrected using the rotation parameters. Spatial deformation of the DTI due to the susceptibility artifact was corrected with non-linear deformation computed from the diffusion images to match the T1-weighted volume using Freesurfer Software (Freesurfer 5.0.0, http://surfer.nmr.mgh.harvard.edu/). The diffusion tensor and the three eigenvalues were computed by fitting a tensor model to corrected-diffusion data using FLS's DTIFIT and resulted in several DTI-based maps, including an FA map.

Tract-Based Spatial Statistics

The following steps here were carried out with the TBSS software module (Smith et al., 2006). A non-linear registration was first applied to align the FA map across subjects. These data were then registered for all the participants to the $1 \times 1 \times 1$ mm^3 MNI152 space (McConnell Brain Imaging Center, Montreal Neurological Institute). A common skeleton from the mean FA image representing the core-structure of the WM tract was created. This skeleton was thresholded at a FA value of 0.2. Normalized FA data were then projected onto this skeleton. These FA images were entered into a voxel-wise General Linear Model (GLM) analysis. To study the potential correlations between each

voxel's FA value and individual visual performance modulation under TMS, we employed as an explanatory covariate in both experiments the visual sensitivity (d′) difference between sham vs. real TMS trials in two separate models with participant's age as confounding covariate. The *randomized* permutation-based nonparametric inference routine was used with 5000 permutations. Finally, Threshold-Free Cluster Enhancement (TFCE) was employed to control for multiple testing. This method avoids the need for an arbitrary initial cluster-forming threshold. Statistical significance threshold was set at $p < 0.05$.

Tractography

The TBSS approach did not reveal any significant correlations between white matter voxels and TMS visual performance outcomes (see Results, sub-section Hypothesis-driven approach: Identification of relevant white matter pathways for details). Therefore, a fiber tracking procedure based on a probabilistic tractography method and the dual-fiber model implemented in FMRIB diffusion (5000 streamlines samples, 0.5 mm step lengths, curvature threshold = 0.2) (Behrens et al., 2007) was used to identify fibers departing from the TMS stimulated site, the right FEF, specifically projecting to the following 4 selected destinations within the right hemisphere: the Intra-parietal Sulcus (IPS), the Supra-Marginal Gyrus (SMG), the Temporo-Parietal Junction (TPJ), and the Superior Colliculus (SC). Such limited number of most likely destinations and WM tracts were selected on the basis of their strong anatomical plausibility, their known contributions to the modulation of attentional orienting and visual perception and their hypothesized implication in network-wide modulations of visual behaviors from the right FEF site. This hypothesis-driven tractography analysis was performed in each participant's native diffusion space. The right FEF and the above mentioned 4 distant right hemisphere regions were used respectively as seed and termination masks in four independent tractography analyses. All tracts were in the end overlaid on the anatomical MRI volume, visually checked for consistency with regards to the known human brain anatomy, and normalized using the MNI template. A 15% threshold of the maximum voxel intensity of each individual fasciculus was applied to remove extraneous tracts, and used for their presentation in figures.

ROI delineation

Using the Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 7.11.0 (Math-Works, Natick, MA), T1-weighted images were registered linearly to the b0 images. Each region-of-interest (ROI) was then created on the T1 Montreal Neurological Institute (MNI) standard brain and denormalized in the native diffusion space of each subject. The anatomical localization of each subject's ROIs was verified on T1-weighted images. Anatomical verification on structural images allowed a more accurate localization of ROIs and tracts than in the native diffusion space (Basser et al., 2000). A sphere of 1 cm radius centered on the TMS targeted right FEF coordinates was used as frontal ROI. The size of this sphere was adapted on the basis of an estimated spatial resolution for TMS pulses using a standard 70 mm figure-of-eight coil of 1.5–2.0 cm^2 (Thielscher and Kammer, 2004; Valero-Cabré et al., 2005). For the IPS, TPJ and SMG ROIs, 0.425 cm radius spheres centered on the Talairach (IPS: $x = 16$, $y = -63$, $z = 47$, TPJ: $x = 51$, $y = -51$, and $z = 26$) or MNI coordinates (SMG: $x = 54$, $y = -37$, and $z = 46$) obtained from prior fMRI studies on attentional orienting networks and probed in TMS studies (Kincade et al., 2005; Chica et al., 2011) were used. The SC ROI was drawn on the T1 MNI template (0.5 mm voxel size) on 12 consecutive axial sections. The radius of the spheres for IPS, SMG, and TPJ was chosen to match the volume of the SC ROI.

White matter bundles–behavioral correlations

Differences among participants in terms of average trajectory count between pairs of ROIs were compared by means of the number of paths from the seed region (in the targeted coordinates of the right FEF) reaching the destination areas within the right hemisphere (IPS, SMG, TPJ and SC). In order to avoid dependence from the number of samples launched by the algorithm, the number of paths was divided by the volume in voxels of the departure ROI. This calculation provided for each fasciculus an estimation of the connection probability between the two regions. By dividing this value by the number of trajectories launched in each seed voxel, i.e. 5000, *a probability of connection* value between 0 and 1 (and then multiplying by 100 to present it as percentage) can be easily calculated. A Wilcoxon signed-rank test was used to test the differences between the four pathways. This difference was considered significant for a p value < 0.05.

We focused particularly on the correlation of visual performance parameters (d′) having shown in our prior study statistically significant group modulations under the combined effect of spatial cues and single TMS pulses delivered to the FEF (Experiment 2), as this was the only data set in which attentional orientation was explicitly manipulated by means of spatial cues (Chanes et al., 2012). As in a repeated measures ANOVA, the significant double interaction included the factors TMS pulse type (sham, real) and cue validity (valid, invalid) but excluded target location (right, left), we assumed that the facilitatory effects driven by right FEF TMS spanned bilaterally to both visual hemifields (Grosbras and Paus, 2003). Accordingly, perceptual sensitivity modulations for both hemifields were grouped for further correlational analyses (Chanes et al., 2012). Improved visual detection performance under the effects of single-pulse TMS was presented for each subject in terms of perceptual sensitivity (d′) levels under the effects of interleaved *active* vs. *sham* TMS pulses. The difference between these two TMS conditions was calculated to obtain the relative visual sensitivity gain (Δd′) induced in active TMS trials with respect to sham TMS trials. Spearman's rank correlation coefficients were calculated using statistical analysis software (JMP 8.0, SAS, Cary, NC USA). Bonferroni post-hoc correction, which lowers the alpha value to account for the number of comparisons being performed, was used to avoid spurious positives (*uncorrected* $p < 0.05$; *corrected* 0.05/4 tracts $p < 0.0125$). To provide a convincing proof of the robustness of our statistically significant correlation, a permutation test (Groppe et al., 2011) based on Spearman's rank correlation coefficient with 5000 permutations was applied. The null hypothesis of the permutation test is that every possible order of a given observation is as likely as a correlation obtained by chance. Finally, to further ensure the correlation of a given pathway with behavioral outcomes, independent of the influence of the other bundles considered in the analyses, we implemented a multiple linear regression analysis based on the General Linear Model (GLM) implemented in Matlab (7.11.0 Math-Works, Natick, MA). The GLM expresses behavioral data as a linear combination of a set of explanatory variables, such in our case, the WM pathway's probability of connection. This test was considered significant for a p value <0.05.

Anatomical description of significantly correlated pathway

The anatomical trajectories of the significantly correlated pathways were described in detail. To this end, tractography trajectories were normalized to the standardized MNI template and their group average calculated (final image resolution of $2 \times 2 \times 2$ mm^3). As indicated above, in order to remove extraneous tracts, a threshold of 15% of the maximum voxel intensity for each individual fasciculus was applied. This threshold was calculated for each individual participant before the tracts were averaged across participants in MNI space and thus it played no role or influenced in any way the correlations between white matter and behavioral outcomes; it was simply used for figure presentation purposes. Finally, a detailed and highly magnified description of each pathway' trajectory was performed on serial axial slices for each subject, and for the group average pathway, under the supervision of an experienced neuroradiologist and a neuroanatomist. The MRIcroGL software (http://www.mccauslandcenter.sc.edu/mricrogl) was used for glass brain illustrations.

Results

Individual detection sensitivity modulation induced by TMS

As reported elsewhere at a group level, pre-target onset TMS pulses combined with valid spatial cues in those subjects able to efficiently capture and orient attention in space increased visual *detection* sensitivity (d′) for active as compared to sham TMS. No differences between active and sham TMS were observed for invalid trials, in which the cue incorrectly signaled the location of the target. Finally, no modulations were observed for the *categorization* task (see Experiment 2, Chanes et al., 2012). Interestingly however, the 13 participants demonstrated some level of variability in the magnitude and direction of the above-mentioned visual sensitivity modulations (Δd′). More specifically, 1 participant seemed to experience no TMS-driven effects, 2 participants displayed an apparent deterioration of their visual performance, and the magnitude of visual sensitivity improvements (d′TMS − d′sham TMS) experienced by the remaining 10 subjects oscillated greatly between Δd′ values of 0.06 and 0.43 (see Fig. 2 for details).

Hypothesis-free approach: Tract-based Spatial Statistics (TBSS) results

We tested the correlations between voxel-wise analysis of FA and TMS visual sensitivity modulations (Δd′) using for Experiment 1, data of sham and real TMS trials including exclusively pulses delivered 80 ms pre-target; and for Experiment 2, data from sham and real TMS trials encompassing TMS pulses delivered 80 ms pre-target combined with peripheral predictive cues. No significant correlations between the FA and behavioral performance, fully corrected for multiple comparisons across space, were found for any of these two behavioral datasets ($p > 0.05$). An additional test for such correlations with a lower p value ($p < 0.001$) using non-corrected correlation maps did not yield any significant result either. In sum, in our data sets, the TBSS approach did not capture any significant correlation between white matter anisotropy measures and visual performance modulations.

Hypothesis-driven approach: identification of relevant white matter pathways

For our group of 13 subjects, we tracked a total of 4 right hemisphere tracts, all seeded in the coordinates of the right FEF region targeted in our TMS experiment: FEF–IPS, FEF–SMG, FEF–TPJ, and FEF–SC (see Figs. 2 and 3). As indicated in the Material and methods section this limited set of potential connections was selected on the basis of their anatomical plausibility, their contribution to attentional orienting and visual perception and their hypothesized implication in network-wide modulations of visual behaviors from the right FEF site. Our results showed that the right FEF–IPS and FEF–SC white matter tracts shared similar average trajectory count values (2.48 ± 5.88 vs. 2.77 ± 3.05, $p = 0.37$). In contrast, the FEF–TPJ (0.25 ± 0.53) tract appeared as significantly less connected than the FEF–IPS ($p = 0.013$) and the FEF–SC ($p = 0.013$). Finally, the FEF-SMG (0.44 ± 0.56) appeared as not statistically differently connected than the FEF–IPS ($p = 0.41$) or the FEF–TPJ ($p = 0.31$), but significantly less connected than the FEF–SC white matter tract ($p = 0.008$). This across-tract statistical comparison should however be taken cautiously as connection probability may depend on the tract length and curvature, factors that cannot be easily accounted for in our study. Note that such low values of average trajectory count, which are also common in other probabilistic tractography studies are explained by sharp decreases in anisotropy and high levels of noise affecting diffusion signal as the launched trajectories approach cortical regions (Behrens et al., 2007).

White matter bundles–behavioral correlations

We then computed the correlations between the individual behavioral effects expressed in terms of perceptual sensitivity differences (Δd′) for the combination of a pre-target TMS pulse and valid spatial cues with the individual average trajectory count of our 4 pre-selected WM pathways (Figs. 2 and 3). The only statistically significant correlation was found between the FEF–SC and improvements induced by the combination of TMS and valid cues for

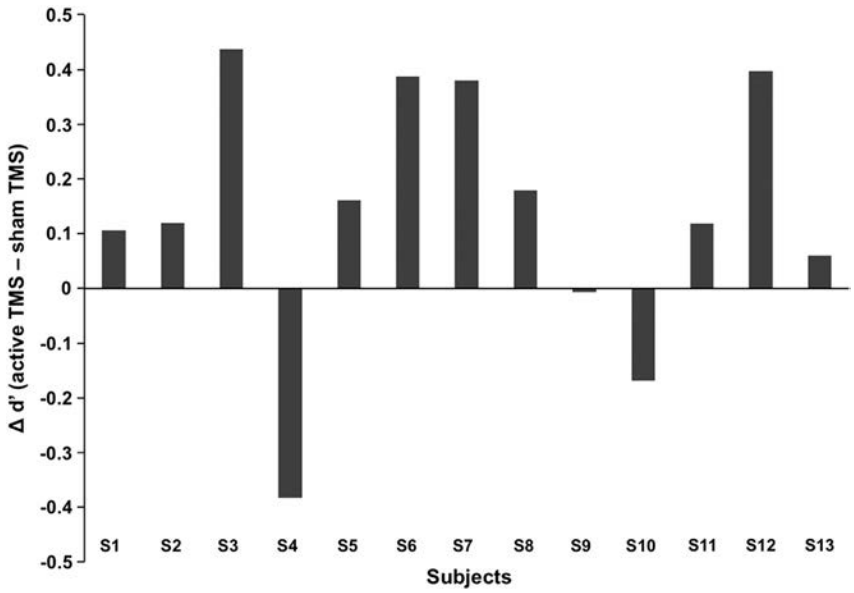


Fig. 2. Individual behavioral data displaying visual detection sensitivity differences (Δd′) induced by the effects of TMS (active TMS–sham TMS) for each of the 13 participants (S1 to S13) in the study. Positive values indicate detection sensitivity increases, hence better visual detection performance under real than sham TMS. Negative values indicate detection sensitivity decreases, and thus worse detection performance under real than sham TMS. Notice that even if as a group, statistically significantly improvements of visual sensitivity under real TMS were found for those participants who correctly oriented their attention in response to valid spatial cues (Chanes et al., 2012), there was a degree of behavioral variability in the direction and magnitude of visual performance effects across the population of 13 participants who were included in the current study.

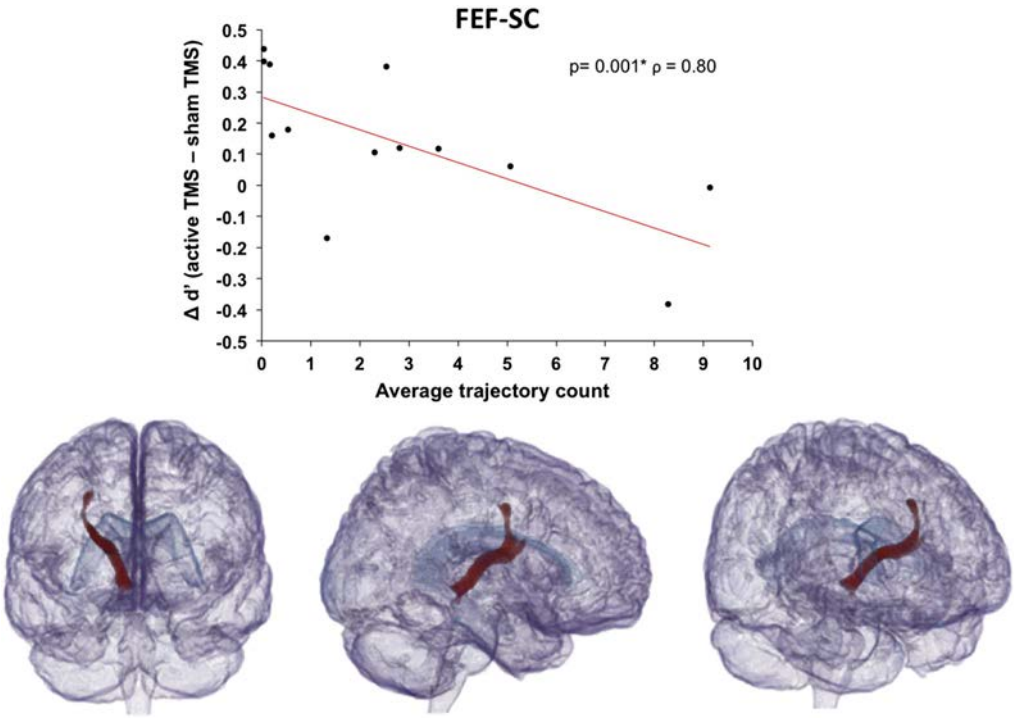


Fig. 3. Correlation plot (top) representing the magnitude of the TMS-driven modulations in visual sensitivity (Δd′) (active TMS–sham TMS) for the detection of validly cued visual targets (Chanes et al., 2012), crossed with the average trajectory counts between the right FEF and the ipsilateral SC according to diffusion data. See (bottom) three dimensional glass brain views (left to right: front view, side view, and ¾ quarter rear right view) represented in MNI standardized space, corresponding to the mean FEF–SC tract recorded in our population of 13 participants. Notice that it was only for this tract that our data revealed a statistically significant correlation between the average trajectory counts between the FEF and the SC and the modulation of visual perceptual sensitivity (active TMS–sham TMS). By dividing the average trajectory count values by the number of trajectories launched from each seed voxel, i.e. 5000, a probability of connection between 0 and 1 can be calculated.

bilateral visual stimuli ($\rho = -0.80$, $p = 0.001$). Interestingly, this correlation was negative, i.e., the higher the fronto-tectal probability of connection, the lower the magnitude of the TMS-driven visual facilitatory effects or vice versa (Fig. 3). As indicated above, no significant correlations were found for any of the remaining three white matter bundles considering either corrected or uncorrected p threshold significance values (FEF–IPS: $\rho = 0.033$, $p = 0.915$, FEF–SMG: $\rho = -0.214$, $p = 0.482$, FEF–TPJ: $\rho = -0.131$, $p = 0.654$) (Fig. 4). For the only pathway (FEF–SC) significantly correlated to TMS-driven visual sensitivity measures, the non-parametric permutation test confirmed the robustness of the finding ($p = 0.002$).

A multiple linear regression analysis using the General Linear Model (GLM) with the statistically significant pathway as explanatory variable and the non-significant pathways and participant's age as confound regressors was tested. To rule out if other measurable factors could have bearing on the current behavioral results, skull-thickness at the stimulation site, straight distance from the skull to the FEF site, the estimated magnetic field strength in the targeted area, the TMS intensity ultimately used to stimulate each subject and the individual motor thresholds as a measure of cortical excitability, were also used as covariables in the GLM model. This analysis also confirmed that the FEF–SC pathway was significantly correlated with the reported visual behavioral outcomes ($t = -4.66$, $p = 0.005$, $df = 3$).

We also verified post-hoc a potential interaction between the identified fronto-tectal pathway and the effects of cue-driven attentional orienting in absence of effective TMS stimulation on visual sensitivity. This was explored by considering only trials (data from Experiment 2) including visuo-spatial attentional cues combined with interleaved sham TMS pulses (sham TMS validly cued trials–invalidly cued trials). The correlations for such behavioral outcomes proved once more non-statistically significant ($r^2 = 0.089$, $p = 0.320$), suggesting that cue-driven attentional orienting per se could not explain the significant correlation found between TMS modulated visual performance outcomes and the probability of connection for the right FEF–SC pathway. Finally, we tested post-hoc a potential correlation between the right FEF–SC pathway and the effects of isolated pre-target onset TMS pulses in absence of visuo-spatial cues (data from Experiment 1). Once more, no significant correlation was found ($r^2 = 0.045$, $p = 0.505$), suggesting that it was rather the combined effects of both events, attentional orienting induced by valid spatial cues and right FEF TMS stimulation, and not the isolated effects of either one or the other, which were influenced by the previously identified fronto-tectal WM tract.

Anatomical description of the fronto-tectal pathway trajectory

The fronto-tectal (FEF–SC) pathway was the only tract in our hypothesis-based correlational approach holding statistically significant correlations with visual detection facilitatory effects. According to our mean tract calculations this white matter pathway, defined as departing from the FEF and projecting to the SC, progressed within the *corona radiata* towards the upper part of the anterior limb of the internal capsule. Then, in an almost horizontal trajectory, placed itself in the *genu* of the internal capsule to reach the thalamus. The limited resolution of our DTI anatomical images did not allow to define with sufficient precision, the intrathalamic trajectory of those fibers. Nonetheless, in agreement with previous anatomical description of a compatible fronto-tectal tract in non-human primates explored by tracer injection (Leichnetz et al., 1981), fibers could have progressed within the internal medullary lamina and paralaminar regions of the thalamus. From the posterior portion of the thalamus, fibers reached the brachium of the superior colliculus to terminate in the upper *tectum* (Fig. 5).

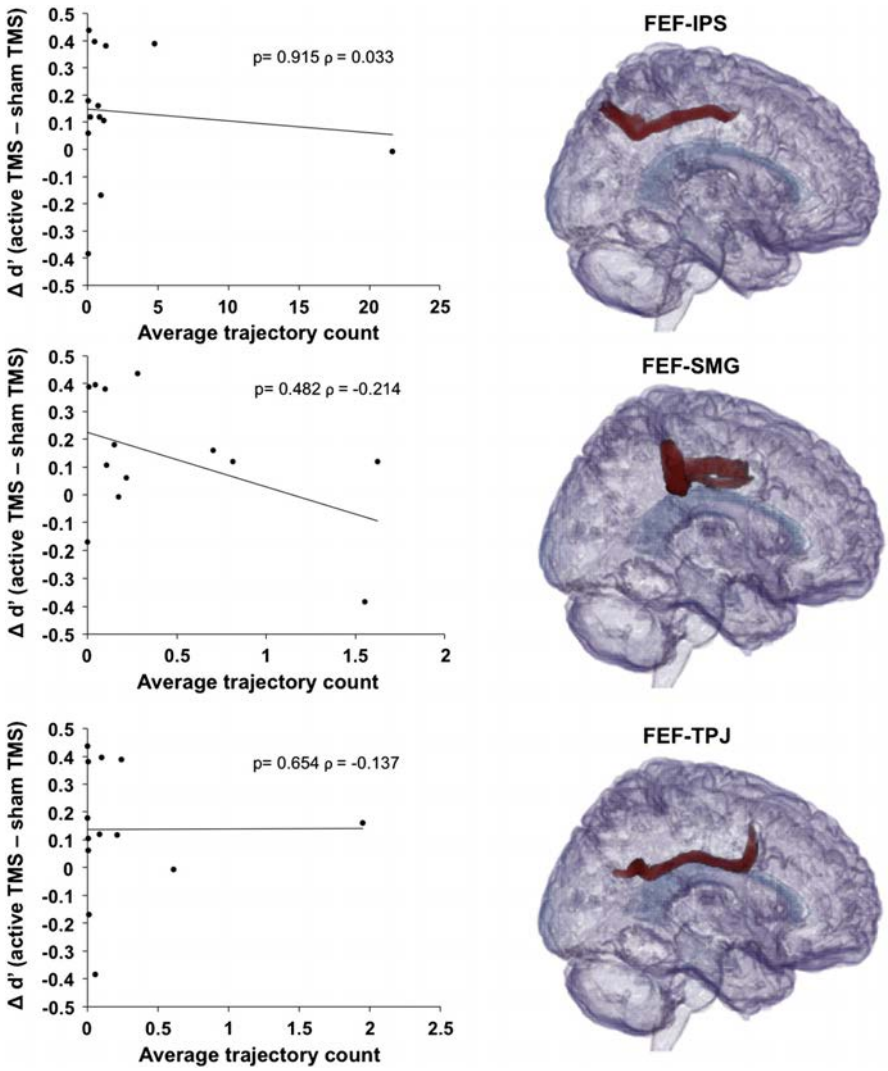


Fig. 4. Correlation plots representing the magnitude of the TMS-driven modulations on visual sensitivity (Δd′) (active TMS–sham TMS) for the detection of validly cued visual targets (Chanes et al., 2012), crossed with the average trajectory counts between the right FEF and the ipsilateral IPS, SMG and TPJ sites (left panels, from top to bottom) respectively. For each of these three tracts (FEF–IPS, FEF–SMG, FEF–TPJ) we present (right panels, from top to bottom) dimensional glass brain selected views in MNI standardized space of the mean white matter tract for the 13 participants of the study. Notice that for none of those three tracts there was any statistically significant correlation between the average trajectory counts and the modulation of visual perceptual sensitivity (active TMS–sham TMS). By dividing the average trajectory count values by the number of trajectories launched from each seed voxel, i.e. 5000, a probability of connection between 0 and 1 can be calculated.

Discussion

In view of the network-distributed effects of TMS on neural systems and their role in performance modulations (Valero-Cabré et al., 2005, 2007), we hypothesized that WM connectivity could be among the important factors explaining interindividual behavioral variability to TMS. We used a combination of TMS and DTI recordings to address, if specific WM fasciculi might have bearing on the individual patterns and magnitudes of visual performance ameliorations induced by the stimulation of the right FEF region. A correlational approach could help to disambiguate which WM tracts and distant visuo-attentional regions were most likely contributing to the propagation of TMS effects from the stimulated cortical site and the reported visual sensitivity improvements. Our final results based on FSL's dual fiber model show that out of a set of the four most plausible right hemisphere tracts included in our correlational study (see Material and methods for details on selection criteria), only a trans-thalamic fronto-tectal projection (FEF–SC) emerged as a WM pathway, whose probability of connection was significantly correlated to the impact of active TMS combined with spatial cues, and their effects on the modulation of visual sensitivity (Δd′).

This hypothesis-driven approach was preceded however by a data-driven method based on a whole brain voxel-wise correlation method, TBSS, which for both, corrected and uncorrected analyses, failed to unearth WM clusters with FA measures significantly correlated to visual performance. Although we cannot rule out additional explanations, the TBSS approach might have been limited to detect significantly correlated clusters related to a fronto-tectal pathway as the one we finally identified, for at least two reasons: first, the FA measure is based on a single diffusion tensor (Basser and Pierpaoli, 1996), and for the fronto-tectal tract, it might be less sensitive in voxels with more than a single direction than the FSL's dual fiber approach (which models two fibers per voxel). Indeed, the FA value depends on a large set of structural and physiological variables, like the number, diameter and myelination level of axons, but is also influenced by the intra-voxel orientational dispersion (Jones et al., 2012). Second, the mean FA skeleton used in TBSS employs the

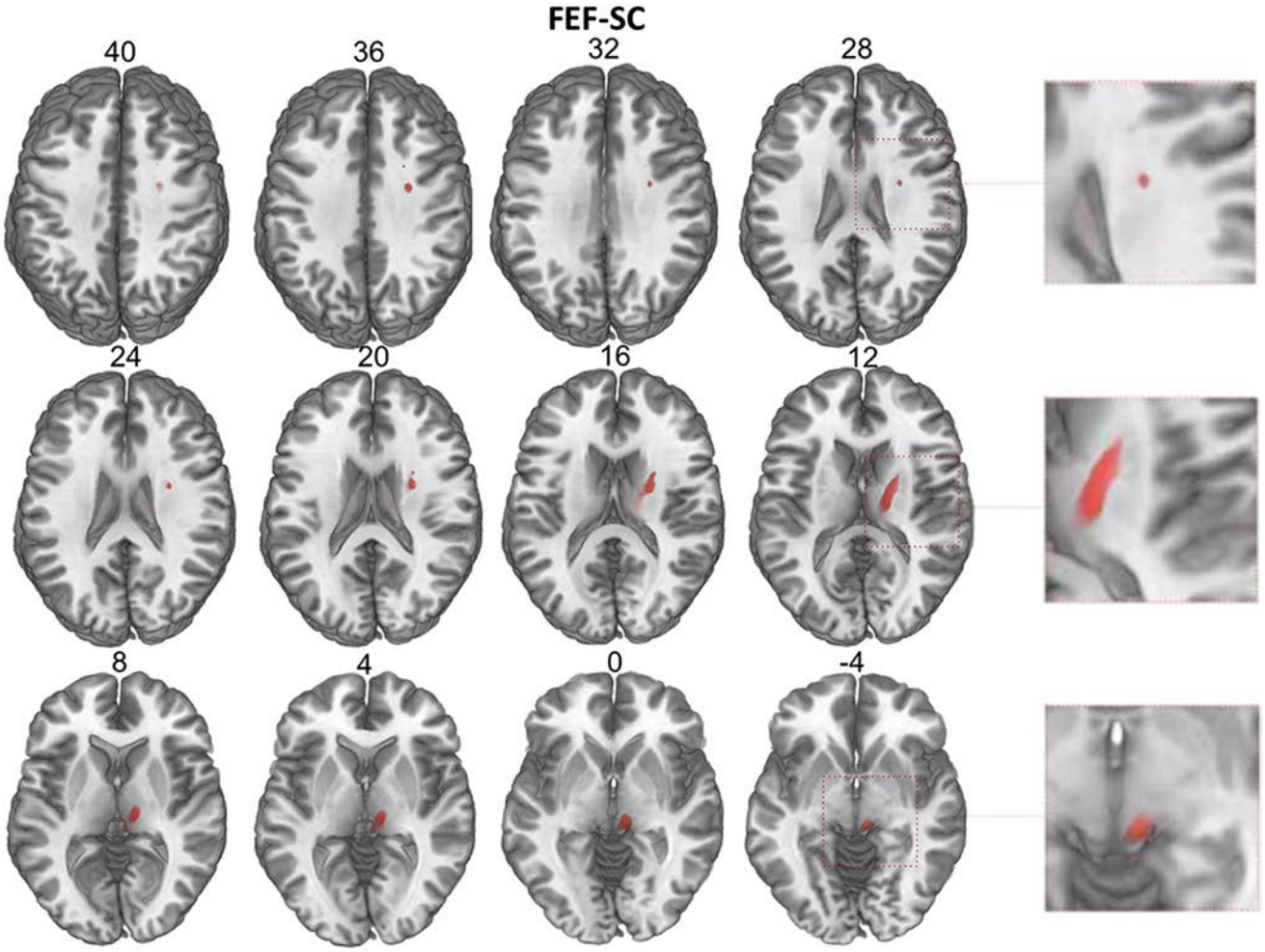


Fig. 5. Mean anatomical trajectory within a brain template of the most probable connection between the FEF and the SC revealed by our study, found correlated with visual sensitivity modulations. The average fronto-tectal pathway from the 13 subjects of the study is presented in MNI standardized space across serial selected axial sections (see z-coordinates) organized from top (WM underneath the FEF level) to bottom (at SC level). Notice the progression of this tract through the *corona radiata* underlying the FEF in the right hemisphere, the internal capsule, and the right posterior thalamus to finally reach the superior colliculus in the upper tectum. The anatomical trajectory of this FEF–SC tract strongly suggests that it could correspond to the trans-thalamic fronto-tectal tract previously reported in monkeys (Leichnetz et al., 1981).

centers of fiber bundles that are common to the whole population of subjects. This method is well-optimized for large intracortical WM projections (Smith et al., 2006), but could be less accurate for thinner cortico-subcortical pathways as the one identified in our study.

Prior studies have demonstrated that WM structure can influence the distribution of neurostimulatory currents (De Lucia et al., 2007), and correlates with cortico-spinal excitability (Klöppel et al., 2008) and the strength of inter-regional connectivity (Boorman et al., 2007). Our results go however one step further and suggest that interindividual differences in anatomical connectivity patterns between the TMS targeted cortical site and other postsynaptic brain regions are likely to influence the behavioral impact derived from *online* non-invasive neurostimulation. Due to its trajectory and thinness, a tract between the right FEF and the SC, a structure that in monkeys rivals the striate cortex as the major source of cortico-tectal connectivity (Leichnetz et al., 1981) has yet to be neuroanatomically reported in human brain specimens. Despite the limited intra-thalamic resolution of the DTI technique, the anatomical trajectory of our FEF–SC tract strongly suggests that it could correspond to the direct trans-thalamic fronto-tectal tract previously described in monkeys (Leichnetz et al., 1981). These fronto-tectal descending fibers may differently convey the TMS impact in terms of efficiency and speed, due to interindividual tract differences. This fact could explain the observed variability in TMS visual modulations. The SC holds important afferent and efferent connections with posterior parietal regions, the occipital cortex and thalamic nuclei, such as the lateral posterior thalamic complex and the pulvinar (Fries, 1984; Robinson and McClurkin, 1989; Sommer and Wurtz, 2000). In addition to its important role in oculomotricity, this midbrain structure is known to be involved in covert attention (Ignashchenkova et al., 2004; Katyal et al., 2010) and visual exploration (Gitelman et al., 2002; Himmelbach et al., 2006; Ignashchenkova et al., 2004). According to some models, interactions between the SC and the pulvinar are considered paramount for mediating attentional influences on perception, under the modulation of cortical regions such as the FEF (Shipp, 2004). Additional support for the modulatory role of fronto-tectal connectivity on visual detection comes from studies demonstrating that FEF stimulation influences neuronal activity in the SC of felines (Guitton and Mandl, 1974) and non-human primates (Schlag-Rey et al., 1992), and affects the modulation of saccadic control and the execution of eye movements during visually guided searches. It is thus well known that the SC plays an important role in the *detection* of visual targets, while driving visually guided eye, head and upper trunk orienting responses towards their location in the extrapersonal space. Nonetheless, its ability to *discriminate* sophisticated visual objects, faces or natural scenes is more severely curtailed by its rough receptor field organization, and for such tasks, striate visual areas would have to be recruited.

Interestingly, the absence of a significant correlation between any of the four WM tracts and the impact of isolated TMS pulses suggests that the underlying WM system encompasses the combined impact of both the stimulation and valid spatial cues, with additive bearing on visual sensitivity improvements. This notion is further supported by the fact that no significant correlation was found for this same pathway when the behavioral effect of valid spatial cues was considered isolately. Furthermore, FEF TMS pre-target pulse induced significant visual sensitivity modulation only for trials in which attention was effectively oriented towards the location of the upcoming target (Chanes et al., 2012). The contribution of the fronto-tectal pathway is only enabled through the engagement of the endogenous attentional network on a valid location by a predictive cue. Such exquisitely specific influence could be underlain by the state-dependency nature of neurostimulation (Silvanto et al., 2008) suggesting that TMS effects strongly depend on the activation status of the stimulated region. Consequently, TMS activations are likely to rely on the natural ability of such circuitry to facilitate improvements in target detection. These phenomena could be also subtended by cue-triggered reverberating activity across tecto-thalamo-frontal connections, or by tonic patterns of activity within the SC. In support of the latter hypothesis, it has been shown that prior to the execution of a saccade, this tectal region remains in a state of tonically sustained activation, a process that has been associated with its engagement in spatial attentional orienting (Basso and Wurtz, 1998; Glimcher and Sparks, 1992).

Very interestingly, the magnitude of the facilitatory effects on visual detection and the connection strength between the FEF and the SC were significantly anticorrelated. In other words, the higher the fronto-tectal probability of connection, the lower the magnitude of the TMS-driven visual sensitivity increases, and vice-versa. Similarly, negative rather than the expected positive correlations between Fractional Anisotropy (FA) and reaction times for a visuo-spatial task have been reported elsewhere (Tuch et al., 2005). Although this explanation remains merely speculative, it could be argued that during the last developmental stages of the central nervous system, a large number of axons linking the FEF and the SC could be pruned out, priming a population of highly selected fibers, which would establish highly excitable connections and induce large postsynaptic potentials in response to weak cortical inputs by neurostimulation. Such pathways could also be more likely denuded from neighboring fibers holding lateral inhibition interactions with the central core of the tract, which might tend to attenuate the extent and weaken connectivity-mediated effects. This explanation is consistent with modeling studies proposing that increasing the focality (thus reducing the number of structures activated by the TMS coil) might minimize "parasitic" downstream neurostimulatory effects driven by non-targeted regions, and thus increase its net postsynaptic effects (Wagner et al., 2009). However, this negative correlation could also suggest an inhibitory role for our fronto-tectal pathway. In the latter case, the observed visual facilitatory effects would be mediated by other brain systems, including the right FEF or projections from this area, whereas the FEF–SC pathway could simple act by preventing such visual facilitatory processes from occurring. Finally, we cannot rule out the possibility that such anticorrelation might have been caused by other WM projections not necessarily emerging from the FEF, crossing through the FEF–SC pathway and sustaining a positive correlation with TMS-behavioral effects. Even if this interpretation is theoretically plausible, it would signify that a WM tract not departing from the cortically stimulated area could be more influential than a directly stimulated pathway, an explanation which is not easy to reconcile with observations of network-specific modulations with effects that decay with distance and synaptic chains from the stimulated region (Valero-Cabré et al., 2005, 2007).

In the current study, we used probabilistic tractography (also known as "stochastic tractography, see Jones et al. (2012)) to define the white matter pathways from the right FEF, which might have been more likely responsible for TMS-driven enhancements of visual performance. This method, based on Markov Chain Monte Carlo sampling, models the diffusion of water molecules in each single brain voxel. This approach efficiently simplifies the real motion of molecules in the brain, but it does fail to capture the whole complexity of diffusion in those regions where more than two bundles intersect or in which the angle between two populations of white matter fibers is below 45° (Behrens et al., 2007). There may also be additional biases associated with the use of the number of trajectories as an index of connection probability and the favoring of the shortest and the simplest path (Jones, 2010), which might not always be the most anatomically realistic and plausible tract between a given origin and a destination in the brain. In consideration of these limitations, the probability of connection reported in our study should be interpreted cautiously and never be taken as a direct measure of the number of axons or as directly correlating with the thickness of their myelin sheaths. Although it is obvious that all these phenomena hold some level of association, the details of such correlates and their covariance remain to be defined. In any case, in accordance with our initial predictions, the FEF–SC pathway which emerged from our correlational study involves the TMS stimulated region with a distant structure such as the SC, whose receptive field organization and processing abilities are compatible with the characteristics (increases of visual *detection* sensitivity) and also the limitations (lack of effects on visual *categorization*) of the visual facilitation patterns underlying the correlations of this study (Chanes et al., 2012). In whole fairness however, we cannot rule out that other WM pathways projecting to nodes, which in our study might not have been selected as optimal candidates for correlation, could have also contributed to the observed effects. At least some of the across subject variability encountered could also be underlied by anatomical differences in the precise location of the right FEF by means of average Talairach coordinates and the behavioral consequences of such.

Furthermore, in this paper we focused in the important but not necessarily unique contribution of WM tracts emerging from the stimulated region. Indeed, it should not be forgotten that other sources of interindividual variability such as the intrinsic excitability of the stimulated regions and associated networks, the thickness, permittivity and conductivity values of the different tissue layers the magnetic field have to go through, and the relative orientation of neuronal layers with regard to the coil surface, to mention some of them, could also have bearing on the TMS induced current distribution field and its ability to induce neuronal activation (Bijsterbosch et al., 2012). As integrative mapping technologies and more sophisticated human brain-based computational models become available, we will be in position to consider the combined contribution of such variables to TMS effects.

Conclusion

Non-invasive neurostimulation is known to act locally by modulating activity in the stimulated regions of cortex. Nonetheless, its effects can be distantly widespread in a connectivity dependent manner throughout networks departing from the targeted site (Valero-Cabré et al., 2005, 2007; Wagner et al., 2007 for a review). As a result, an ambiguity prevails with regards to which neural systems under the influence of focal stimulation, alone or in combination with other ongoing activity patterns, might crucially underlie behavioral interferences or ameliorations. By ultimately determining from a set of coherently short-listed WM pathways which ones might best correlate with TMS induced effects, we aimed to decrease the uncertainty on the tracts that might best explain interindividual differences in visual detection facilitatory effects. Significantly correlated pathways could be then considered the most likely associated to the network-wide effects of the neurostimulation on such visual behaviors. Our findings open the door to develop methods that at the individual level could help to predict the likeability for neurostimulation to induce a behavioral effect upon the features of the anatomical connections between a neurostimulated cortical

site and other interconnected regions. This type of tools and procedures, particularly when supplemented in the near future by additional biophysical and physiological variables which are currently difficult to control in humans could reveal very useful to evaluate in brain-damaged patients under rehabilitation, the likeability of a relevant therapeutic effect prior to the onset of long neurostimulation regimes.

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Conflict of interest

The authors have no conflict of interests to declare.

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7.2. INFLUENCE DU FAISCEAU LONGITUDINAL SUPERIEUR DANS LA MODULATION VISUELLE PAR SMT RYTHMIQUE

Nous avons utilisé dans cette étude la même approche que dans l'étude précédente. Nous avons cette fois-ci récupéré les données individuelles de l'expérience de SMT décrite dans la *Partie 2* du *Chapitre 6* afin de tester si la variabilité de nos effets de modulation perceptive pouvait être reliée à des différences de connectivité anatomique chez nos participants. L'utilisation de la SMT rythmique sur la région FEF droite avec l'hypothèse d'une synchronisation dans le réseau attentionnel nous a conduit à reconstruire le faisceau longitudinal supérieur (SLF) qui relie les aires frontales aux aires pariétales. Ce faisceau se divise en trois branches. La première relie le lobe pariétal supérieur, qui comprend l'IPS, avec le gyrus frontal supérieur et moyen. La deuxième branche relie le gyrus angulaire et la jonction temporo-pariétale avec les régions supérieures et latérales du lobe frontal. Enfin, la troisième branche connecte le gyrus supramarginal et la jonction temporo-pariétale avec les régions ventrales du lobe frontal (Makris et al. 2005; Thiebaut de Schotten et al. 2012). A partir de nos données de diffusion, nous avons modélisé le signal grâce à une méthode récente de déconvolution sphérique qui permet d'observer plusieurs directions de diffusion privilégiées dans un voxel (Dell'acqua et al. 2010). Le SLF croisent dans le cerveau à plusieurs endroits les fibres du corps calleux et le faisceau cortico-spinal, il était primordial d'utiliser une technique permettant de reconstruire plusieurs populations de fibres avec des directions différentes. Nos analyses ont révélé une corrélation négative significative entre le volume de la 1ere branche du SLF à droite et la modulation perceptive induite par la SMT rythmique dans la tâche de détection consciente. Ce faisceau qui relie les aires corticales du réseau dorsal de l'attention semble être impliqué dans la modulation visuelle obtenue par l'induction d'une activité rythmique frontale à 30 Hz. Nous faisons l'hypothèse que des différences de myélinisation dans ce faisceau qui impacte le temps de conduction neuronal entre les aires frontales et pariétales influencent la synchronisation potentielle des aires au sein de ce réseau à cette fréquence spécifique, conduisant à une variabilité de réponse comportementale.

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Fronto-Parietal Anatomical Connections Influence the Modulation of Conscious Visual Perception by High-Beta Frontal Oscillatory Activity

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May white matter connectivity influence rhythmic brain activity underlying visual cognition? We here employed diffusion imaging to reconstruct the fronto-parietal white matter pathways in a group of healthy participants who displayed frequency-specific ameliorations of visual sensitivity during the entrainment of high-beta oscillatory activity by rhythmic transcranial magnetic stimulation over their right frontal eye field. Our analyses reveal a strong tract-specific association between the volume of the first branch of the superior longitudinal fasciculus and improvements of conscious visual detection driven by frontal beta oscillation patterns. These data indicate that the architecture of specific white matter pathways has the ability to influence the distributed effects of rhythmic spatio-temporal activity, and suggest a potentially relevant role for long-range connectivity in the synchronization of oscillatory patterns across fronto-parietal networks subtending the modulation of conscious visual perception.

Keywords: brain, oscillations, synchronization, conscious visual perception, noninvasive neurostimulation, visuo-spatial attention, white matter anatomy

Introduction

Correlational approaches employed to investigate the influence of white matter fasciculi on human behaviors have revealed tract-specific influences on cognitive processes, such as choice selection, visuo-spatial orienting, and motor training (Tuch et al. 2005; Scholz et al. 2009; Thiebaut de Schotten et al. 2011). Similarly, observations in animals (Valero-Cabré et al. 2005, 2007) and humans (Quentin et al. 2013) have strongly suggested an association between interindividual differences of specific white matter pathways linking the targeted region and key postsynaptic sites with the behavioral impact induced by focal patterns of noninvasive neurostimulation.

Here, we specifically addressed whether the behavioral effects derived from frequency-specific oscillation patterns induced by rhythmic noninvasive brain stimulation may be particularly impacted by the individual characteristics of white matter projections. We employed a transcranial magnetic stimulation (TMS) dataset from a recent experiment in which we tested the impact on conscious visual performance of short frequency-specific 30-Hz bursts delivered to the right frontal eye field (FEF) prior to the onset of a low-contrast visual Gabor, displayed either to the right or left of a fixation cross (Chanes et al. 2013) (Fig. 1*a*,*b*). Importantly, we aimed to use frequency-tailored patterns to enhance local oscillations (Romei et al. 2010; Thut et al. 2011) and entrain synchronization throughout a fronto-parietal dorsal network, considered key for spatial attentional orienting and the top-down modulation of visual perception (Chanes et al. 2012).

Stimulation site and frequency were matched to those of a nonhuman primate study reporting the engagement of high-beta (22–34 Hz) activity across frontal and parietal dorsal regions during a visual search task involving endogenous attentional orienting (Buschman and Miller 2007). In our population, short episodes of 30-Hz spatio-temporal activity delivered to the right FEF prior to target onset induced statistically significant improvements of perceptual sensitivity in a visual detection task, which were absent when control nonfrequency-specific stimulation patterns were employed (Chanes et al. 2013). Interestingly, despite robust statistically significant group effects, across-subject performance differences were observed (Fig. 1*c*). As we recently demonstrated for single TMS pulses (Quentin et al. 2013), we hypothesized that such behavioral variability could largely emerge (among other potential factors) from interindividual white matter connectivity differences modulating the distributed impact of frequency-specific bursts throughout fronto-parietal cortical networks (Buschman and Miller 2007).

Diffusion images acquired prior to the experiments were used to track with a deterministic method based on spherical deconvolution (Dell'acqua et al. 2010) the 3 branches of the superior longitudinal fasciculus (SLF) in both hemispheres of each participant's brain. The SLF I is the dorsal-most white matter pathway linking the superior parietal lobule encompassing the intraparietal sulcus (IPS), with the middle and superior frontal gyrus (Thiebaut de Schotten et al. 2011), where the FEF is located. The cortical connection sites of this pathway correspond to the dorsal attentional orienting network involved in endogenous spatial orienting (Kincade et al. 2005). This system can engage in high-beta oscillatory activity and fronto-parietal synchrony during top-down attentional control in monkeys (Buschman and Miller 2007) and humans (Phillips and Takeda 2009), and has been causally associated with the modulation of conscious vision (Chanes et al. 2013). The SLF II, located in the central core of the white matter above the insula, links the angular gyrus to both the superior and lateral prefrontal regions (Makris et al. 2005) and has been considered a potential link between the ventral and dorsal attentional orienting networks (Thiebaut de Schotten et al. 2012). Finally, the SLF III associates the supramarginal gyrus and the temporo-parietal junction to both ventral

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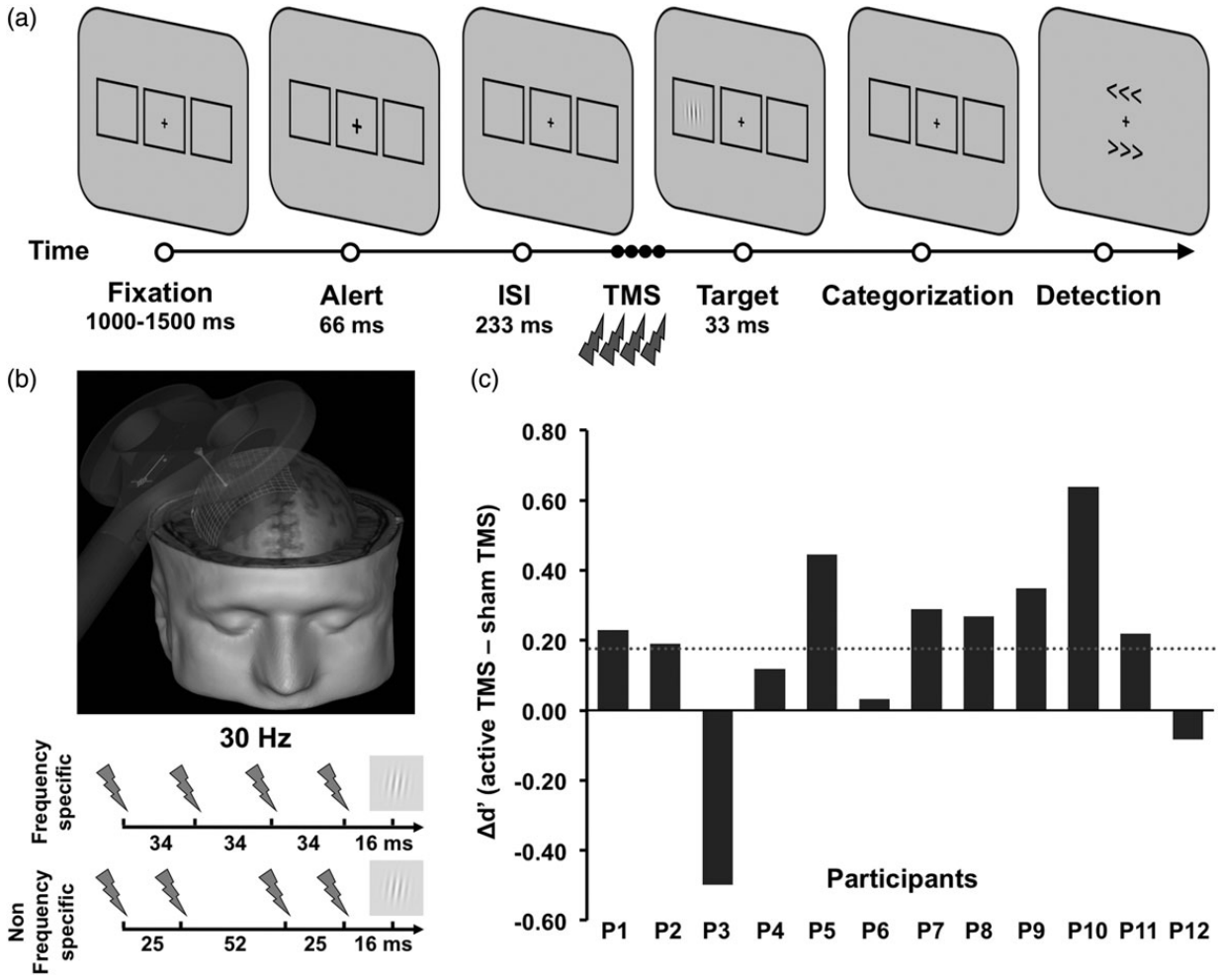


Figure 1. Visual performance task and rhythmic right frontal oscillation patterns used in the study. (*a*) Sequence of events during a representative trial of the visual performance paradigm employed in the study. After variable fixation time, participants were requested to discriminate the orientation of the Gabor lines and indicate if they had or not detected the presence of the target and where (right or left) did this appear in the visual field. (*b*) TMS coil positioning on the right FEF region; temporal distribution of "frequency-specific" and "nonfrequency-specific" spatio-temporal oscillation patterns delivered prior to the Gabor target onset. (*c*) Individual levels of conscious visual detection performance modulated by frequency-specific, high-beta (30 Hz) patterns in each of the 12 participants of our study (from P1 to P12). Data are presented as perceptual sensitivity gains ($\Delta d'$, d' active TMS – d' sham TMS) induced by FEF beta oscillations in the conscious visual detection task. Positive and negative values indicate visual sensitivity (d') increases and decreases, respectively. The horizontal discontinuous gray line signals the mean level of statistically significant visual sensitivity effects induced by high-beta frontal oscillations in the whole group of participants. Note that in spite of significant group d' improvements, participants showed interindividual differences in the magnitude and the direction of such effects.

premotor and prefrontal regions. These areas, which are involved in automatic reorienting toward an unexpected event, correspond to the ventral attentional orienting network (Corbetta et al. 2008; Chica et al. 2011).

Materials and Methods

Study Participants

The data used in this study were extracted from a recently published behavioral-TMS dataset (Chanes et al. 2013). Twelve of 14 participants of the original study for which we had diffusion magnetic resonance imaging (MRI) sequences (7 males and 5 females; mean age = 24.7 ± 3.7 years; minimum age = 20 years; maximum age = 31 years) were included in our analyses. Participants were naïve to both, the purpose of the experiment and the uses of TMS. They freely provided informed written consent prior to their participation and were compensated for taking part in the study. The protocol was reviewed by the INSERM (Institut National de la Santé et la Recherche Scientifique) ethical committee and approved by an Institutional Review Board (CPP Ile de France 1).

Behavioral Paradigm and TMS

Each trial started with a gray (luminance: 75 cd/m^2) resting screen (17″ wide, 1024 × 768) displayed during 2500 ms followed by a central fixation cross (0.5 × 0.5°) lasting randomly between 1000 and 1500 ms, and presented along 3 rectangular placeholders outlined in black (6.0° × 5.5°), 1 located centrally and 2 placed laterally, to the right and left of the fixation cross. Then, the fixation cross became sligthly larger (0.7 × 0.7°) for 66 ms to alert participants of an upcoming event and following an interstimulus interval (ISI) of 233 ms, a low-contrast Gabor stimulus (2 cycles/degree spatial frequency, 3.0° diameter, 0.3° of SD, minimum and maximum Michelson contrast of 0.031 and 0.283, respectively) with lines tilted 1° to 10° to the left or to the right (vertical orientation = 0°) appeared at the center of 1 of the 2 lateral placeholders for 33 ms (Fig. 1*a*). Prior to the session, participants performed a titration block, which started with a high-contrast stimulus. Every 20 trials, target contrast and line tilting were adjusted (in steps of 0.07 Michelson contrast and 1° of tilting, respectively), so that

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approximately 50% of the displayed targets were consciously reported ("detection" task) and 65–85% of the latter were correctly discriminated ("discrimination" task). Throughout the experiment, stimulus parameters were also automatically adjusted every 20 trials to maintain this same titration levels.

Prior to target onset, 4 pulse 30-Hz bursts of sham or active TMS ("frequency-specific" patterns, interpulse intervals between first—second, second–third, and third—fourth pulses = 34, 34, and 34 ms, respectively) were delivered on the right FEF. To verify the behavioral impact of pattern frequency on visual performance, the latter were compared in separate blocks with sham and active nonuniform bursts of equal duration and number of pulses with nonuniformely spaced inner pulses ("nonfrequency-specific patterns," interpulse intervals between pulses 24, 52, and 24 ms, respectively). Importantly, the first and last pulses of both types of bursts were always delivered 118 and 16 ms before target onset, respectively. A frameless stereotaxic neuronavigation system (eximia, Nextim, Helsinki, Finland) was used to guide and maintain on each individual and across experimental blocks the coil location on a set of specific FEF coordinates (Talairach $x = 31$, $y = -2$, $z = 47$) (Fig. 1*b*). For all patterns and blocks, TMS intensity was initially set up at 45% of the TMS maximal machine output. Occasionally in some participants, intensity had to be slightly decreased to abolish temporal involuntary muscle activation, involuntary blinks, or others types of facial sensations. Participants were stimulated at an average intensity of 44 ± 1.5% (which corresponded to 72 ± 13% of their resting motor threshold). In half of the trials, a short burst of 4 real TMS pulses was applied directly to the right FEF (active TMS trials). In the other half (sham TMS trials), the same burst was delivered by a second TMS coil placed next to the stimulation site, with the coil surface perpendicular to the head surface, preventing the magnetic field from reaching the skull and stimulating the brain. The order of active and sham TMS trials was randomized (Chanes et al. 2013).

After the delivery of the TMS burst and the presentation of the Gabor, participants were first required to determine with their right hand the "right" or "left" orientation of the "Gabor" lines ("discrimination task") as accurately as possible. They were also forced to guess a response, even when the target was not present or they did not consciously perceive it. Then, participants were requested to report with their left hand whether they perceived the Gabor on the "left," or the "right" of the fixation cross, or they did not see it ("detection task") (Fig. 1*a*). Discrimination performance was analyzed through accuracy measures (correct grating orientation categorization). Perceptual sensitivity (d') and response bias (beta) used in signal detection theory served to assess the modulation of conscious visual detection. Participants were requested to keep their gaze on the fixation cross throughout the trial. Eye movements were controlled by an eye-tracker system, and fixation was considered broken when gaze position was recorded outside the central box, that is, 3° of angle away from the fixation cross horizontally, and 2.75° vertically (Chanes et al. 2013). Each of the 2 blocks consisted of 200 trials, and included 40 trials in which the target was absent (20% of the trials of each block). Participants were allowed to take a short break every 40 trials and at the end of each sub-block they received feedback about their performance and fixation violation rates.

MRI Acquisition

Diffusion MRI scans were obtained on a 3-T MRI scanner (Tim Trio, Siemens Healthcare, Erlangen, Germany) located at the CENIR (Centre de Neuro-Imagerie de Recherche) at the Hôpital de la Pitié Salpêtriére, in Paris (France). Using a 32-channel array coil and a maximum gradient of 28 mT/m, diffusion weighting was isotropically distributed along 60 directions and 6 nondiffusion-weighted volumes were acquired. The first *b*0 image served as an anatomical reference for the correction of eddy currents. Imaging parameters were as follows: voxel size = 1.7 × 1.7 × 1.7, repetition time (TR) = 12 800 ms, echo time (TE) = 88 ms, $b = 1500$ s/mm^2, and matrix size = 129 × 129 × 71. Each set of images contained 71 contiguous slices with a 1.7-mm thickness. Total acquisition time was 14 min and 43 s. A three-dimensional (3D) structural T_1-weighted MRI also employed to neuronavigate the TMS coil was acquired on each subject (TR = 2300 ms, TE = 4.18 ms, field of view = 265 mm, matrix size = 256 × 256 and 176 sagittal slices with 1 mm thickness).

Data Processing and Estimation of Fiber Orientation

Diffusion images were corrected for head motion and eddy current distortions using affine registration to the first nondiffusion-weighted volume implemented in the FSL software package (FSL 4.1.6—www.fmrib.ox.ac.uk/fsl/). Spatial deformations of the DTI dataset due to susceptibility artifacts were corrected with nonlinear deformation computed from the diffusion images to match the T_1-weighted volume using the Freesurfer Software (Freesurfer 5.0.0, http://surfer.nmr.mgh.harvard.edu/). A spherical deconvolution approach (Tournier et al. 2007) with a modified damped version of the Richardson-Lucy algorithm (Dell'acqua et al. 2010) was employed to estimate fiber orientation in each white matter voxel. This approach was chosen to allow the reconstruction of several orientations in voxels containing different populations of crossing fibers. An absolute and a relative threshold were used to exclude spurious local maxima of fiber orientation distribution (Thiebaut de Schotten et al. 2011).

Tractography

Whole-brain tractography was performed starting from every voxel with at least one fiber orientation as a seed voxel. From these voxels and for each fiber orientation, a modified fiber assignment using a continuous tracking algorithm was used to reconstruct streamlines by sequentially piecing together discrete and shortly spaced estimates of fiber orientation forming continuous trajectories. When entering a region with crossing white matter bundles, the algorithm followed the orientation vector of least curvature. Streamlines were halted when a voxel without fiber orientation was reached or when the curvature between 2 steps exceeded a threshold of 45°. The software estimating and reconstructing the orientation vectors and the trajectories from diffusion MRI was implemented in Matlab 7.8 (MathWorks, Natick, MA, USA). Each SLF branch was normalized to the Montreal Neurological Institute (MNI) mean brain volume using SPM (http://www.fil.ion.ucl.ac.uk/spm) to create a mean tractography image.

SLF Dissection

A previously validated method (Thiebaut de Schotten et al. 2011) was used to dissect the 3 branches of the SLF. Fasciculi from both hemispheres were considered, as visual detection enhancements induced by rhythmic TMS patterns proved bilateral (Chanes et al. 2013). To delineate the SLF I, II, and III, 3 regions of interest (ROIs) encompassing the white matter of the superior, middle, and inferior/precentral frontal gyri were outlined on a coronal section at the anterior commissure's level. A parietal ROI was also delineated on a coronal section at the level of the posterior commissure. This "AND" ROI was common to the 3 branches of the SLF. A temporal ROI was used to exclude streamlines of the arcuate fasciculus, which are not integrated in fronto-parietal white matter projections. When required, an ROI encompassing the internal and external capsules was employed to eliminate descending fibers.

White Matter Pathways—Behavioral Correlations

The volume of the 3 branches of the SLF was determined and divided by the total tracked white matter volume of each participant. The relative conscious visual detection sensitivity gains ($\Delta d'$) induced by active versus sham neurostimulation was used to estimate perceptual improvements of conscious vision caused by high-beta (30 Hz) frontal TMS patterns, which demonstrated significant visual sensitivity (d') increases at the group level. Similar correlations were also performed for the modulation of identical visual outcome measures by nonfrequency-specific frontal control bursts, which did not reach statistical significance at the group level. A Shapiro–Wilk test was used to verify the Gaussian distribution of these variables (all $P > 0.12$). The Pearson's correlation coefficient between tract volume and $\Delta d'$ was calculated for each branch of the SLF white matter tract (JMP 10.0.0, SAS, Cary, NC, USA). Bonferroni post hoc correction was used to compensate for the family-wise error rate in multiple comparisons (uncorrected $^*P < 0.05$; corrected $^{**}P < 0.05/12 \approx 0.004$). To provide additional and convincing proof of the robustness of our statistically significant correlation, a permutation test (Groppe et al. 2011) based on Pearson's correlation coefficient with 5000 permutations was also applied. We permuted the SLF I pathway volume in both hemispheres within our group of 12 participants and recalculated the correlation with each new version of this

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modified dataset. The null hypothesis of the permutation test is that the correlation obtained with the initial order is as likely as the correlation obtained with random permutations. The skipped correlation procedure (Rousselet and Pernet 2012), which performs a robust Pearson correlation on data cleaned up for bivariate outliers, was also employed. The correlation coefficients between specific tract volume and visual modulations induced by either frequency-specific or nonfrequency-specific patterns were statistically compared using the method reported in Steiger et al. (1980). Finally, a General Linear Model (GLM) implemented on Matlab 7.11.0 (MathWorks) was also used to further verify the correlation of a given pathway with conscious visual outcome measures, independently of the participant's age, motor threshold, other SLF branch volumes, and the total brain's tracked white matter volume.

Results

We first analyzed the normalized volume of each of the 3 SLF branches across our group of participants. When comparing the 2 hemispheres, a previously reported branch-specific right hemispheric lateralization pattern (Thiebaut de Schotten et al. 2011) involving the SLF III ($t = 3.93$; $P = 0.002$, df = 11) but neither the SLF I nor the SLF II branches ($t < 1$) was found. This finding, which replicates such influential outcome, suggests the reproducibility of the white matter tracking method employed in this study for the SLF. We then calculated performance differences between active and sham rhythmic 30-Hz TMS patterns to obtain the relative visual sensitivity gain ($\Delta d'$) for conscious detection. Interestingly, this measure significantly correlated with the right hemisphere's SLF I volume ($r = -0.83$; $P < 0.001$, Bonferroni corrected), whereas visual performance correlations with the SLF II ($r = 0.17$; $P = 0.60$) and the SLF III ($r = -0.49$; $P = 0.10$) tract volume failed to reach statistical significance. A significant correlation between $\Delta d'$ and the left hemisphere's SLF I ($r = -0.68$; $P = 0.015$, uncorrected), but neither with the SLF II ($r = -0.33$; $P = 0.29$) nor the SLF III ($r = 0.03$; $P = 0.92$) was also found. Importantly, similar significance for the right ($r = -0.83$; $t = -4.78$) and left SLF I branch ($r = -0.68$; $t = -2.91$) was also found when the skipped correlation approach was employed on this same dataset.

Correlations between individual visual sensitivity (d') modulations induced by nonfrequency-specific TMS patterns and white matter pathway volumes were also tested. Importantly, none of the 6 white matter pathways' volume significantly correlated with the above-mentioned perceptual outcome measure (right SLF I: $r = -0.39$; $P = 0.21$, left SLF I: $r = -0.24$; $P = 0.44$, right SLF II: $r = 0.50$; $P = 0.09$, left SLF II: $r = -0.19$; $P = 0.55$, right SLF III: $r = -0.40$; $P = 0.19$, and left SLF III: $r = -0.10$; $P = 0.74$).

To further corroborate that this effect was specifically related to stimulation frequency, we confirmed that the correlation coefficient between the right SLF I volume and visual modulations induced by frequency-specific TMS pattern was significantly higher than the one established between this same branch volume and visual performance shifts yielded by nonfrequency-specific neurostimulation patterns ($P = 0.03$). Moreover, a permutation test confirmed these results for the correlations between the right ($P = 0.0032$) and left SLF I ($P = 0.024$) and the impact of spatio-temporal right frontal beta activity on visual sensitivity shifts. Finally, a multiple linear regression analysis based on the GLM t-test with the 2 statistically significant pathways, the right and left SLF I, as explanatory variables and the nonsignificant pathways, participant's age, motor threshold, and total tracked brain volume as confound regressors confirmed once more that only the dorsalmost SLF branch (SLF I) covaried significantly with conscious visual performance outcomes ($t = -3.32$; $P = 0.005$; df = 8, Bonferroni corrected) (Fig. 2).

To avoid any ceiling effects, target contrast was adjusted prior to task onset and during the task itself, every 20 trials, to keep steady performance rates at 50% of correct conscious detection (see Chanes et al. 2013 for details). Importantly, individual contrast levels required to ensure such specific levels of performance did neither correlate with white matter pathway volumes for the 6 branches analyzed in the study ($r = -0.49$, $P = 0.10$), nor with the effects of frequency-specific frontal TMS patterns on visual sensitivity ($r = 0.45$, $P = 0.14$).

As indicated elsewhere (Quentin et al. 2013), others sources of interindividual variability (e.g. the intrinsic excitability levels of the stimulated frontal region and its associated networks, cortical shape, the distribution of cerebro-spinal fluid, or the relative orientation of neuronal layers with regard to the coil surface, to provide some examples) cannot be accurately characterized with current human neuroimaging methods and may have contributed to some extent to variability in TMS efficacy and by extension to performance variability (Bijsterbosch et al. 2012).

Discussion

Our data indicate that the ability of spatio-temporal right frontal neurostimulation patterns to induce sensitivity improvements of conscious vision is primarily modulated by the volume of the SLF I white matter branch, connecting the FEF and the IPS regions. This result applies only to the impact of frequency-specific frontal beta patterns at 30 Hz, as no significant correlations were found for the effects of nonfrequency-specific patterns delivered to this same frontal location.

Like only the correlation with the right SLF I survived a Bonferroni correction and oscillation patterns were induced on the right FEF, further analyses focused on the right hemisphere's SLF I tract. It would be tempting to interpret the uncorrected correlation with the left SLF I tract as the substrate of the bilateral visual detection improvements reported by Chanes et al. (2013). Nonetheless, since the first branch of the SLF has been shown not to be anatomically lateralized either to the left or the right hemisphere (Thiebaut de Schotten et al. 2011), this trend could be simply due to the fact that the volumes of these 2 tracts are strongly correlated ($P = 0.001$).

Like in a recent study employing single-pulse TMS (Quentin et al. 2013), the correlation between the behavioral impact of rhythmic TMS on d' and the SLF I volume proved to be negative. Despite differences in the stimulation patterns employed on each case, the current outcome provides additional experimental support in favor of an inverse association between TMS modulated behaviors and white matter connectivity (Quentin et al. 2013). This result might seem counterintuitive, as larger tract volumes or higher probability of connection acting under physiological conditions have been often associated with more effective connectivity and information transfer (Glasser and Rilling 2008; Thiebaut de Schotten et al. 2011). Alternatively, however, thinner pathways could prove more efficient in conveying neural signal particularly when those are artificially induced by nonsufficiently focal noninvasive neurostimulation sources. Indeed, as hypothesized elsewhere (Wagner et al. 2009), smaller and less populous white matter tracts, with features and properties which may be innately determined (van Kooij et al. 2011) and also shaped by postnatal training

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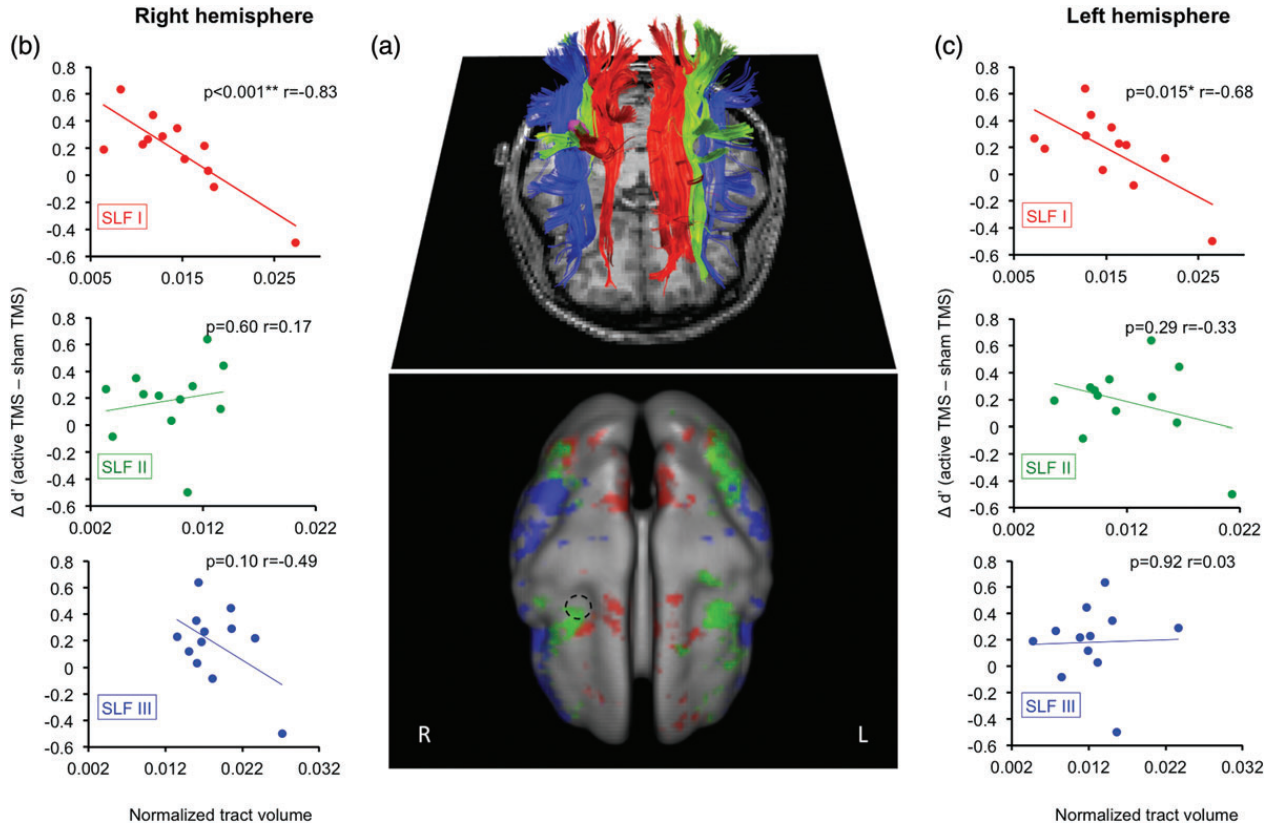


Figure 2. Correlations between white matter diffusion imaging data and conscious visual detection performance associated with the manipulation of frontal oscillatory activity. (*a*) Upper middle panel: Tractographic rendering of the 3 branches of the SLF (SLF I in red, SLF II in green, and the SLF III in blue) in a representative participant. The purple region signals the cortical location of the stimulated area; lower middle panel: top view, image representing on a 3D MNI white matter template the mean cortical projections of the 3 SLF branches (SLF I in red, SLF II in green, and the SLF III in blue). The black circle signals the cortical location of the stimulated region, the right FEF. (Right and left panels, *b* and *c*) Correlation plots between conscious visual detection sensitivity gains ($\Delta d'$) (d' for active TMS – d' for sham TMS) and the normalized volume of each of the 3 SLF branches. Correlations are presented for the right (*b*) and the left (*c*) hemispheres, respectively. Note that only the right SLF I ($r = -0.83$; $P < 0.001$, Bonferroni corrected) and left SLF I ($r = -0.68$; $P = 0.015$, uncorrected) branches linking the FEF to the IPS regions showed a significant correlation between white matter volume and visual sensitivity gains. Asterisk indicates: * uncorrected ($P < 0.05$); ** Bonferroni corrected ($P < 0.05/12$).

experience (Imfeld et al. 2009), could prove less prone to "parasitic" phenomena such as interferences caused by center-surround inhibitory effects of fibers running within the same tract, when forcedly activated by TMS. Such projections could convey less noisy and more robust signals to postsynaptic parietal and occipital sites (see Quentin et al. 2013 for further discussion of this issue). If the latter remains a plausible hypothesis, one needs to remain very cautious when attempting to derive physiological explanations from purely structural data (Jbabdi and Johansen-Berg 2011; Jones et al. 2012) and further experiments are absolutely required to better understand the basis of this association. Alternatively, this result could also be explained by the fact that participants with larger white matter tracts may benefit from a more selective top-down control on visual performance, allowing higher baseline levels of detection performance which would limit the leverage to experience further visual sensitivity increases. This explanation seems, however, implausible as no significant correlations were found, neither between the stimulus contrast levels required to keep baseline visual detection rates constant and white matter pathway volumes, nor between those contrast levels and the visual impact of frequency-specific frontal beta patterns.

Most importantly, our results are novel and could prove relevant to establish potential links between cerebral synchronization and the anatomical pathways conveying such activity throughout fronto-parietal networks of the right hemisphere. Focal noninvasive neurostimulation by TMS has already demonstrated a primary impact on the stimulated region that spreads remotely, and its ability to modulate an entire network of areas connected by anatomical white matter projections in animals (Valero-Cabré et al. 2005, 2007) and humans (Quentin et al. 2013). Moreover, recent monkey electrophysiological evidence and causal neurostimulation studies in humans support frequency-specific oscillatory activity in top-down spatial orienting and visual performance (Buschman and Miller 2007; Romei et al. 2012; Chanes et al. 2013). Based on our own observations, and prior electrophysiological monkey and human evidence (Buschman and Miller 2007; Phillips and Takeda 2009), we here present the working hypothesis that high-beta oscillation patterns entrained in a right frontal region might not remain local, but likely spread out along the dorsal attentional network, and that such activity patterns could be subtended by fibers of the first branch of the SLF.

In the past, similar modulations of visual performance have also been explained by long-range connectivity effects of stimulated frontal and parietal regions operating on the input gain and signal strength of visual stimuli processed at occipital and tectal

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regions (Ruff et al. 2006; Quentin et al. 2013). The current results call, however, for a hypothesis able to better substantiate in physiological terms the relation between white matter connectivity and interregional synchrony between frontal and the dorsal and posterior portions of the parietal cortex. Prior reports have suggested that visual cognition relies on fronto-parietal synchronization, and that such processes increase the coupling between brain regions, enhancing sensory evidence (Fries 2005; Buschman and Miller 2007; Miller and Buschman 2013). Consequently, anatomical differences in white matter tracts may impact how spatio-temporal patterns are reverberated across extended brain networks and could determine their ability to modulate conscious visual behaviors. Interestingly, tract volume is associated with factors such as axonal diameter and myelination rates, which determine the conduction speed of neural signals across white matter pathways. In this particular framework, our data may suggest that interregional synchronization processes entrained at a specific frequency are strongly influenced by the biophysical properties of the specific white matter tracts established between sets of cortical regions and their derived impact on time lag and conduction velocity, indicating that greater axonal conduction velocity may allow for more reliable synchronization at higher oscillation frequencies (Zaehle and Herrmann 2011). In our study, this notion would entail, if proven correct, that the visual consequences of rhythmic high-beta frontal activity patterns specifically delivered at 30 Hz depend on the individual conduction time lag between frontal and parietal regions and the ulterior ability of this network to synchronize activity at this specific frequency band. Consequently, individual performance under rhythmic TMS patterns could depend on the suitability of the entrained oscillation frequency to the structural and physiological properties of white matter tracts mediating interregional coupling and synchrony. Individual differences in anatomical connectivity and interregional conduction time lag could also explain the relatively broad bandwidth of oscillation frequencies, which in electrophysiological studies have been associated (within a given band such as alpha, beta, or gamma) with processes such as visuo-spatial attention, perception, and visual consciousness (Wyart and Tallon-Baudry 2009; Thut et al. 2011). Although this was out of the scope of the current study, by ascertaining an exquisite dependency between behavioral outcomes and rhythmic neurostimulation bursts at several values slightly below and above a central 30-Hz pattern, co-varying with individual SLF I measures could provide further causal confirmation in favor of this interesting hypothesis.

Nonetheless, in the absence of interleaved TMS-electrophysiological online evidence, a mechanistic hypothesis based on synchronization within the fronto-parietal network cannot be here fully demonstrated. Thus, as previously hypothesized in this discussion, effects on perception could also reflect a local FEF impact and a top-down propagation from this site that is dependent of fronto-parietal fibers and stronger under the influence of beta-stimulation patterns, without any necessary contribution of coherent beta activity from parietal sites.

In summary, our study suggests a strong association between fronto-parietal white matter anatomy, rhythmic brain activity, and the emergence of conscious visual perception, and supports a future role for individual white matter patterns in tailoring the frequency of rhythmic neurostimulation in future research and clinical applications.

Author's Contributions

A.V.-C. developed the main concept of this project, provided the funding and was in the charge of its supervision. A.V.-C. and R.Q. developed the specific hypotheses and ideas; A.V.-C. and R.Q. co-designed the study; L.C., R.Q., and A.V.-C. performed the TMS experiments; L.C. and A.V.-C. analyzed the behavioral data; R.Q. analyzed the DTI data and computed the correlations; A.V.-C. and R.Q. interpreted the data. A.V.-C., R.Q. and M.V. prepared the final figures and wrote the manuscript.

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CHAPITRE 8. MODULATION VISUELLE A DIFFERENTS CONTRASTES PAR SMT RYTHMIQUE ET INFLUENCE DU FAISCEAU LONGITUDINAL SUPERIEUR

Dans cette étude, nous avons observé en détail le type de modulation perceptive visuelle provoquée par la stimulation rythmique à 30 Hz sur la région du FEF dans l'hémisphère droit. En particulier, nous avons testé si l'amélioration perceptuelle obtenue dans nos études précédentes pouvait être étendue à l'ensemble de la courbe de sensibilité visuelle. Nous avons utilisé une tâche de détection visuelle à choix forcé et nous avons fait varier le contraste au cours de l'expérience. Pour reconstruire l'ensemble de la courbe psychométrique, nous avons utilisé une méthode adaptative d'estimation bayésienne du seuil et de la pente. Ce type de méthode prend en compte les réponses du participant aux essais précédents pour choisir la valeur de contraste de l'essai suivant. A chaque essai, l'estimation des deux paramètres de la courbe est réévaluée et la valeur suivante du contraste est choisie afin de minimiser l'incertitude sur cette estimation. Les résultats observés lors de la stimulation à 30 Hz montrent une amélioration visuelle sur l'ensemble de la courbe, observée par un déplacement à gauche de celle-ci. Aucune modulation visuelle n'a été observée dans la condition contrôle sans fréquence spécifique. Afin de quantifier des différences dans la substance blanche entre nos participants, nous avons utilisé un index d'anisotropie (HMOA) spécifique à la direction du faisceau d'intérêt. Ce paramètre est sensible à des différences de micro-structure dans la substance blanche comme la myélinisation, la densité axonale ou le diamètre des axones (Dell'Acqua et al. 2013). L'analyse de ces données montre une corrélation négative entre la modulation des performances visuelles et l'anisotropie dans la 1ere branche du SLF. Ces résultats confirment les observations de l'étude précédente avec une tâche de psychophysique différente et l'utilisation d'un paramètre plus sensible à des changements microstructuraux comme la myélinisation. Cette étude renforce notre hypothèse d'une synchronisation fronto-pariétale dont la fréquence est reliée à la structure des faisceaux anatomiques du réseau.

Causal contributions and white matter correlates of right frontal rhythmic activity to visual contrast sensitivity modulation in humans

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Abbreviated Title: White matter & frontal oscillatory activity

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Abstract

Electrophysiological evidence in human and non-human primates has correlated frontal high-beta activity with the orienting of endogenous attention during visual search tasks. We recently reported in humans a visual detection improvement for near-threshold targets, causally associated with the induction of high-beta rhythmic patterns on the right Frontal Eye Field (FEF). Here, we delivered identical patterns to this same area and recorded their impact on the contrast sensitivity function. By doing so, we explored for the first time if visual improvements causally associated to this rhythmic activity were specifically restricted to near-threshold targets or could be extended to other levels of stimulus contrast. Our results suggest that frequency-specific activity patterns engaged in the right FEF have the ability to induce a global leftward shift of the psychometric function, indicating increases in visual detection rates for lateralized targets across different levels of stimulus contrast. Moreover, micro-structural measures of white matter connectivity performed in this same population of participants suggest a strong implication of fronto-parietal connectivity linking the right FEF and the intraparietal sulcus (IPS) in propagating high-beta rhythmic signals across brain networks and subtending top-down frontal influences on visual performance.

Introduction

Local oscillations and interregional synchrony are considered crucial processes for the understanding of cognitive coding throughout brain networks. Although the causal nature of such contributions remains to be fully demonstrated, a significant number of animal and human studies have highlighted associations between oscillation frequencies and cognitive operations (Buzsáki et Draguhn 2004; Fries 2005; Cannon et al. 2014). In the human attention and perception domain for example, alpha oscillations in occipito-parietal areas have been found highly correlated with the orienting of attention in space (Foxe et al. 1998; Worden et al. 2000; Sauseng et al. 2005) and capable to predict visual detection performance (Ergenoglu et al. 2004; Thut et al. 2006; Gould et al. 2011). At higher frequency bands, fronto-parietal synchronization at the high beta band (22-34 Hz) has been found to signal, in both monkeys (Buschman et Miller 2007) and humans (Phillips et Takeda 2009), the deployment of endogenous spatial orienting during a visual search paradigm.

This emerging field of research has thus far relied on correlational evidence. However, the recently developed ability to entrain brain oscillatory activity with rhythmic patterns of Transcranial Magnetic Stimulation (TMS) (Sauseng et al. 2009; Romei et al. 2010; Romei et al. 2011; Thut et al. 2011; Romei et al. 2012; Chanes et al. 2013) provides a unique non-invasive approach to enrich with causal evidence the above-mentioned associations in human participants. Indeed, interleaved TMS-EEG recordings have substantiated evidence of oscillation phase resetting (Fuggetta et al. 2005; Van Der Werf and Paus 2006), enhancements of natural rhythm characteristic of a cortical region (Rosanova et al. 2009), and also the episodic entrainment of regional oscillatory activity at the input frequency (Thut et al. 2011). Furthermore, these rhythmic patterns have demonstrated the ability to modulate specific aspects of human visuo-spatial cognition, such as visual short-term memory capacity, global vs. local feature-based attention and visual sensitivity (Sauseng et al. 2009; Romei et al. 2010; Romei et al. 2011; Romei et al. 2012; Chanes et al. 2013).

In a prior study using this approach, we demonstrated that pre-target rhythmic patterns delivered to the right Frontal Eye Field (FEF) and tuned at the high beta-range (30 Hz) enhanced visual sensitivity for near-threshold targets (Chanes et al. 2013). To isolate the specific contribution of the oscillation frequency, the impact of non-uniform bursts with an equal number of pulses delivered at the same pre target onset time window, or gamma (50 Hz) bursts were also tested along and compared to the former. Interestingly, high-beta specific modulations of visual sensitivity proved strongly correlated to interindividual differences in volume of the first branch of the superior longitudinal fasciculus (SLF), linking the stimulated FEF region with the intraparietal sulcus (IPS) in the right hemisphere (Quentin et al. 2014). This finding puts forward the notion that white matter structure and myelination properties might strongly influence interregional synchronization at a specific frequency (Zaehle et Herrmann 2011).

However, this prior evidence collected by Chanes et al. (2013) only referred to near-threshold vision, and hence it remains to be explored whether these effects also hold or not for a full spectrum of stimulus contrast. This question is important as such dataset could help determining whether the TMS effects are or not independent of stimulus intensity (Reynolds et Desimone 1999; Carrasco et al. 2004). Hence, here we employed a complete psychometric contrast sensitivity function to determine whether the facilitatory effects induced by *high-beta frequency specific* patterns on the right FEF activity (as compared to a *random non frequency specific* activity) could also be extended to other stimulus contrast levels. In this same population of participants, the anatomical connectivity estimates of white matter pathways linking frontal and parietal sites, and specifically those known to depart from the stimulated right FEF, were correlated to behavioral outcomes and employed to further support a potential role for fronto-parietal anatomical networks in propagating high-beta rhythmic signals across networks subtending the modulation of visual performance.

Materials and Methods

Study participants

A group of 14 participants (9 women and 5 men, mean age=24.2±3.0 years) reporting no history of neurological or psychiatric disorders and normal or corrected-to-normal vision took part in this experiment. All participants freely provided informed written consent prior to their participation and were compensated for taking part in the study. The protocol was reviewed by the INSERM (*Institut National de la Santé et de la Recherche Médicale*) ethical committee and approved by an Institutional Review Board (CPP Ile de France 1).

Behavioral Paradigm and contrast sensitivity function

A psychometric function relating visual detection performance with stimulus contrast levels was calculated using an adaptive estimation of psychometric function parameters (Kontsevich et Tyler 1999) implemented in the Matlab toolbox Palamedes (Kingdom et Prins 2009, www.palamedestoolbox.org). This method uses a bayesian adaptive estimation of the slope and threshold of the psychometric curve and sets the stimulus intensity for each trial that maximises the expected information to be gained by the participant's response.

Visual stimuli were displayed on a monitor (Hewlett Packard, HP ZR22w, 21.5 inches diagonally measured, and a resolution of 1920 x 1080 pixels) using a computer (Hewlett Packard, HPZ800) and standard stimulus presentation software (Psychophysics Toolbox Version 3, PTB-3) running under Matlab 8.0 (MathWorks, Natick, MA, USA). Each trial started with a gray resting screen (Luminance: 31 cd/m^2) presenting for 2000 ms, followed by a central fixation cross (0.5° x 0.5°) presented along with two laterally located rectangular placeholders (6.0° x 5.5°) centered 8.5° to the left and to the right of the screen center, and randomly lasting between 1000 and 1500 ms. Then, the fixation cross became slightly bigger (0.7°x 0.7°, 66 ms) to alert participants of an upcoming event. After an interstimulus interval of 233 ms along which TMS patterns were delivered (see further details below), a target appeared for 33 ms at the center of one of the two placeholders. The target consisted of a Gabor stimulus (3 cycles/degrees spatial frequency, 3.0° diameter, minimum and maximum Michelson contrast of 0.005 and 1). Participants were

requested to report the Gabor's location by pressing with their right hand the corresponding button on a computer keyboard ("1" for left and "2" for right) (Figure 2a). They were required to respond as quickly and as accurately as possible, and forced to provide a response, even when they did not consciously perceive any target during the trial. If the participant did not respond after a 3000 ms response window, the next trial began. Eye movements were monitored across the trial to ensure correct central fixation by means of a high frequency eye-tracker (Eyelink 1000, SR research, Missisauga, ON, Canada). Fixation was considered broken when participants' gaze was recorded outside a circular spot of 2° radius around the center of the fixation cross, during the 300 ms preceding the target onset and until its offset. In that eventuality, participants received an alert message on the screen and the trial was repeated.

Psychometric contrast sensitivity functions were built using the psi-method (Kontsevich et Tyler 1999), an adaptive procedure pursuing both, an estimate of the location and the slope of the psychometric function relating stimulus contrast with detection performance. In an adaptive procedure, an algorithm considers the prior history of the participant's responses to select the contrast intensity for the next trial. In particular, the psi-method selects a contrast level for an upcoming trial by updating a distribution defined across possible threshold and slope values that minimizes the expected entropy, i.e. the uncertainty, in the distribution after the completion of the trial. By decreasing the entropy of the distribution, this method increases after each trial the precision of the parameter estimates (Kingdom et Prins 2009). This method allowed us to estimate both threshold and slope, and thus reconstruct a psychometric function after only 300 trials (Kontsevich et Tyler 1999) (Figure 1). The generating function employed in all experimental condition was a Gumbel (log-Weibull) function with a threshold estimated at 80.34% performance,, fixed values of lapse rate of 2% and a guess rate of 50%, according to a two-alternative forced-choice task. Using the above reported procedures, two independent psychometric functions (one for real and another for sham TMS trials, see further details below) were compiled in parallel during the same testing block. Participants performed a total of 300 trials for each of the two psychometric curves and were allowed to take a short break every 75 trials to minimize fatigue effects.

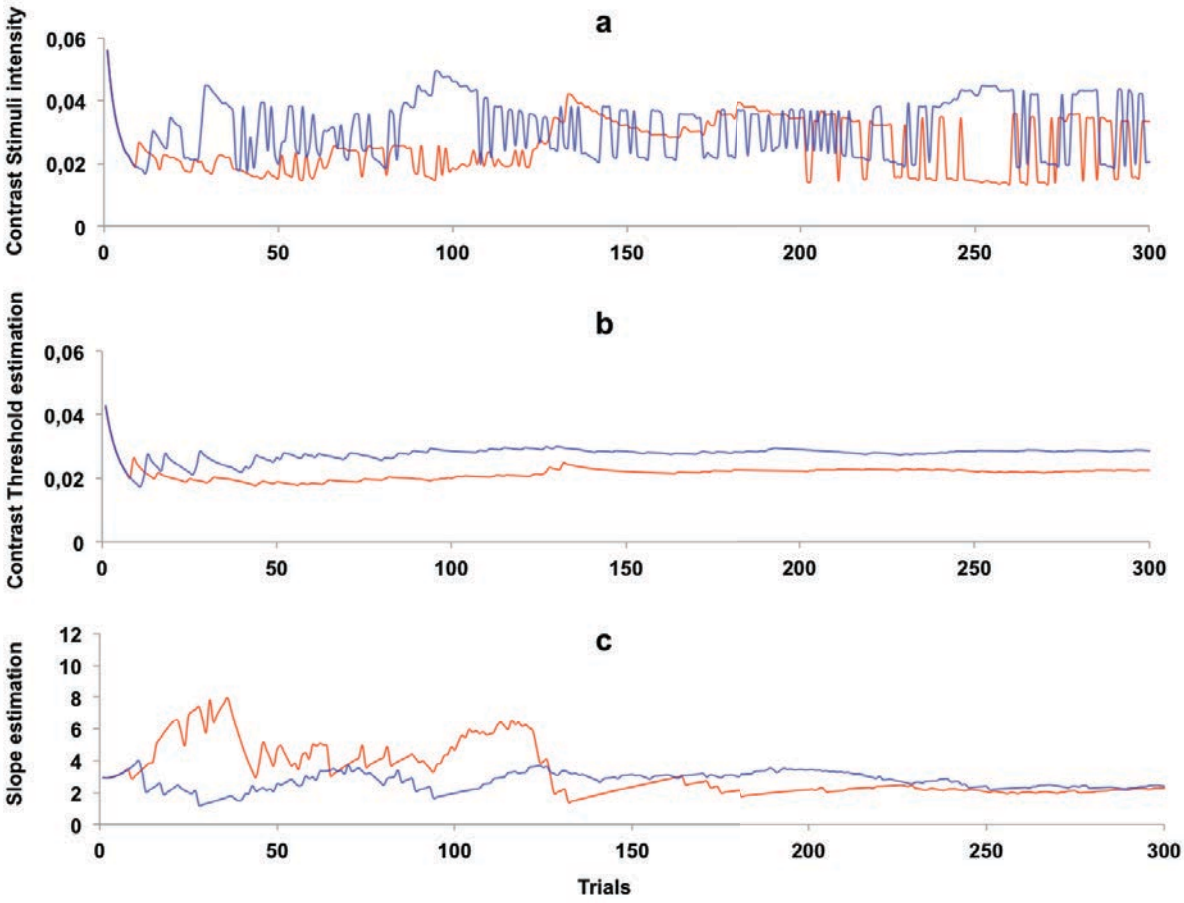


FIGURE 2. ALGORYTHMICAL PROCEDURE EMPLOYED TO ESTIMATE THE CONTRAST SENSTIVITY FUNCTIONS FOR THE DIFFERENT TMS MODIALTIES AND FEF PATTERN CONDITIONS OF THE STUDY.

Stimulus contrast levels presented during the procedure leading to the estimation of the psychmetric function. Updated trial-by-trial estimates of contrast threshold and slope updated across the 300 trials of the psychometric functions with active (in red) or sham (in blue) high beta patterns of stimulation from a representative participant. ***a.*** *Contrast stimuli levels presented across the testing block for the active and sham TMS psychometric functions; the stimulus contrast value of the upcoming trial is chosen to minimize the uncertainty on the posterior distribution, i.e., on the contrast threshold and the slope of the psychometric function.* ***b and c.*** *Estimation of contrast threshold and the slope throughout an experimental block leading to the determination of the active and sham TMS psychometric functions, updated after each trial, from a representative participant. Note that both parameters reach stable values after only 50 trials.*

Transcranial Magnetic Stimulation procedures

TMS pulses were delivered by means of a biphasic repetitive stimulator using a 70 mm diameter figure-of-eight coil (Magstim SuperRapid 2, The Magstim Company Limited, Whitland, UK Kingdom). The right FEF region was localized on each individual's MRI using Talairach coordinates x=31, y=-2, z=47 (Paus 1996) which have been successfully employed in prior

experiments to manipulate and improve in humans conscious visual perception (Chanes et al. 2012; Chanes et al. 2013) (Figure 2c). The structural T1-weighted MRI scan was uploaded into a stereotaxic system and reconstructed in 3D for its use in an online TMS neuronavigation system (Brainsight, Rogue Research, Montreal Quebec, Canada). At all times, the TMS coil was held tangentially to the skull, with its handle oriented ~45° in a rostral-to-caudal and lateral-to-medial orientation, i.e. approximately parallel to the central sulcus. During the experiment, the position of the active coil was tracked online throughout the experiment and kept steady within an area < 2 mm radius from the targeted site. At the end of the session, for population characterization purposes, the cortical representation of the right primary motor cortex of the *Abductor Pollicis Brevis* muscle was localized, and following standard procedures, the motor threshold at these sites were determined as the intensity of single TMS pulses able to induce an activation of this muscle in 50% of the attempts.

TMS stimulation procedures followed those which in a prior studiy by our group had demonstrated improvements of visual detection performance for near-threshold targets (Chanes et al. 2013). TMS patterns consisted in bursts delivered to the FEF prior to target onset. Half of trials included 4-pulse-bursts of active TMS whereas the other half employed equivalent patterns of sham TMS delivered by a second TMS coil placed next to the stimulation site, with the coil's surface perpendicular to the scalp, preventing the magnetic field from reaching the skull and stimulating the brain. The order of active and sham TMS patterns was randomized across trials. The first and last pulses of either sham or real TMS bursts were delivered 118 ms and 16 ms prior to target onset respectively. Stimulation intensity was set up 45 % of the maximal TMS machine output, which corresponded to 71±12 % of their individual motor threshold.

In this experiment, each participant performed two blocks of trials which were counterbalanced in order across subjects. In the *high beta frequency-specific block* we employed either sham or real bursts of 4 TMS pulses uniformly delivered at 30 Hz across a 102 ms interval (interpulse intervals between 1st-2nd, 2nd-3rd, and 3rd-4th pulses = 34 ms, 34 ms and 34 ms). Nonetheless, in order to isolate the effect of the frequency, we compared the latter block to a

random non frequency specific block in which we employed also 102 ms long sham or real 4-pulse-bursts with the 2nd and the 3rd pulses randomly shifted in time on a trial-by-trial basis , according to the following constraints: two TMS pulses could not be delivered closer than 19 ms to ensure constant recharge time and pulse intensity by the TMS machine, and the 4 pulses of the burst could not be equally distributed across the burst interval to avoid occurences of the 30 Hz *rhythmic frequency-specific* patterns tested in the main condition (Figure 2b).

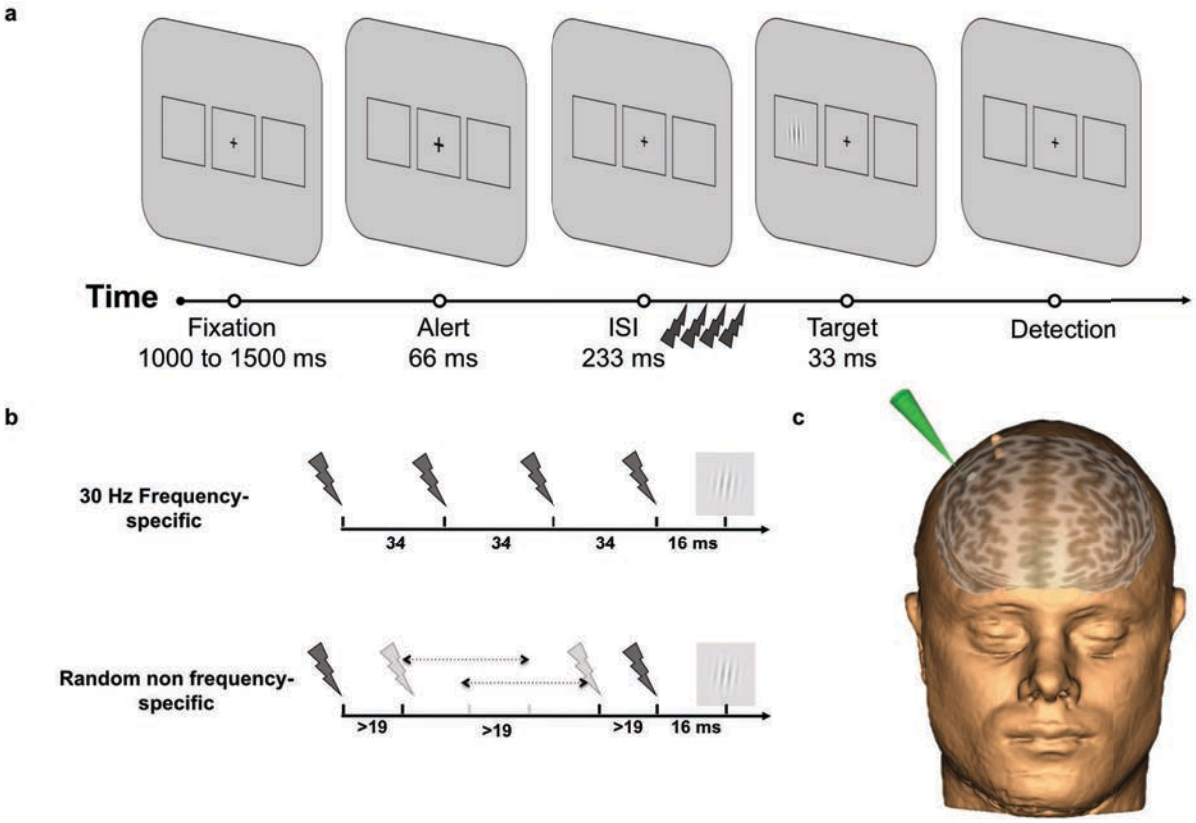


FIGURE 2. VISUAL DETECTION PARADIGM AND RHYTHMIC TMS PATTERNS EMPLOYED IN THE EXPERIMENT TO ADDRESS THE MODULATORY EFFECTS OF HIGH-BETA SPATIO-TEMPORAL RIGHT FRONTAL ACTIVITY

a. *Sequence of events during a representative trial of the visual paradigm employed in the study to estimate the contrast sensitivity curve. After a variable fixation time, participants were requested to localize a target consisting in a Gabor in the left or right placeholder.* ***b****. Temporal distribution of sham or active TMS for high beta (30 Hz) frequency specific and random non frequency specific delivered to the right FEF prior to the target onset.* ***c****. TMS coil positioning on the right FEF region of a representative participant.*

Magnetic Ressonace Imaging Acquisition

Diffusion MRI scans were obtained on a 3 Tesla MRI scanner (Tim Trio, Siemens Healthcare, Erlangen, Germany) located at the CENIR (Centre de Neuro-Imagerie de Recherche)

at the Hôpital de la Pitié Salpétrière, in Paris (France). Using a 32-channel array coil and a maximum gradient of 28 mT/m, diffusion weighting was isotropically distributed along 60 directions and 6 non-diffusion-weighted volumes were acquired. The first b0 image served as an anatomically reference for the correction of participant movements and eddy currents. Imaging parameters were as follows: voxel size = 1.7 × 1.7 × 1.7 mm^3, repetition time (TR)=12800 ms, echo time (TE)=88 ms, b=1500 s/mm^2, and matrix size=129 × 129 × 71. Total acquisition time was 14 min and 43 s. A three-dimensional (3D) structural T1-weighted MRI employed to neuronavigate the TMS coil was also recorded from each participant (TR=2300 ms, TE=4.18 ms, matrix size = 256 × 256 and 176 sagittal slices with 1 mm thickness). For technical reasons, diffusion images from one of the participants in the TMS experiment could not be obtained and this data could not be included in white matter analyse.

Diffusion data processing and estimation of fiber orientation

Diffusion images were corrected for head motion and eddy current distortions using affine registration to the first non-diffusion-weighted volume implemented in the FSL software package (FSL 4.1.6-www.fmrib.ox.ac.uk/fsl/). Spatial deformation of the DTI dataset due to susceptibility artifacts were corrected with nonlinear deformation computed from the diffusion images to match the T1-weighted volume using the Freesurfer Software (Freesurfer 5.0.0, http://surfer.nmr.mgh.harvard.edu/). A spherical deconvolution approach based on the damped version of the Richardson Lucy algorithm as described in Dell'Acqua et al. (2010) was employed to estimate fiber orientation distribution (FOD) in each white matter voxel. A first absolute threshold was used to exclude small spurious local maxima due to noise or isotropic voxels and a second relative threshold of 5% of the maximum amplitude of the FOD was applied to remove the remaining local maxima with values greater than the absolute threshold.

Tractography procedures and dissection of the Superior logitudinal Fasciculus

Whole brain tractography was performed starting from every voxel with at least one fiber orientation as a seed. From these voxels and for each fiber orientation, a modified fiber assignment using a continuous tracking algorithm was used to reconstruct streamlines by sequentially piecing together discrete and shortly spaced estimates of fiber orientation forming continuous trajectories. When entering a region with crossing white matter bundles, the algorithm followed the orientation vector of least curvature. Streamlines were halted when a voxel without fiber orientation was reached or when the curvature between 2 steps exceeded a threshold of 45°. The software used to estimate and reconstruct the orientation vectors and the trajectories from diffusion MRI data was implemented in Matlab 7.11 (MathWorks, Natick, MA, USA).

The three branches of the SLF were dissected in both hemispheres following the previously reported procedure (Thiebaut de Schotten et al. 2011; Quentin et al. 2014). To delineate the SLF I, II and III, three regions of interest (ROIs) encompassing the white matter of the superior, middle, and inferior/precentral frontal gyri were outlined on a coronal section at the anterior commissure's level. A parietal ROI was also delineated on a coronal section at the level of the posterior commissure. This "and" ROI was common to the three branches of the SLF. A temporal ROI on an axial section was used to exclude streamlines of the arcuate fasciculus, which are not part of the SLF. When required, an ROI outlined on an axial section encompassing the internal and external capsules was employed to eliminate descending fibers. Likewise, a mid-plane ROI encompassing the corpus callosum was used to exclude fibers passing in the opposite hemisphere. Each SLF branch was normalized to the Montreal Neurological Institute (MNI) mean brain volume using SPM (www.fil.ion.ucl.ac.uk/spm) to create a mean tractography image.

Constrast senstivity data presentation and white matter-visual performance correlations

Contrast threshold and slope values obtained from the estimated contrast sensitivity functions (see prior *ad hoc* method section for details on the Bayesian adaptive procedure employed) were presented in a logarhythmic scale and compared between the sham and active

TMS conditions. The so called "low" and "high" stimulus contrast ranges presented in the results section of this manuscript correspond respectively to 65-75% and 85-95% correct detection performance. Potential visual detection performance differences for these contrast ranges were estimated by calculating the area between psychometric functions obtained under sham and active TMS.

A commercially available statistical software package (JMP 10.0.0, SAS, Cary, NC, USA) was used to analyze visual behavioral outcomes and compute the correlations between neurostimulation and tractographic data sets. The volume of the 3 branches of the SLF was determined and divided by the total white matter volume tracked on each participant. The mean *hindrance modulated orientational anisotropy* (HMOA) defined as the absolute amplitude of each lobe of the fiber orientation distribution and considered highly sensitive to axonal myelination, fiber diameter and axonal density (Dell'Acqua et al. 2013), was individually calculated for each of the three SLF branches. In parallel, we also calculated performance differences at the contrast threshold level from the measured contrast sensitivity functions under active and sham TMS (see Figure 3) and we employed this parameter as a measure of the relative visual detection performance gains.

The Pearson's correlation coefficient between the latter measure and the mean HMOA for each branch of the SLF was calculated (JMP 10.0.0, SAS, Cary, NC, USA). A post-hoc Bonferroni correction was used to compensate for the family-wise error rate in multiple comparisons (uncorrected * $P < 0.05$; corrected ** $P < 0.05/12 = 0.004$). The Kolmogorov-Smirnov test was also employed to verify the Gaussian distribution of these variables. Correlation coefficients between each SLF branch volume and the visual modulations induced by *frequency-specific* or *random non-frequency-specific* patterns were compared using the method reported in Steiger et al. (1980). To provide additional support of the robustness of our statistically significant correlations between visual performance outcomes and the HMOA of the SLF I branch, a permutation test based on Pearson's correlation coefficient with 5000 random permutations was also implemented (Groppe 2011). To this end, the mean HMOA of the SLF I in each hemisphere was permuted across our group of participants and the correlation with visual detection gains recalculated for

each new version of the modified dataset. The null hypothesis of the permutation test is that the correlation obtained with the initial order is as likely as the correlation obtained with the random permutations of the data.

Results

Impact of high beta frequency-specific frontal patterns on contrast sensitivity function

We compared different parameters extracted from the estimated contrast sensitivity function under the impact of either active or sham high-beta *frequency-specific* right FEF patterns or their *random non frequency-specific* counterparts. Neither contrast threshold (two-tailed t-test, t=-1.14, p=0.26) nor slope modulation (two-tailed t-test, t=0.04, p=0.97) showed differences between frequency and non-frequency pattern. Nonetheless, based on prior results showing visual detection improvements under identical right frontal *frequency-specific patterns* for near threshold targets (Chanes et al. 2013), we analyzed separately the outcomes of these two conditions. Interestingly, the contrast threshold was significantly lower for the active than for the sham in the *frequency-specific* condition (paired t-test, t=-2.52, p=0.025) but not in the *random non-frequency-specific* (paired t-test, t=-1.099, p=0.29) condition. In contrast, TMS induced no significant effect on the slope of the estimated function in either condition (*frequency-specific*: paired t-test, t=0.95, p=0.36; *random non frequency-specific:* paired t-test, t=1.06, p=031) (Figure 3).

In order to assess differences in TMS-induced visual modulations for high vs. low stimulus contrast separately, we calculated areas between the active TMS curve and the sham for low (65-75% correct detection) and high (85-95%) target contrast levels. No significant differences emerged for the *frequency-specific* condition (two tailed t-test, t=-1.22, p=0.24) or the *non-frequency-specific* condition (two-tailed t-test, t=-1.12, p=0.28), a result that is coherent with the lack of statistically significant differences on the slope between active *vs.* sham TMS in these two experimental conditions. Interestingly however, in the *frequency-specific* condition, the area for high stimulus contrast levels (one sample t-test, t=3.35, p=0.005), but not that for low (one

sample t-test, t=1.19,p=0.25) proved significantly different from zero, whereas neither the high (t=0.33, p=0.75), nor the low (t=1.67, p=0.12) area in the *random non-frequency* condition did.

Our rhythmic TMS behavioral data supports prior evidence on the ability of high-beta rhythmic oscillatory in the right FEF to improve visual sensitivity (Chanes et al. 2013). As an important novelty, it extends such results beyond near-threshold contrast levels, demonstrating their ability to induce a leftward shift of the contrast sensitivity function without modifying its slope, hence driving a global enhancement of visual performance properties, which appears to be larger for supraliminal contrast levels.

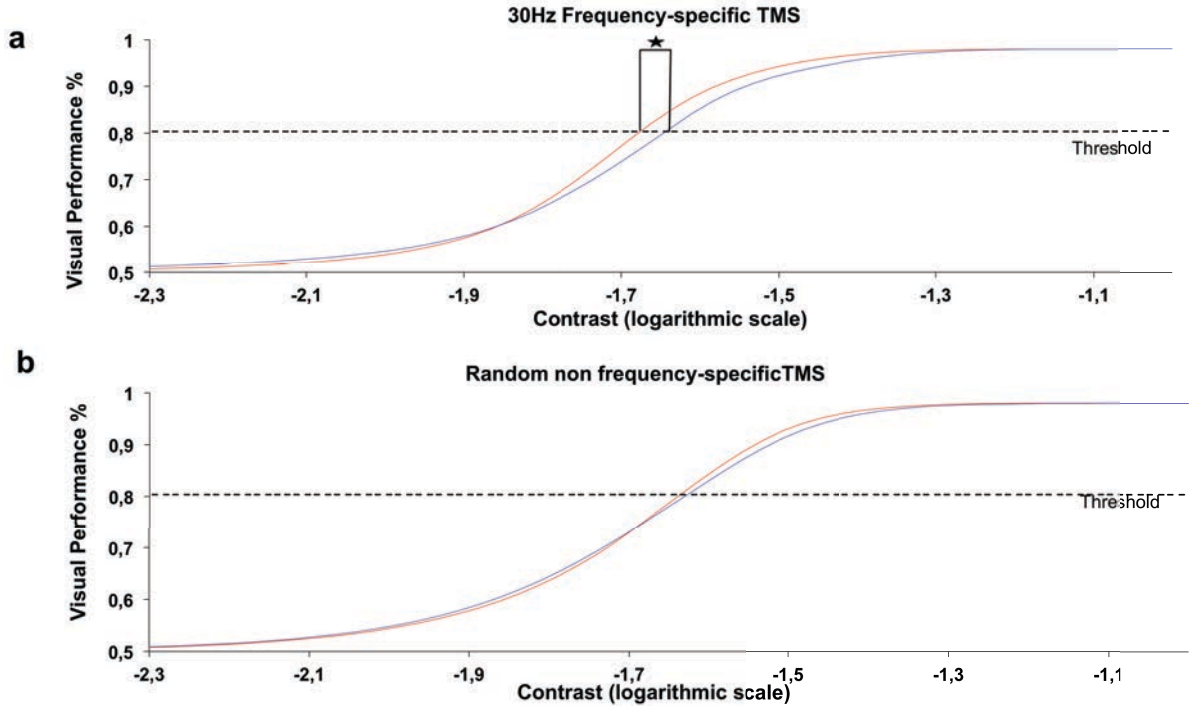


FIGURE 3. ESTIMATED CONTRAST SENSITIVITY FUNCTION WITH HIGH BETA FREQUENCY SPECIFIC AND RANDOM NON-FREQUENCY SPECIFIC FEF PATTERNS.

Sham TMS condition is represented by the blue function and active TMS by the red function. Contrast values are presented in logarithmic scale. The horizontal dotted line represents performance threshold level (80.3%). ***a****. Mean contrast sensitivity psychometric function from our cohort of participants under the effects of active (red) and sham (blue) 4-pulses 30 Hz frequency specific patterns. Notice the significant leftward shift in contrast thresholds for the active as compared to the sham condition (* p<0.05).* ***b****. Mean contrast sensitivity psychometric function from our participants under the effects of active or sham random non-frequency specific patterns.*

White matter tractography analyses and correlations

In order to confirm previous findings about hemispheric lateralization and validate our tracking method, we started our analyses by comparing the normalized volume between the three SLF branches of the right and left hemisphere. In agreement with prior reports (Thiebaut de Schotten et al. 2011; Quentin et al. 2014), a branch-specific right hemispheric lateralization pattern involving the SLF III ($t=-3.641$, $p=0.003$), but neither the SLF I nor the SLF II ($t<1$) was found once more. We then calculated for each individual participant the visual performance gains (active TMS-sham TMS) at contrast threshold level for the high beta *frequency specific condition* (Figure 4).

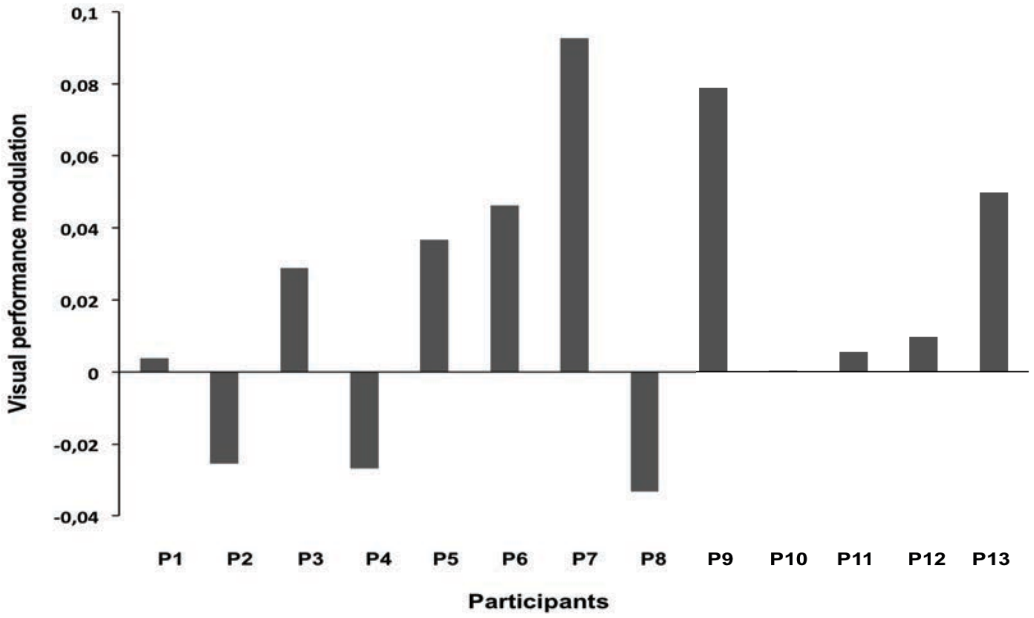


FIGURE 4. INDIVIDUAL LEVELS OF VISUAL PERFORMANCE GAINS UNDER THE EFFECTS OF HIGH BETA RIGHT FRONTAL FREQUENCY-SPECIFIC PATTERNS.

Data are presented as visual detection gains for study participants included in white matter analyses. This parameter was calculated by subtracting correct detection performance under the impact of active vs. sham stimulation for visual stimuli at threshold contrast levels. The horizontal discontinuous gray line signals the group average visual detection gains. Notice the large degree of interindividual variability in the outcomes, with 6 participants showing large performance increases, 3 participants with moderate to null visual facilitatory effects and 3 participants who experienced performance decreases, with the 30 Hz frequency specific right frontal stimulation patterns.

This behavioral measure correlated significantly with the mean HMOA index of the right SLF I branch ($r = -0.78$, $p = 0.0017$), but not with that of the remaining right or left SLF branches (rSLF II: $r = -0.20$, $p = 0.51$; rSLF III : $r = -0.39$, $p = 0.19$; lSLF I: $r = -0.17$, $p = 0.58$; lSLF II: $r =$

0.45, p = 0.12; lSLF III: r = -0.06, p = 0.83) (Figure 4). An *ad hoc* permutation test confirmed the robustness of the correlation (p=0.0012). Moreover, correlation between individual visual performance gains (Sham TMS-Active TMS) induced by the *random non frequency specific* patterns and the HMOA index of each SLF branch were also tested, proving non statistically significant (all p > 0.10). To further corroborate that the correlation in the *frequency-specific* condition was specifically related to stimulation frequency, we also confirmed that the correlation coefficient between the SLF I's *HMOA* index and the visual performance gains induced by *frequency-specific* TMS pattern was significantly higher than the one produced by *random non frequency-specific* patterns (p=0.01).

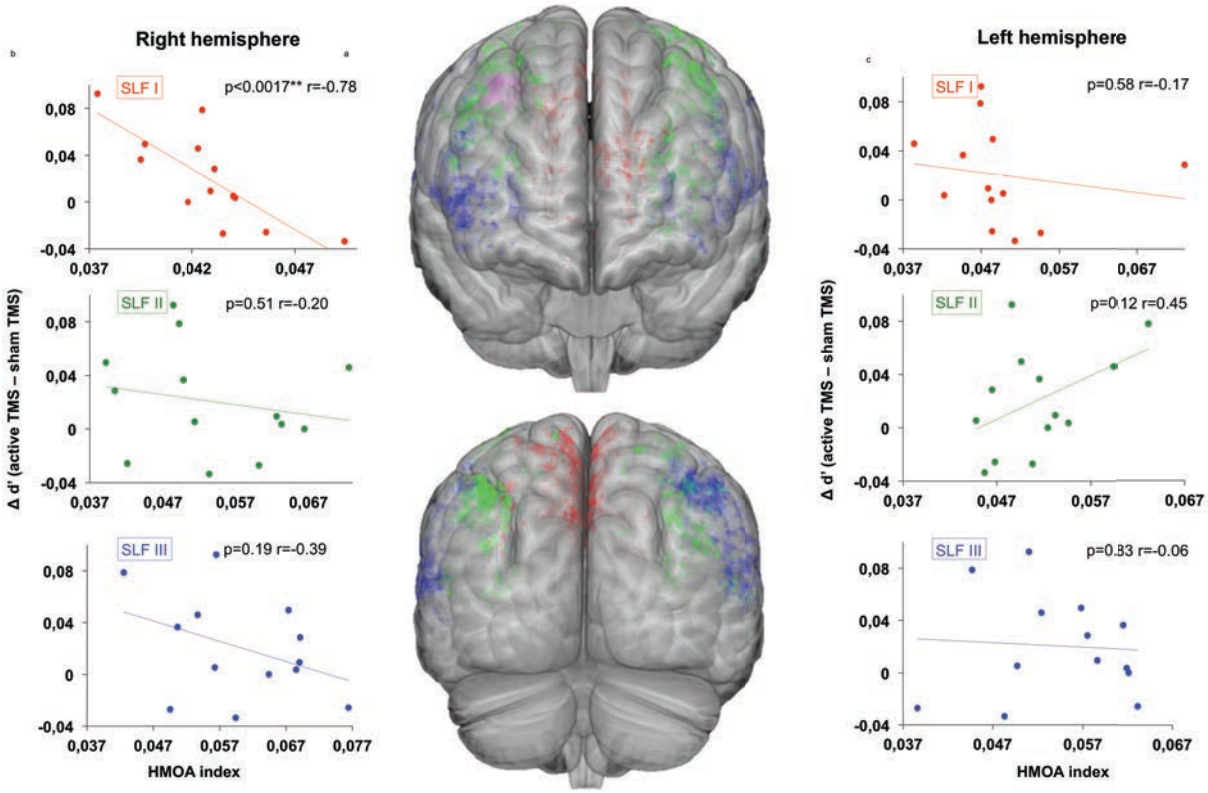


FIGURE 5. CORRELATIONS BETWEEN WHITE MATTER DIFFUSION IMAGING DATA AND VISUAL DETECTION GAINS ASSOCIATED TO FREQUENCY SPECIFIC RIGHT FRONTAL ACTIVITY

a. *Sum of endpoints of the three SLF branches in each participant normalized in MNI template (SLF I in red, SLF II in green and the SLF III in blue) The brain is rendered slightly transparent with MRICroGL The purple region signals the cortical localization of the TMS stimulated area.* ***b & c*** *Correlation plots of percentage of visual detection gain at threshold contrast levels (Active TMS –Sham TMS) and the HMOA white matter index of the three SLF branches for the right left hemispheres. Notice that only the right SLF I (r=-0.78; p<0.005 Bonferroni corrected) branch linking the FEF to the IPS regions showed a significant correlation between HMOA index and visual detection gains. Asterisk indicates: * uncorrected (p<0.05); ** Bonferroni corrected (p<0.05/12).*

Discussion

The results of the current study indicate that frequency-specific right FEF activity at 30 Hz is able to induce a significant decrease in contrast thresholds and a general leftward shift of the contrast sensitivity function, resulting in a global enhancement of visual performance along a large continuum of stimulus contrast levels. Importantly, modulations of contrast threshold were not accompanied by shifts in the slope of the psychometric function. To the best of our knowledge, this is the first report showing a modulation of contrast sensitivity causally associated to the manipulation of right frontal activity, not restricted to a near-threshold contrast levels, but valid for a full spectrum of contrast values.

The rhythmic stimulation pattern employed to manipulate frontal activity was inspired from a non human primate study (Buschman et Miller 2007) showing the engagement of the 22-34 Hz oscillatory activity along a right fronto-parietal system during visual search task involving the allocation of endogenous attention. Interestingly enough, the modulation of the contrast sensitivity function here reported matches the effects induced by the engagement of endogenous attention by means of predictive visuo-spatial cues (Ling and Carrasco 2006). This similarity can not be taken as a direct demonstration, but put together with the fact that our effects were induced in a well-know frontal node of the dorsal attentional network, it strengthens the hypothesis that the facilitatory effects on visual performance could have been mediated by the activation of top-down attentional orienting mechanisms operating in the right dorsal fronto-parietal system linking the FEF and the IPS (Corbetta and Shulman 2002; Corbetta and Shulman 2008; Chica et al. 2011). Moreover, the general leftward shift of the psychometric curve, without significant differences between high vs. low stimulus contrast levels, suggests that visual facilitatory effects are independent of stimulus intensity, providing support in favor of the contrast gain hypothesis as a mechanism for our visual performance improvements (Reynolds et Desimone 1999; Carrasco et al. 2004) causally related to right frontal high-beta oscillatory activity. Nonetheless, since performance shifts between sham and active TMS frequency specific patterns proved significant for the upper but not the lower segment of the contrast sensitivity function, the possibility that the underlying mechanism is based on a response gain function in

which performance modulation is dependent of the stimulus intensity can not be ruled out completely.

In a prior study (Chanes et al. 2013), we studied the impact of the same frequency-specific high beta frontal patterns and demonstrated bilateral improvements of conscious visual detection performance for near threshold targets. Our current study has been able to reproduce this same outcome employing a two alternative forced-choice visual detection task, not integrating an explicit and conscious report of target absence or presence, hence suggesting that the contributions of the right FEF to visual perception can operate through long-range frontal connections on early visual areas, and not necessarily by acting on higher level frontal computations leading to visual conscious access. This possibility is coherent with studies showing attentional modulation in striate and extra-striate visual cortices (Reynolds and Desimone 1999; Reynolds et al. 2000; Hol and Treue 2001; Saenz et al. 2002) and also with reports suggesting a direct impact of FEF stimulation on primary visual areas in humans (Ruff et al. 2006) and non-human primates (Ekstrom et al. 2009; Reynolds and Chelazzi 2004).

In spite of the statistical significance of our intervention which was present only when active frequency-specific TMS patterns were employed, the mean performance modulation at the threshold levels, which was around 2.6%, appeared below the magnitude achieved by the deployment of covert attention on contrast appearance (Carrasco et al. 2004). An inspection of individual results suggests however that the low magnitude of this effect is likely caused by the large inter-individual behavioral variability in response to frontal stimulation, which has been recently associated with inter-individual differences in white matter pathways linking the stimulated region and other cortical or subcortical sites of a specific network (Quentin et al. 2013; Quentin et al. 2014). Computer simulations (Tononi et al. 1994; Pajevic et al. 2014) and electrophysiological (Fernández et al. 2011; Zaehle et Herrmann 2011) experimental approaches have related white matter pathways and their ability to provide an adequate anatomical basis for interregional synchrony at specific frequency ranges. These hypotheses received further back up from observations suggesting a direct impact of white matter tract maturation during adolescence, likely induced by an increase in myelination (Giedd 2004) subtending a progressive

shift toward faster frequencies of oscillatory activity across this same period (Gasser et al. 1988; Segalowitz et al. 2010). Interestingly, we found that the causal contribution of such high-beta right frontal patterns to visual detection significantly co-varied with interindividual differences of the mean anisotropy index (HMOA) calculated for the first SLF's branch. This subset of SLF fibers are known to link the right FEF and the right IPS (Thiebaut de Schotten et al. 2011), two sites involved in endogenous attentional orienting (Corbetta et Shulman 2002; Corbetta et al. 2008; Chica et al. 2011). Similarly, our correlation between rhythmic TMS modulations and white matter pathway differences could reflect the individual ability of a particular network to synchronize these two sites at a specific frequency according to its specific connectivity.

At difference with our prior report (Quentin et al. 2014) in which we correlated TMS behavioral outcomes and white matter tract volume, we here employed the HMOA index, defined as the absolute amplitude of each lobe of the fiber orientation distribution. This parameter reflects the microstructural properties specific to a single fiber population and has demonstrated a high sensitivity to fiber tract myelination, axonal diameter and axonal density (Dell'Acqua et al. 2013). These first two physiological parameters are known to impact the conduction time. In the fronto-parietal synchronization hypothesis, action potentials elicited by the first of the 4 pulses uniformly delivered to the right FEF need to reach a parietal postsynaptic region at a particular timing, coherent with the delivery of the following pulse 33 ms. Across-subject differences in white matter myelination do impact conduction velocity and either slightly accelerate or delay conduction time by a few milliseconds, precluding an efficient synchronization of the network at a very specific frequency and leading to less or no visual enhancement. In that context, this correlation points out a crucial role for fronto-parietal pathway in the potential synchronization leading to visual improvement and identified at very similar frequencies by mean of electrophysiological recordings (Buschman et Miller 2007; Phillips et Takeda 2009).

Finally, and not less interestingly, despite differences (Quentin et al. 2013) or similitudes (Quentin et al. 2014) in the stimulation patterns employed on each case, the current outcome provides additional experimental support in favor of an inverse association between TMS modulated behaviors and white matter connectivity. As mentioned elsewhere, this result might

seem counterintuitive, as larger tract volumes or higher probability of connection have been often associated to more effective connectivity and information transfer (Glasser et Rilling 2008; Michel Thiebaut de Schotten et al. 2011). Alternatively, as argued elsewhere, less anisotropic pathways could prove more efficient in conveying neural signal, particularly when those are artificially induced by not sufficiently focal non-invasive neurostimulation sources (Quentin et al. 2013; Quentin et al. 2014).

In summary, our study provides novel and converging evidence that pre-target onset patterns of high beta rhythmic activity on the right FEF play a major role in top-down visual modulation. We also gathered additional support for the notion that the appearance of this modulation is strongly dependent on the microstructure of the right SLF I, suggesting an association between these pathway and the ability to convey rhythmic signal from frontal regions to parietal regions.

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Competing Financial Interest

The authors declare no competing financial interests.

Author contributions

AV-C developed the main concept of this project, provided the funding and was in charge of its supervision. AV-C, RQ and SEF developed the specific hypotheses and ideas and co-designed the study; RQ, MV, AV-C, LC and MT performed the TMS experiments; RQ analyzed the behavioral data, the DTI data and computed the correlations; AV-C, RQ and MV interpreted the data. AV-C and RQ prepared the final figures and wrote the draft of the manuscript and MV, LC and PB contributed to this endeavor. PB was also the responsible PI of the IRB protocol covering the study.

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CHAPITRE 9. DISCUSSION GENERALE

9.1. PRINCIPAUX RESULTATS

Cette section est l'occasion de résumer nos résultats de façon synthétique. Nous allons dans un premier temps présenter ceux des expériences de SMT pour ensuite décrire les résultats des études de diffusion.

Les expériences décrites dans la *Partie 1* du *Chapitre 6* montrent que l'activité de la région FEF droite avant l'apparition d'une cible module nos capacités de détection consciente, en particulier lorsque la stimulation intervient 80 ms avant la cible. De plus, l'impact de la stimulation change si le participant oriente son attention à l'endroit où va apparaître la cible ou non. En effet, lorsque des indices sont présents, la SMT augmente la détection consciente seulement pour les essais valides. L'activité de la région FEF avant l'apparition d'un stimulus visuel peut donc augmenter nos capacités de perception consciente et cette augmentation dépend de l'orientation attentionnelle.

Dans la *Partie 2* du *Chapitre 6*, nous nous sommes intéressés à la contribution de l'activité oscillatoire de la même région sur les performances visuelles de discrimination et de détection consciente. Nous avons exploré l'effet de deux rafales de quatre impulsions à 30 Hz et 50 Hz comparé à l'effet de quatre impulsions dans la même fenêtre temporelle mais sans fréquence spécifique. Une double dissociation a été observée entre la fréquence de stimulation et le type de modulations comportementales. La stimulation rythmique à 30 Hz augmente la détection consciente alors que celle à 50 Hz diminue le critère de réponse (le participant est plus enclin à reporter qu'il a perçu la cible). Cette étude montre qu'il est possible, en induisant une activité rythmique dans la région FEF droite à une fréquence spécifique, de moduler la perception visuelle. De plus, l'utilisation de deux fréquences différentes sur la même région mène à des modulations comportementales différentes.

Le *Chapitre 8* a démontré la robustesse de l'amélioration perceptive visuelle après stimulation rythmique frontale à 30 Hz et étend cette amélioration, démontrée au niveau du seuil de perception dans le *Chapitre 6*, à l'ensemble de la courbe psychométrique. La modulation significative du seuil, identifiable par un déplacement vers la gauche de la courbe, sans changement significatif de la pente, correspond à un mécanisme de gain en contraste. Cependant, l'amélioration significative des performances, observée dans la partie haute de la courbe mais non dans la partie basse, ne nous permet pas d'exclure un mécanisme de gain en réponse, dans lequel la modulation perceptive varie positivement en fonction du contraste.

Nous nous focalisons maintenant sur les résultats des études de l'influence de la connectivité anatomique dans les processus de modulation visuelle.

Le premier constat général est que dans nos trois expériences de stimulation magnétique des FEFs droits menant à une augmentation significative des performances visuelles du groupe de participants, un faisceau de substance blanche connectant la région stimulée semble à chaque fois jouer un rôle dans la variabilité de la modulation visuelle entre les participants. Des paramètres du faisceau fronto-tectal dans la première étude (Chapitre 7, *Partie 1)* et du faisceau longitudinal supérieur (SLF) dans la deuxième et la troisième étude (Chapitre 7, *Partie 2 et Chapitre 8)* corrèlent de façon significative avec la taille des effets de la SMT lorsque l'on compare stimulation active et stimulation *sham*. Dans ces trois études, nous avons eu l'occasion de faire

varier les séquences de diffusion, les techniques de tractographie, l'utilisation de la SMT ainsi que les paradigmes psychophysiques. Ces trois études démontrent que la substance blanche, et en particulier les faisceaux anatomiques connectant la région stimulée, influencent l'effet comportemental de la stimulation.

Nous avons observé dans la première étude (*Chapitre 7, Partie* 1) une corrélation négative significative entre, d'une part, la probabilité de connexion entre les FEFs droits et le colliculus supérieur droit et, d'autre part, la modulation de la perception visuelle consciente par SMT lors des essais valides. Cette corrélation entre le faisceau fronto-tectal et la modulation visuelle induite par stimulation n'existe pas en l'absence d'indice. L'influence de ce faisceau est présente seulement lorsque le participant oriente son attention à l'endroit de l'espace où va apparaître la cible. Elle dépend donc de l'état du participant, ce qui rappelle la modulation des effets de la stimulation par l'activité corticale spontanée avant stimulation démontrée par l'équipe de Silvanto (Silvanto et al. 2008).

Nous avons utilisé dans les deuxième et troisième études (*Chapitre 7, Partie 2 et Chapitre 8)* des résultats issus d'expériences de SMT rythmique. L'hypothèse était de moduler l'activité synchronisée au sein du réseau fronto-pariétal avant l'apparition d'une cible visuelle. Pour cette raison, nous nous sommes intéressés aux 3 branches du SLF qui relient le lobe frontal avec le lobe pariétal. Après les résultats de la première expérience, il aurait cependant été intéressant de reconstruire également le faisceau fronto-tectal pour observer son impact potentiel. Malheureusement, la technique de tractographie utilisée dans ces deuxième et troisième études de diffusion ne nous a pas permis de reconstituer ces fibres.

Les deux études de SMT rythmique ont montré une amélioration significative des performances visuelles du groupe, lors d'une tâche de détection consciente ou lors d'une tâche de localisation d'une cible en choix forcé. Dans les deux études, la taille de la modulation visuelle chez chaque participant corrèle fortement avec des caractéristiques biophysiques de la 1ère branche du SLF droit. Ce faisceau relie le gyrus frontal supérieur, comprenant les FEFs, avec le gyrus pariétal supérieur, comprenant l'IPS (Thiebaut de Schotten et al. 2011). Il connecte donc les régions corticales du réseau dorsal de l'attention spatiale. Les corrélations significatives de ce faisceau avec les modulations visuelles provoquées par la stimulation rythmique dans deux études différentes confortent l'idée que la substance blanche impacte les effets de la stimulation magnétique non-invasive ainsi que l'hypothèse d'une synchronisation fronto-pariétale. Plus précisément, dans la *Partie 2* du *Chapitre 7*, la modulation de la détection visuelle consciente liée à la SMT corrèle de façon négative avec le volume normalisé du SLF I dans l'hémisphère droit et dans le *Chapitre 7,* la modulation du pourcentage de réponses correctes dans une détection en choix forcé corrèle de façon négative avec un index d'anisotropie (*HMOA*) dans ce même faisceau. L'index d'anisotropie utilisé dans ce second temps n'existait pas encore lors de la première observation sur l'influence du SLF I. Bien que cet index soit plus proche de la réalité physiologique des fibres, nous avons testé si le volume normalisé du SLF I corrélait à nouveau avec la modulation visuelle lors du choix forcé. La corrélation obtenue est négative mais, bien que proche, n'atteint pas le seuil de significativité ($r = -0.46$, $p = 0.11$). Les deux paramètres peuvent dépendre de la densité, du diamètre ou de la myélinisation des axones et peuvent donc influer sur le temps de conduction neuronal. Comme nous l'avons déjà mentionné plusieurs fois, l'orientation endogène de l'attention a été associée de façon corrélationnelle à une synchronisation fronto-pariétale autour de 30 Hz (Buschman & Miller 2007; Phillips & Takeda 2009). Dans ce cadre, la corrélation entre des modulations visuelles induites par une activité rythmique dans les régions frontales et un paramètre structurel du SLF I influençant le temps de conduction entre les régions au sein d'un réseau suggère que la structure de ce faisceau détermine la fréquence exacte de synchronisation au sein du réseau dorsal de l'attention. Une corrélation entre fréquence de

synchronisation et micro-structure de la substance blanche dans certaines fibres a été observé lors d'une expérience d'EEG et de diffusion (Zaehle & Herrmann 2011). Nous suggérons que ce mécanisme soit présent dans nos études et expliquent la variabilité de réponse de nos participants.

Enfin, nous notons que les trois corrélations observées entre la connectivité anatomique et la modulation visuelle après stimulation non-invasive frontale dans les trois études de diffusion de cette thèse (*chapitres 7 et 8)* sont négatives, quel que soit le *pattern* de SMT ou le faisceau impliqué. Un faisceau plus dense ou contenant plus de fibres semble être moins efficace pour conduire à une amélioration perceptive visuelle après stimulation frontale. L'hypothèse habituelle des études utilisant l'imagerie de diffusion est qu'un faisceau plus volumineux ou plus anisotrope reflète une connexion plus efficace ou un transfert d'information plus grand. Par exemple, une asymétrie gauche du faisceau arqué est observée dans plusieurs études et représente d'après leurs auteurs le corrélat anatomique de la spécialisation hémisphérique gauche du langage (Powell et al. 2006; Glasser & Rilling 2008). Le même constat est fait entre l'asymétrie droite de la 3e branche du SLF et la spécialisation hémisphérique droite de l'attention spatiale (Thiebaut de Schotten et al. 2011). Ces observations rendent contre-intuitives nos résultats de corrélations négatives entre l'anatomie et nos modulations comportementales. Cependant, nous ne sommes pas dans des conditions physiologiques normales. Nous stimulons de façon artificielle un nombre important de neurones au niveau de la région stimulée. Dans une telle condition, nous pouvons faire l'hypothèse qu'un faisceau moins dense aura tendance à transmettre un signal moins bruité aux régions connectées, en évitant les phénomènes d'inhibition latérale. Ce n'est évidemment pas la seule hypothèse que nous pouvons faire et des mécanismes d'inhibitions dans les régions connectées peuvent être à l'origine de nos observations. Enfin, comme nous l'avons proposé précedemment, nous suggérons également que la fréquence exacte de stimulation optimisant l'amélioration perceptive dépend du temps de conduction entre les aires pariéto-occipitales.

9.2. CONSEQUENCES THEORIQUES ET METHODOLOGIQUES

La relation entre le cerveau anatomique et fonctionnel est fondamentale dans la recherche actuelle en neuroscience. Nos études apportent des informations précieuses sur l'organisation anatomique et fonctionnelle des réseaux de la modulation perceptive. L'imagerie de diffusion, première technique non-invasive in-vivo permettant d'observer l'architecture des connexions neuronales, a largement favorisé une conception hodologique du cerveau. Cette évolution théorique a changé la manière de concevoir le cerveau fonctionnel. L'importance des connexions anatomiques dans la façon dont le cerveau est pensé a forcé le développement de méthodes décrivant le cerveau comme un système de communication global, à l'exemple de l'utilisation de la théorie des graphes, et a proposé une vision holistique de certaines pathologies (Catani & ffytche 2005; Bartolomeo et al. 2007).

Dans nos études de SMT, nous avons prouvé plusieurs fois que la manipulation de l'activité de la région FEF permet de provoquer une amélioration des performances visuelles. De plus, l'utilisation de la SMT rythmique nous a permis d'observer des effets comportementaux différents (amélioration perceptive et changement du critère de réponse) après stimulation de la même région avec des fréquences différentes. Ces études suggèrent donc qu'une même région cérébrale est dans la mesure de coder de façon fréquentielle différents signaux, menant à des sorties comportementales différentes.

Nos travaux, en démontrant plusieurs fois lors d'études indépendantes une relation entre les faisceaux de substance blanche et la taille de la modulation visuelle induite par stimulation, prouvent qu'il est important de concevoir les études de stimulation non-invasive non pas seulement à la lumière des effets locaux mais comme impactant l'ensemble d'un réseau neuronal dont la région stimulée devient la porte d'entrée. Dans cette ligne de pensée, Nummenmaa et al. ont récemment publié une méthode de tractographie permettant de prédire le positionnement et l'orientation de la bobine de SMT afin de cibler des fibres spécifiques de substance blanche (Nummenma et al. 2013).

Nous avons décrit dans la *Partie 1* du *Chapitre 6* un faisceau fronto-tectal déjà décrit chez le singe au moyen de techniques de traceur neuronal mais jamais rapporté chez l'Homme. La corrélation entre la probabilité de connexion de ce faisceau et la modulation visuelle induite par SMT, seulement lors d'une orientation attentionnelle au bon endroit de l'espace, suggère que ce faisceau, au delà de son rôle oculomoteur, est impliqué dans la modulation visuelle lors de l'orientation endogène de l'attention.

Les corrélations entre l'amélioration visuelle par SMT rythmique et la 1ère branche du SLF, deux fois observées, confortent la représentation d'une modulation *top-down* des processus visuels par le réseau dorsal de l'attention dont les régions corticales sont connectées par ce faisceau. Ces études nous ont permis de développer l'idée originale que la fréquence de synchronisation dépend directement des connexions entre régions. A terme, il est possible d'imaginer adapter à chaque individu la stimulation, en particulier sa fréquence, en se basant sur des données anatomiques individuelles.

9.3. LIMITES

Comme dans toute recherche scientifique, en particulier en neurosciences cognitives et en neuroimagerie où les résultats expérimentaux peuvent souvent mener à différentes interprétations, il est important de faire un point sur les limites, pour la plupart déjà débattues dans les discussions des articles.

Notre approche qui consiste à utiliser la variabilité individuelle de la modulation visuelle par la stimulation non-invasive afin d'observer l'impact de la substance blanche ne nous permet pas d'observer le rôle général de celle-ci dans les effets de la stimulation. En effet, il est fort probable que plusieurs structures dans la substance grise ou blanche soient également impliquées dans les modulations visuelles que nous avons observées sans pour autant que des différences anatomique inter-individuelles dans ces structures influent sur la taille de nos effets comportementaux.

De plus, malgré l'utilisation de la neuronavigation qui assure de cibler l'aire stimulée avec une grande précision spatiale, la variabilité des effets comportementaux en SMT est courante et notre hypothèse principale d'une influence de la substance blanche n'enlève pas le fait que d'autres facteurs influencent ces effets comme la forme du cortex, la répartition du liquide cérébro-spinal sous la bobine de SMT, des variations anatomiques de la région FEF ou des variations d'états cognitifs entre les participants pendant les tâches. Nous avons cependant utilisé un modèle linéaire général pour vérifier l'absence d'influence des variables que nous possédions, comme l'âge ou le seuil moteur.

Il est important aussi d'être clair sur le fait que nos calculs portant sur la connectivité anatomique ne représentent jamais une réalité physiologique directe comme le nombre ou le

diamètre des axones mais sont le résultat d'un modèle de reconstruction des connexions plus ou moins sensible à des changements au niveau cellulaire. En particulier, les différences de connectivité anatomique entre les participants que nous observons dépendent de plusieurs facteurs physiologiques qu'il n'est pas possible de séparer les uns des autres. L'utilisation dans la dernière étude, grâce aux déconvolutions sphériques, de l'index d'anisotropie spécifique au faisceau, nous permet de nous affranchir des biais de reconstruction des trajectoires, comme la longueur ou la courbe, qui influent sur le nombre de trajectoires ou le volume des faisceaux observés (Jones et al. 2012).

En ce qui concerne les expériences utilisant la SMT rythmique, notre hypothèse de travail est que nous modulons l'activité de la région stimulée dans la bande de fréquence utilisée. Il a été démontré par Thut et al. qu'il était possible d'entrainer l'activité oscillatoire des régions pariétales à la fréquence de stimulation lorsque celle-ci était choisie en fonction de la signature oscillatoire individuelle enregistrée chez chaque participant dans cette région en MEG (Thut et al. 2011). L'utilisation de *pattern* de stimulation sans fréquence spécifique mais avec le même nombre d'impulsions dans la même fenêtre temporelle apparaît comme un contrôle robuste. Cependant, l'hypothèse de l'entrainement des oscillations à cette fréquence dans les régions frontales ne peut se vérifier qu'avec l'enregistrement simultané d'EEG. Des résultats préliminaires d'expériences combinant la SMT et l'EEG dans notre équipe vont bien dans le sens d'un entrainement à 30 Hz dans les régions frontales.

9.4. PERSPECTIVES

Les études réunies dans cette thèse doctorale ont démontré grâce à plusieurs paradigmes expérimentaux de psychophysique, de stimulation et de tractographie que la substance blanche joue un rôle important dans les effets obtenus lors de la stimulation non-invasive de régions cérébrales. Malheureusement, les limites inhérentes à l'imagerie de diffusion ne nous permettent pas de caractériser de façon précise les causes physiologiques à l'origine de nos corrélations entre les effets comportementaux de la stimulation et les faisceaux anatomiques. Les progrès dans ce domaine de l'imagerie commencent à rendre possible l'observation spécifique de la myélinisation et pourrait donc nous apporter des informations cruciales dans la confirmation de nos hypothèses. A la fin de ces travaux, la question de la relation entre synchronisation et connectivité anatomique est au centre de nos intérêts. Nous avons par ailleurs débuté une expérience dans laquelle la fréquence de stimulation varie légèrement autour de 30 Hz. L'objectif est d'observer si le système fronto-pariétal est flexible et peut accepter des changements de quelques Hertz dans la fréquence d'activation. Les données d'imagerie de diffusion nous permettront d'étudier si la fréquence à laquelle le système répond de manière optimale, observée grâce aux résultats comportementaux, dépend de la connectivité anatomique du réseau cérébral. Dans ce cadre, il apparaît évident que des données électrophysiologiques (EEG ou MEG) pourraient nous permettre de mieux appréhender la relation entre les rythmes cérébraux et la connectivité anatomique.

Plusieurs études ont observé l'implication de *pattern* d'activité oscillatoire dans des maladies neuropsychiatriques (Buzsaki & Watson 2012). Plusieurs options peuvent être explorées afin d'accéder à ces rythmes cérébraux déficients et les moduler dans le but d'améliorer les symptômes liés à ces maladies. La SMT rythmique semble être parmi les plus prometteuses. Cependant, chaque cerveau est différent en terme de taille et de connectivité anatomique et fonctionnelle. Ignorées, ces différences risquent de conduire à l'échec des techniques de stimulation thérapeutique si elles ne sont pas individualisées et basées sur les données

anatomiques de chaque patient. Il apparaît essentiel de combiner les différentes techniques de neuroimagerie afin de mieux comprendre les liens entre l'anatomie, la fonction et le comportement dans le but d'appliquer un traitement individuel de neurostimulation qui sera en mesure d'améliorer les symptômes des patients.

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