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**The action of prism adaptation on intact visuospatial cognition -
when time matters to space**

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The function of ignoring, of inattention, is as vital a factor in mental progress as the function of attention itself.

William James, In *The Principles of Psychology* (1918).

To Fabiola

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PREFACE

We are, functionally and structurally, asymmetric bodies. One foot is often smaller than the other one, and one leg longer than its counterpart. Our facial expressions are also asymmetric, with the left side appearing more expressive than the right. From the bottom to the top, from the feet to the brain, we are a dichotomy working together to create the unique person we are. Even with our brains, similar to many other mammals, our two cerebral hemispheres differ in their anatomy and functions. This hemispheric specialization has been thought to be so strong as to determine even our personality and skills, and has led to the *popularly-held* belief that there are “right-brain” and “left-brain” people. While this belief belongs in the realm of pseudoscience, what has been demonstrated is that some cognitive abilities, such as language and spatial perception, do indeed depend predominantly on the left and right hemispheres, but that the two hemispheres work in synergy to ensure, at first sight, balanced visuospatial cognition and full language abilities. In fact, the perfect symmetry we subjectively experience through vision of the space around us is, to some extent, an illusion. When we are asked to judge spatial quantities across the vertical meridian of our visual field an asymmetry can be readily detected. This asymmetry in visuospatial cognition can be quantified behaviorally with a simple task such as the line bisection task. If we are asked to mark or judge the center of a horizontal line most of us will bisect it slightly to the left of its true center. This bias, typical of neurologically healthy subjects, is predominantly leftward in young subjects and moves rightward with age, and can reach pathological levels after right brain damage when the center of a line is sometimes perceived very far to the right of the true center. This pathological rightward bias is one of the symptoms very often exhibited by people affected by unilateral spatial neglect syndrome (USN), which is a pervasive and multi-componential syndrome that can affect diverse aspects of daily life. From bisecting a line rightward or copying only the right side of a drawing, to shaving only the right cheek or omitting to eat food on the left side of the dish, USN is a condition that very often limits the functional outcome of patients who are usually recovering from the stroke that caused this severely handicapping but fascinating pathology. Performance on line bisection tasks has also been shown to be relatively manipulable in both pathological and intact brains. Among the different ways of

modulating it, prism adaptation (PA) can both ameliorate USN symptoms (induce a leftward shift in line bisection judgments – towards the true midline), and induce neglect-like behavior in healthy subjects (induce a rightward shift in line bisection judgments).

Despite years of research, however, how this relatively simple visuomotor adaptation can modulate and remediate spatial cognition is still unknown. Uncovering the mechanism responsible for the PA-induced shift in line bisection judgments in healthy individuals would not only answer this question but would also shed light on the pathology of USN *per se* and contribute to our general understanding of visuospatial cognition.

ABSTRACT

We are functionally and structurally asymmetric. The perfect symmetry we subjectively experience through vision of the space around us is, to some extent, an illusion. Visuospatial cognition, as indexed by performance on line bisection tasks, is generally biased leftward in healthy individuals and pathologically rightward after right brain damage causing unilateral spatial neglect (USN). These biases can be modulated and prism adaptation (PA) is capable of both alleviating USN symptoms and inducing a rightward shift (the so-called “neglect-like behavior”) in healthy individuals. How this type of sensorimotor adaptation modulates spatial cognition is still debated. The goal of this thesis was to use both behavioral and physiological approaches to investigate the underlying mechanisms of PA’s effects on visuospatial cognition in healthy individuals. In a first behavioral study we found the presence of a temporal dynamic in PA after-effects. Based on this first finding we tested, over a longer period of time the PA after-effects following both right and leftward PA and unveiled, with the second study, different temporal dynamics depending on PA direction. In a third study we used transcranial magnetic stimulation to investigate the physiology underlying the effective visuospatial modulation induced by PA. The results of this thesis call for a refinement of the current models of PA action on visuospatial cognition.

RÉSUMÉ

Nous sommes fonctionnellement et structurellement asymétriques. La symétrie parfaite que nous expérimentons subjectivement en observant l'espace qui nous entoure est, dans une certaine mesure, une illusion. La cognition visuospatiale, comme indiqué par les tâches de bissection de lignes, est généralement biaisée à gauche chez les sujets sains et à droite suite à des lésions de l'hémisphère droit causant la Négligence Spatiale Unilatérale (NSU). Ces biais peuvent être modulés et l'adaptation prismatique (AP) a démontré sa capacité à réduire les symptômes de la NSU et à induire des comportements similaires à la NSU chez les individus sains. La question de savoir comment ce type d'adaptation sensorimotrice module la cognition spatiale est encore débattue. L'objectif de cette thèse était d'utiliser des approches comportementales et physiologiques, pour examiner les mécanismes sous-jacents des effets de l'AP sur la cognition visuospatiale d'individus sains. Dans une 1ère étude comportementale, nous avons observé la présence d'une dynamique temporelle des effets survenant après l'AP. Suite à ce premier résultat, nous avons testé sur une période de temps plus longue les effets faisant suite à l'AP déviant la vision vers la droite ou la gauche, et nous avons dévoilé, dans une 2ème étude, des dynamiques temporelles différentes en fonction de la direction de l'AP. Dans une 3ème étude, nous avons utilisé la stimulation magnétique transcrânienne pour étudier la physiologie sous-tendant la modulation visuospatiale efficacement induite par l'AP. Les résultats de cette thèse appellent à un raffinement des modèles actuels de l'action de l'AP sur la cognition visuospatiale.

LIST OF PUBLICATIONS

This thesis is based on the following publications:

Schintu S, Pisella L, Jacobs S, Salemme R, Reilly KT, Farnè A. (2014). Prism adaptation in the healthy brain: The shift in line bisection judgments is long lasting and fluctuates. *Neuropsychologia*, 53, 165-170.

Schintu S, Patané I, Salemme R, Reilly KT, Pisella L, Farnè A. Time matters: Both rightward and leftward prism adaptation bias line bisection but with different temporal dynamics. (In preparation).

Schintu S, Pisella L, Rossetti Y, Vesia M, Farnè A, Reilly KT. Modulations of PPC-M1 functional connectivity after LPA and shifts in line bisection judgments reflect individual differences in pseudoneglect. (In preparation).

Additional publications not included the thesis:

Knutson, KM, Dal Monte, O, **Schintu, S**, Wassermann, EM, Raymond, V, Grafman, J, Krueger, F. (2014). Areas of Brain Damage Underlying Increased Reports of Behavioral Disinhibition. *The Journal of Neuropsychiatry and Clinical Neuroscience*. (In press).

Schintu S, Hadj-Bouziane F, Dal Monte O, Knutson KM, Pardini M, Wassermann EM, Grafman J, Krueger F. (2014). Object and space perception – Is it a matter of hemisphere? *Cortex*, 57, 244-253.

Dal Monte O, **Schintu S**, Pardini M, Berti A, Wassermann EM, Grafman J, Krueger F. (2014). The left inferior frontal gyrus is crucial for reading the mind in the eyes. Brain lesion evidence. *Cortex*, 58, 9-17.

Pardini M, Gialloreti L E, Mascolo M, Benassi F, Abate L, Guida S, Viani E, Dal Monte O, **Schintu S**, Krueger F, and Cocito L. (2012). Isolated theory of mind deficits and risk for frontotemporal dementia: a longitudinal pilot study. *Journal of Neurology, Neurosurgery & Psychiatry*, 84(7), 818-821.

Dal Monte O, Krueger F, Solomon J, **Schintu S**, Knutson KM, Strenziok M, Pardini M, Leopold A, Raymond V, and Grafman J. (2012). Facial emotion recognition following penetrating traumatic brain injury: A lesion mapping study. *Social Cognitive and Affective Neuroscience*, 8(6), 632-9.

Di Monaco M, **Schintu S**, Dotta M, Barba S, Tappero R, and Gindri P. (2011). Severity of unilateral spatial neglect is an independent predictor of the functional outcome after acute inpatient rehabilitation in right-hemisphere stroke people. *Archives of Physical Medicine and Rehabilitation*, 92(8), 1250-1256.

RÉSUMÉ SUBSTANTIELLE

On est, fonctionnellement et structurellement, des corps asymétriques. Un pied est souvent plus petit que l'autre, et une jambe plus longue que sa jumelle. Une asymétrie évidente est également présente au niveau de l'anatomie cérébrale. On observe des protubérances des hémisphères, ainsi qu'un aspect faisant évoquer une torsion des deux hémisphères.

Ces asymétries ne sont pas seulement présentes au niveau anatomique, mais également au niveau structurel et fonctionnel. Cependant, la question de savoir comment cette asymétrie de l'organisation anatomique et structurelle est traduite en une asymétrie des fonctions visuospatiales est encore débattue. A niveau de la connectivité cérébrale il a été récemment démontré que le diamètre des fibres du réseau pariéto-frontal est plus large dans l'hémisphère droit que dans l'hémisphère gauche (Thiebaut de Schotten et al., 2011). Cette asymétrie de la connectivité structurelle, et précisément du deuxième faisceau longitudinal supérieur (SLFI II) se retrouve également au niveau comportemental. En effet, plus la latéralisation du SLF II est importante, plus l'asymétrie montrée dans la cognition visuospatiale l'est également. La cognition visuospatiale, et donc l'attention visuospatiale, sont asymétriques et cette asymétrie peut être soit pathologique, comme dans le syndrome de négligence spatiale unilatérale (NSU), ou inhérente aux cerveaux intacts dans les phénomènes de pseudo-négligence (pseudoneglect).

Dans cette thèse, on s'est principalement intéressé à cette asymétrie inhérente (pseudoneglect) et pathologique (NSU) de la cognition visuospatiale.

La NSU est un syndrome multifactoriel qui est responsable de difficultés à prendre en compte, à percevoir et / ou à répondre à des stimuli émanant de l'espace contralésionnel, sans que ceci ne puisse être attribué aux déficits sensoriels ou moteurs primaires (Vallar, 1993). Les patients ayant une NSU peuvent présenter différents symptômes, par exemple ils ne copient que la partie droite d'un dessin, oublient de se raser la joue gauche, ne mangent que la partie droite de leur assiette. Cette incapacité à utiliser des objets et / ou même son propre corps dans la partie contralésionnelle de l'espace rend ce syndrome, qui affecte jusqu'à 82% des personnes après un AVC de l'hémisphère droit (HD), très invalidant (Stone et al., 1993). Non

seulement la NSU réduit l'indépendance fonctionnelle de ces patients, conduisant à des difficultés dans les activités quotidiennes (Luauté et al., 2006a), mais elle est également associée à un mauvais pronostic d'évolution après rééducation par rapport aux patients cérébrolésés droits sans NSU (Jehkonen et al., 2006). De même sa gravité prédit la qualité du résultat fonctionnel après la rééducation de soins (Di Monaco et al., 2011). La NSU a longtemps été considérée comme un trouble attentionnel visuel, car le déficit de traitement de l'information dans l'espace contralésionnel peut se produire sans déficit du champ visuel. Plusieurs études ont tenté de déterminer les corrélats anatomiques principaux de la NSU pour mieux relier les déficits comportementaux au rôle fonctionnel des substrats anatomiques sous-jacents et ainsi, clarifier leur rôle dans la cognition visuospatiale du cerveau normal. Même si les premiers rapports anatomiques lésionnels de patients atteints de NSU datent de la deuxième moitié du XIX^{ème} siècle (Hughlings Jackson, 1932; Pick, 1898), c'est seulement dans la deuxième moitié du XX^{ème} siècle que la NSU a été systématiquement associée à une lésion pariétale droite (par exemple, Brain, 1941; Critchley, 1953). Le premier lien explicite entre les lésions du lobe pariétal et des déficits d'attention ou de la conscience perceptive s'est fait par la description du neurologue britannique Dr. Brain, qui, en 1941 rapporte les cas de trois patients présentant des lésions unilatérales du lobe pariétal et atteints à des degrés variables de déficits de l'attention. Cependant, à ce jour, seul un consensus partiel a été atteint, ceci étant probablement en lien avec la grande variabilité des manifestations cliniques de la NSU d'un patient à l'autre, malgré des lésions anatomiquement proches. Une des raisons pour lesquelles il serait d'autant plus difficile d'identifier ces relations vient du fait que le syndrome très multiforme de la NSU, permet à de nombreux autres déficits de coexister chez des patients présentant des lésions légèrement différentes.

Cette asymétrie pathologique de la cognition visuospatiale peut être quantifiée sur le plan comportemental, grâce à une tâche simple : la bissection de ligne (Shenkemberger 1981).

Cette tâche est devenue l'un des tests neuropsychologiques les plus classiques pour explorer la NSU, car il permet de mieux comprendre les processus fonctionnels impliqués lors de différentes conditions, comme la localisation spatiale, la perception de la longueur de la ligne ainsi que le repérage spatial. La tâche de la bissection de ligne repose principalement sur le cortex pariétal postérieur droit (PPC) (Fink et al.,

2000). Cette tâche dite « papier-crayon » se fait classiquement passer de la manière suivante : il est demandé au sujet de tracer avec un stylo ce qui lui semble être le milieu de la ligne qui lui est présentée sur feuille imprimée. Les patients présentant une NSU indiquent habituellement cette marque de façon nettement déviée vers la droite par rapport au milieu réel. Cette tâche a été largement utilisée dans des populations pathologiques, mais également chez des sujets sains, le plus souvent pour servir de groupe témoin.

En étudiant les performances de bisections de ligne chez les sujets sains, il a été mis en évidence que la cognition visuospatiale présente une asymétrie inhérente qui a été qualifiée de pseudoneglect, car le biais retrouvé chez les individus sains est dirigé dans le sens opposé à celui présenté par les patients (donc vers la gauche). En effet, la parfaite symétrie dont on fait l'expérience subjective à travers la vision de l'espace autour de nous est, dans une certaine mesure, une illusion. Lorsqu'on est amené à juger des grandeurs spatiales via le méridien vertical de notre champ visuel, une asymétrie peut être facilement détectée. S'il nous est demandé d'indiquer ou de juger le centre d'une ligne horizontale, la plupart d'entre nous indique le milieu subjectif légèrement à gauche du centre réel. Ce biais est retrouvé principalement à gauche chez les sujets sains et se déplace progressivement vers la droite avec l'âge. La pseudo-négligence, qui représente un biais visuospatiale constant dans la population saine étudié en recherche fondamentale, intéresse les chercheurs non seulement parce qu'elle permet d'étudier et de comprendre la cognition visuospatiale intacte mais aussi parce qu'elle pourrait représenter l'expression inverse du biais vers la droite retrouvé dans ce fascinant syndrome qu'est la NSU.

Comprendre la fonction visuospatiale et ses modulations dans le cerveau sain peut ainsi contribuer à mieux comprendre la NSU en tant que telle et la cognition visuospatiale non pathologique.

En parallèle des méthodes de rééducation conventionnelles et utilisées depuis longtemps, des techniques de stimulation cérébrale non invasive (NIBS) comme la stimulation magnétique transcrânienne (TMS) ou la stimulation transcrânienne à courant continu (tDCS) ont été adoptées. Ces techniques ont récemment suscité beaucoup d'intérêt (par exemple Miniussi et Vallar, 2011), et sont apparues ces dernières décennies comme des outils de réadaptation potentiellement intéressants

(pour une revue voir (Fasotti et Van Kessel, 2013), pour améliorer les processus cognitifs de sujets sains, comme pour réduire les déficits des patients atteints de troubles neurologiques. Malgré des études montrant que plusieurs séances de stimulation peuvent apporter des résultats prometteurs et encourageants, d'autres études sont encore nécessaires pour déterminer les effets à long terme et généraliser ces différents traitements. Une méthode unique de quantification de l'amélioration induite par NIBS dans la vie quotidienne est nécessaire (Fasotti et Van Kessel, 2013), ainsi que l'évaluation des facteurs économiques (et autres) qui peuvent être décisifs pour l'introduction de la rTMS par exemple comme une option thérapeutique (Wassermann et Zimmermann, 2012). Ces techniques NIBS ont été utilisées non seulement pour la rééducation de la NSU, mais également pour étudier la cognition visuospatiale des cerveaux sains. Ceci représente un point important dans la compréhension de la physiologie et la physiopathologie des fonctions corticales, notamment par le fait que les déductions sur le fonctionnement cérébral normal sont issues de constatations faites sur des patients cérébro-lésés (Walsh et Cowey, 1998). Il a été démontré que les méthodes de stimulations cérébrales non invasives modulaient efficacement la cognition visuospatiale, permettant ainsi d'améliorer les symptômes de NSU en inhibant le cortex pariétal gauche ou en excitant le cortex pariétal droit, et d'induire un comportement de négligence chez le sujet sain en inhibant ou perturbant surtout l'activité du cortex pariétal droit. Comme l'adaptation prismatique (AP) est capable à la fois d'améliorer les symptômes du NSU et d'induire un comportement de négligence chez les sujets sains, la question qui se pose est de savoir si le mécanisme de l'AP pourrait agir sur le cerveau de façon similaire à celui des NIBS.

La cognition visuospatiale, reflétée par exemple par le résultat à une tâche de bissection de ligne, est relativement manipulable, autant chez les sujets sains que chez les cérébro-lésés, par d'autres méthodes similaires à celles évoquées ci-dessus, en particulier grâce à l'adaptation prismatique (AP). En effet, l'adaptation prismatique a montré sa capacité à améliorer la NSU en utilisant des prismes droits et à induire des comportements de pseudo-négligence chez le sujet sains après utilisation des prismes gauches, ce qui en fait un outil très utile pour étudier la NSU. L'adaptation prismatique, qui consiste à s'adapter à des verres prismatiques, est une méthode simple et rapide qui permet de produire non seulement des effets visuo-moteurs de bas niveau, mesurables comme effets après exposition aux prismes (effets sensori-

moteurs), mais également d'améliorer les déficits cognitifs des fonctions supérieures, comme ceux retrouvés dans la NSU (Rossetti et al., 1998). Rossetti et ses collègues (1998) ont retrouvé non seulement une réduction significative des symptômes de négligence après adaptation droite, mais également que l'amélioration induite par le port de prismes durait et même augmentait au cours des deux heures suivant la séance, ce qui est beaucoup plus long que les améliorations décrites après des méthodes de rééducation conventionnelle. L'adaptation prismatique a suscité beaucoup d'intérêt et de nombreuses études ont vu le jour au cours des dernières années, y compris chez les sujets sains. Aujourd'hui, elle est considérée comme l'une des techniques les plus prometteuses de rééducation de la NSU (Luauté et al., 2006a), même si une recherche translationnelle plus rigoureuse est nécessaire pour combler le manque de connaissances qui actuellement freine la mise en œuvre de l'adaptation prismatique en hospitalisation (Barrett et al., 2012). Les effets positifs de l'adaptation prismatique sur les représentations spatiales et la cognition spatiale sont maintenant reconnus, ce qui a soulevé de nombreuses nouvelles questions (Newport et Schenk, 2012). Les mécanismes sous-jacents permettant un transfert entre l'adaptation visuo-motrice de bas niveau et les effets sur les fonctions supérieures font toujours l'objet d'études visant à mieux les comprendre. On suppose actuellement que l'effet clinique de l'AP droite dans la NSU repose sur un réseau dans lequel i) le signal d'erreur généré par l'AP droite est initialement traité dans le cortex occipital gauche, ii) l'information étant ensuite transférée vers le cervelet droit, où le réalignement visuo-moteur a lieu (c'est à dire «l'adaptation vraie»), iii) puis un signal bottom-up émanant du cervelet module les zones pariétales de l'hémisphère gauche. On suppose que l'AP agit avec le même mécanisme sur les cerveaux sains et lésés en modulant l'équilibre interhémisphérique par hypoactivation du cortex pariétal controlatéral à la déviation prismatique (Michel et al., 2003; Rode et al, 2003; Pisella et al., 2005). Cependant, la complexité anatomique et fonctionnelle du cervelet et l'absence de critères comportementaux clairs permettant d'identifier la transition d'un processus (sensori-moteur) à l'autre (modulation cognitive) en font une question difficile (Newport et Schenk, 2012). Il est aussi nécessaire de mettre en place un cadre cohérent intégrant un siècle d'études sur l'AP et la récente littérature sur les patients cérébro-lésés et les sujets sains (Redding et Wallace, 2006).

L'objectif de cette thèse était d'étudier, tant au niveau comportemental que neuronal, les mécanismes sous-tendant les effets de l'AP sur la cognition visuospatiale des individus sains.

Découvrir le mécanisme responsable des effets cognitifs de l'AP, permet non seulement de répondre à cette question, mais aussi permettrait d'éclairer la NSU en elle-même. Afin de caractériser physiologiquement les mécanismes rendant l'adaptation sensori-motrice possible au moyen de l'AP, un puissant outil pour moduler et assainir la cognition spatiale, il nous faut tout d'abord déterminer la durée des effets cognitifs induit par l'AP.

Lors de la 1^{ère} étude, on a abordé cette question en étudiant, chez les jeunes participants, la durée du biais induit par l'adaptation aux prismes gauche, (qui induit des comportements de pseudo-négligence chez le sujet sains) et droit (comme chez les patients et qui, comme supposé, induit un biais vers la gauche). On a mesuré l'effet sensorimoteur induit par le prisme au moyen d'une tâche de pointage vers une cible et l'effet cognitif des prismes au moyen d'une version perceptive de la bissection de lignes. La version perceptive de la bissection de lignes consiste à présenter aux sujets une série de lignes déjà bissectées de façon légèrement déviée par rapport au vrai milieu, en leur demandant de quel côté se trouvait la déviation. En nous basant sur leur réponse des lignes bissectées, on a calculé ce qu'on appelle le point d'égalité subjective (PSE) c'est à dire le centre perçu par le sujet. L'effet cognitif et sensorimoteur étaient mesurés avant (baseline) et plusieurs fois après l'AP gauche (toutes les 5 minutes) pendant 40 minutes. On a constaté que l'AP gauche induisait un biais significatif vers la droite, c'est-à-dire que le PSE était dévié vers la droite par rapport au PSE calculé en baseline). Cette modulation visuospatiale nécessitait un certain temps (~ 5 minutes) pour devenir statistiquement significative, durait au moins 35 minutes après le retrait des lunettes, et fluctuait dans le temps. En revanche, l'AP droite a induit des effets sensori-moteurs comparables (en termes d'amplitude et de dynamique), mais n'a pas réussi à induire un changement significatif de la cognition visuospatiale dans la fenêtre de temps testée en post-adaptation (40 minutes). Dans cette première étude, on a montré pour la première fois que la dynamique temporelle des effets visuo-spatiaux post-adaptation n'est pas la même que celle des effets sensorimoteurs. En revanche, l'AP droite a induit des effets post-adaptation (en termes d'amplitude et de dynamique), qui étaient maximisés immédiatement après

l'exposition et qui ont progressivement diminué avec le temps, mais qui n'ont induit aucun effet significatif sur la cognition visuospatiale dans la fenêtre de temps testée en post-adaptation (40 minutes).

L'observation de l'impact différent qu'ont l'AP droite et gauche sur la cognition visuospatiale ne représentait pas un résultat complètement inattendu puisque l'AP droite n'a induit aucun changement de PSE significative dans la fenêtre de temps testée dans la première expérience). En effet, il a été largement démontré que l'AP a une action asymétrique sur la cognition visuospatiale chez l'individu sain et chez les patients cérébro-lésés. Ces études montrant que l'AP gauche affecte la perception visuospatiale des participants sains n'avaient jusque là démontré aucun effet de l'AP droite (Colent et al., 2000; Berberovic et Mattingley, 2003; Michel et al, 2003;. Loftus et al, 2009;. Bultitude et al, 2013;. Reed et Dassonville, 2014), même si les effets post-adaptation sensori-moteurs (confirmant l'existence du phénomène d'adaptation) induits à la fois par l'AP gauche et droite ont des amplitudes et des directions opposées comparables. Une exception est la modulation de l'estimation du temps, initialement démontrée comme étant directionnelle et immédiatement modulée par l'AP dans les deux sens (Magnani et al., 2012). Cette preuve négative dans la littérature concernant l'AP droite et l'absence d'un effet sur la cognition visuospatiale intacte contraste avec la prédiction du modèle anatomo-fonctionnel proposée par Pisella et ses collègues (2006). Selon ce modèle, l'AP agit en hypo-activant le PPC controlatéral à la direction de la déviation prismatique modifiant ainsi l'équilibre hémisphérique. Avec un seul mécanisme, il explique à la fois les effets thérapeutiques chez les patients négligents et l'induction d'une pseudo négligence chez les sujets sains. Ce modèle suppose que l'AP droite comme gauche modulent le PPC controlatéral, et donc que les deux directions d'AP devraient moduler la cognition visuospatiale dans des directions opposées chez les individus sains. Si ce modèle est exact, pourquoi alors l'AP droite et gauche ne provoquent pas des biais visuo-spatiaux égaux mais opposés, c'est-à-dire dans le sens inverse, sachant qu'ils induisent des effets sensori-moteurs post-adaptation opposés mais égaux ? La nouveauté de la dynamique temporelle qu'on a observé sur les effets cognitifs post-adaptation à l'AP gauche nous a conduits à nous demander si une dynamique temporelle différente aurait pu être responsable de l'absence de données d'une modulation visuospatiale significative induite par l'AP droite. ON formule donc l'hypothèse que l'AP droite

pourrait avoir besoin de plus de temps que l'AP gauche (c'est-à-dire au moins 35 minutes puisque cette fenêtre de temps ne nous a pas permis de mettre en évidence un changement de PSE significative après AP droite) pour induire une modulation de comportement.

Si le modèle de l'AP proposé (Pisella et al., 2006) est correct, on devrait observer une modulation opposée des résultats de la bissection de lignes après des AP réalisées en sens opposé. ON a testé cette hypothèse dans le 2ème étude dans laquelle on a mesuré de façon répétée (comme dans l'étude 1) l'effet sensorimoteur et l'effet cognitif (au moyen de la tâche de bissection de lignes perceptive) induit par les prismes gauche et droit pendant trois jours après AP gauche ou droite. Les résultats de cette deuxième étude ont montré que les AP droite et gauche modulent significativement et avec une spécificité directionnelle la cognition visuospatiale, confirmant la prédiction générée par le modèle (Pisella et al, 2006) ; ceci avec deux dynamiques temporelles différentes. En accord avec nos prédictions, on a montré que les deux directions d'AP induisaient un biais directionnel dans la bissection de lignes, mais avec des délais différents : l'AP gauche induit un biais significatif vers la droite entre 5 et 10 minutes après adaptation, et est retrouvé quatre et huit heures plus tard, ce qui suggère que ce biais fluctue bien au-delà du délai d'1 heure. En revanche, l'effet de l'AP droite a émergé progressivement et le biais vers la gauche est devenu significatif seulement six heures après l'adaptation. Surtout, les effets sensori-moteurs en post-adaptation avaient des dynamiques temporelles comparables pour les deux directions d'AP. En fournissant des preuves que l'AP droite induit des biais gauches en bissection, nos résultats soutiennent le modèle selon lequel un mécanisme cérébello-pariétal unique expliquerait à la fois la diminution et l'induction de symptômes de négligence. On suggère que les différentes dynamiques de l'AP gauche et droite sont produites par des asymétries directionnelles dans la communication inter-hémisphérique.

Comme les résultats de la deuxième expérience soutenaient la prédiction du modèle (Pisella et al., 2006), on a décidé d'investiguer avec une troisième étude la physiologie de la modulation cognitive induite par l'AP gauche efficace chez les sujets sains, via la mesure des interactions entre le cortex pariétal et moteur (PPC-M1). Si l'AP agit au niveau physiologique comme le modèle le prédit (Pisella et al., 2006), c'est à dire en hypo-activant l'hémisphère droit(HD), libérant ainsi

l'hémisphère gauche (HG), une modification des PPC-M1 dans l'HD (diminution) et éventuellement une modulation opposée dans l'HG (augmentation) est attendue.

Avec la 3ème étude, on a étudié le mécanisme physiologique possible associé à la modulation de la cognition visuospatiale induite par l'AP gauche. Pour évaluer les changements induits par l'AP gauche au niveau de l'activation du PPC gauche et droit, on a utilisé le protocole dual site paired pulse TMS proposé par Koch et ses collègues (2007, 2008a), ce qui permet de quantifier l'influence de PPC sur M1 dans chaque hémisphère et donc de fournir une idée de l'intensité de la connectivité fonctionnelle fronto-pariétale. On émet l'hypothèse suivante : la pseudo-négligence induite par l'AP gauche, mesurée par la bissection de lignes perceptive, diminue la force de connectivité PPC-M1 dans l'HD, et l'augmente dans l'HG à la suite de la libération de l'inhibition interhémisphérique. Chez les sujets sains, on a mesuré la connectivité PPC-M1, avant et après l'AP, au moyen de la bissection de ligne perceptive. Les résultats de cette 3ème étude ont révélé qu'au niveau du groupe, on n'a pas réussi à reproduire nos propres résultats montrant un biais droit significatif sur des jugements de bissection de ligne après AP gauche. Après avoir examiné de plus près ces résultats comportementaux on a observé que cet effet était présent dans un sous-groupe de sujets seulement (ceux stimulés sur l'hémisphère gauche pour qui le biais initial se trouvait à gauche du centre objectif, c'est à dire qui ont présenté des symptômes de pseudo-négligence). Les résultats physiologiques ont révélé que la force de l'interaction PPC-M1 a été modifiée après AP gauche dans l'HG mais pas dans l'HD, et que (comme pour le comportement) cette modulation différait selon le biais initial présenté par les sujets. Dans le groupe présentant une pseudo-négligence, l'AP gauche diminuait les interactions PPC-M1 tout en déplaçant leur PSE vers la droite, alors que dans le groupe ne montrant aucune pseudo-négligence, l'AP gauche augmentait l'interaction PPC-M1 et décalait vers la gauche leur PSE. En résumé, dans le groupe HG, l'AP gauche a induit des modifications comportementales et physiologiques opposées entre les sous-populations présentant ou non une pseudo-négligence. Le fait que les biais opposés induits par l'AP gauche ne se limitaient pas à la performance comportementale, mais affectaient aussi la mesure physiologique (connectivité PPC-M1), renforce l'idée que la mesure de base de la bissection de ligne pourrait refléter un état du système. Nos données actuelles ne nous permettent pas de savoir quelle caractéristique du système détermine cet état initial. Une possibilité est

que les différences physiologiques entre les deux populations se situent dans l'excitabilité relative de leur connectivité PPC-M1 dans les deux hémisphères, mais puisque les groupes TMS de l'HD ou de l'HG étaient composés d'individus distincts, nous ne pouvons répondre à cette hypothèse avec les données que l'on possède. Cependant, on dispose de données de l'HG des deux groupes qui suggèrent que les sous-groupes pseudo-négligence et absence de pseudo-négligence pourraient différer au niveau de l'excitabilité moyenne des connexions PPC-M1 dans l'hémisphère gauche, puisque les participants pseudo-négligents avaient des amplitudes normalisées en MEP légèrement supérieures à celles des participants non pseudo-négligents. Des travaux supplémentaires sont nécessaires pour tester cette possibilité.

Le temps est une dimension qui a jusqu'ici été négligée dans la recherche AP chez les individus sains. Considérant que la durée de l'amélioration, suite à l'AP, des symptômes de la NSU a été étudiée en raison de sa pertinence clinique, la durée de la modulation de l'AP de la cognition chez les participants en bonne santé n'a non seulement jamais été explicitement étudiée, mais a été implicitement supposée être éphémère. Ainsi, la découverte de la présence d'une dynamique temporelle dans laquelle l'AP module la cognition visuospatiale est complètement nouvelle, et la présence de différentes dynamiques pour l'AP droite et gauche est une étape cruciale vers la compréhension des mécanismes d'action de l'AP. Les résultats de la seconde étude soutiennent le modèle (Pisella et al., 2006), qui prévoit que l'AP gauche et droite sont capables de moduler la cognition visuospatiale chez les individus sains. Ceci suggère que les deux types d'adaptation prismatique (droite et gauche) pourraient contribuer à la transformation locale de la bissection de ligne en modulant l'équilibre interhémisphérique chez les participants en bonne santé, et la restauration sans doute du déséquilibre de l'hémisphère pathologique chez les patients.

Une question qui découle logiquement de la découverte d'une dynamique temporelle de la modulation visuospatiale induite par l'AP est de savoir si l'AP a aussi une dynamique dans la lutte contre les symptômes de NSU. On a vu dans notre deuxième expérience que les effets de l'AP droite ont cessé d'augmenter et ont atteint un sommet à six heures après l'adaptation. Même si plusieurs études ont évalué à

plusieurs reprises les effets de l'AP droite après quelques heures et quelques jours en post-adaptation, à ma connaissance, il n'existe aucune étude dans laquelle ces after-effects aient été mesurés à maintes reprises à des intervalles courts et espacés régulièrement. S'il y a une dynamique temporelle à laquelle on ne s'attend pas suite à une adaptation prismatique droite chez des patients NSU, souffrant dont des symptômes inhérents à cette pathologie, alors il est possible d'envisager un suivi individuel dans lequel on prendrait en compte cette notion temporelle. En effet, les études cliniques portant sur la mesure de l'AP comme outil de réadaptation n'ont pas tenu compte de toute la variabilité individuelle, ce qui signifie que l'entraînement prismatique est effectué à un moment fixe (arbitraire), par exemple tous les matins, à la même heure, et pendant autant de temps, le tout se déroulent sur quelques jours. Si une dynamique temporelle est responsable des améliorations des symptômes est également retrouvée chez les patients, il peut indiquer le moment où la répétition de l'AP pourrait être ré-testée, dans l'idée de renforcer son effet bénéfique. En effet, si les effets post-adaptation (after-effects) sont encore en phase ascendante, la répétition de l'entraînement peut ne pas en valoir la peine. En revanche, cela peut être bénéfique pour le patient de répéter l'entraînement si les effets post-adaptation se trouvent dans une phase descendante. De ce fait, les effets pourraient être renforcés ou consolidés. Comme déjà abordé, des séances répétées de l'AP dans la NSU peuvent induire une récupération de longue durée qui pourrait être encore plus efficace si elle est adaptée à chaque patient, c'est-à-dire si elle est adaptée à la propre dynamique temporelle du patient.

D'autres études cependant encore nécessaires pour clarifier leur origine et faire une comparaison stricte entre les cours temporelle des effets induits par l'AP dans les deux populations; les fluctuations qu'on a observées chez les participants en bonne santé peuvent être pertinentes dans le cadre de la négligence à la fois la pathologie et sa récupération. Bien qu'il soit nécessaire de favoriser les études pour clarifier l'origine de ces fluctuations et faire une comparaison stricte entre les différents effets post-adaptation chez les deux populations, les fluctuations que nous observons chez les sujets sains se révèlent être pertinentes à la fois dans le cadre des symptômes retrouvés dans la pathologie et mais aussi de sa récupération.

Les résultats de cette thèse fournissent des renseignements importants sur les modèles actuels des mécanismes de l'AP et de la cognition visuospatiale. Effectivement, la

dimension temporelle de la l'AP, jusqu'à présent négligée, se révèle être importante et parfois même critique. De ce fait, il serait intéressant voire primordial de la prendre en compte dans les futures études pour comprendre les mécanismes de plasticité induits par l'AP, autant chez les sujets sains que chez les patients. Nos résultats peuvent contribuer d'une part au développement de futurs outils de rééducation faits « sur mesure » pour les patients souffrant de NSU, et d'autre part à l'amélioration de notre compréhension de ce syndrome.

En suggérant que les différences individuelles observées chez les sujets sains sont significativement différentes au niveau fonctionnel, on fournit une explication possible pour la variabilité dans les performances de la tâches ligne de bissection constatée dans la littérature pour les deux populations. Enfin, nos résultats confirment l'importance de la contribution de l'hémisphère gauche dans la genèse des biais visuo-spatiaux. Ces résultats fournissent la première preuve que l'AP gauche peut moduler la résistance de la connectivité pariéto-frontal chez les individus sains. Les résultats de cette troisième étude montrent non seulement les possibles corrélats neuronaux des mécanismes d'action de la AP, mais ils aussi soulignent la pertinence potentielle de sous-types des participants avec des traits spécifiques neurophysiologiques. L'adaptation prismatique module les performances dans la tâche de bissection de ligne autant chez les individus sains et les patients. De ce fait, on suggère que l'AP gauche est plus susceptible de moduler la connectivité fonctionnelle de PPC-M1 de l'hémisphère gauche, entraînant ainsi une perception du côté droit de l'espace (dans la tâche de bissection de ligne).

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1. INTRODUCTION

The human brain's gross anatomy and functional organization are both asymmetric. This lateralized specialization is thought to originate from phylogenetic and ontogenetic factors. The massive evolutionary expansion of the brain might have resulted in a level of complexity in which the duplication of structures was no longer efficient compared with the specialization of functions within a hemisphere. For example, the duplication of structures is less efficient compared to the specialization of functions within a hemisphere. These asymmetries can also be influenced by handedness, gender and age, along with genetic and hormonal factors. Asymmetries can also be affected by pathological factors, and their loss or modulation, such as in disorders like dyslexia, dementia, and USN, are of particular interest to researchers (Toga and Thompson, 2003).

1.1 BRAIN ASYMMETRIES

The first evident asymmetry is in the gross anatomy of our brain. Fig. 1 below shows a 3D rendering of the inferior surface of the human brain. In this figure we can clearly see the prominent asymmetries of the two cerebral hemispheres. We can

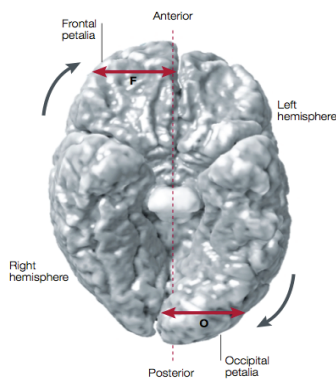


Figure 1 Petalia and Yakovlevian torque. (From Toga and Thompson, 2003)

observe protrusions of the hemispheres both anteriorly and posteriorly, as well as differences in the widths of the frontal (F) and occipital (O) lobes. These protuberances produce imprints on the inner skull surface that are called *petalia*. If we keep looking at the image, we can also notice that the two hemispheres look like they have been twisted; this twisting effect is called *Yakovlevian torque*, and it refers to the fact that the structures surrounding the right Sylvian fissure are ‘torqued

forward’ compared with their left counterparts, and the occipital lobe is splayed across the midline and bends rightward into the interhemispheric fissure. Furthermore, the occipital horns of the lateral ventricles tend to project more deeply into the occipital lobes on the left than on the right hemisphere (Toga and Thompson, 2003). Using arteriography LeMay and Culebras (1972) showed definite morphologic

differences between the right and left hemispheres in a region of major importance for language - the parietal opercula. They found the parietal operculum to be more highly developed on the left hemisphere (LH) than on the right hemisphere (RH) in the majority of their sample (38 of 44 persons); differences that were already present in Neanderthal man. The frontal (right > left) and occipital (left > right) asymmetry in the petalias, the presence of left-greater-than-right asymmetries in several posterior language areas, including the planum temporale and the angular gyrus, the asymmetries in the cingulate sulcus (right > left) and the caudate nucleus (right > left) were all confirmed by a Voxel-based Statistical Analysis of 142 healthy young adults examining hemispheric asymmetries in regional 'amounts' of gray matter. The authors also found highly significant asymmetries in a previously unreported brain region; the insular cortex (right > left) (Watkins et al., 2001).

Asymmetries in brain organization are also present at the cellular level. Cytoarchitectural studies found a perfect rank-order correlation between gross planum temporale asymmetry and the surrounding cellular field, which is implicated in higher-order auditory processing (Galaburda et al., 1978). Similar asymmetries were found in parietal architectonic regions (for example, the language area) (Eidelberg and Galaburda, 1982), and Scheibel and colleagues (1985) reported that although total dendritic length of the basilar dendritic array seemed characteristic of an area independent of side, the extent of high-order dendritic branching (high-order branches are thin branches that lie far away from the main dendrite) was greater in the LH speech areas (including Broca's area) than in the contralateral homologous areas where lower-order dendrites were longer. Rosen (1996), using a technique that labeled neurons undergoing their last mitosis and tracking cellular changes in cortical development, assessed the developmental processes that result in anatomical asymmetries and found no subsequent hemispheric differences in labelling ratios between left and right sides (regardless of the degree of asymmetry), implicating early developmental events in the formation of asymmetrical cortical areas. Furthermore, when compared with asymmetric brains, symmetric brains have relatively large numbers of callosal fibers and termination patches, suggesting that if anatomic asymmetry is responsible for functional lateralization, this may be more related to the different organization of symmetric and asymmetric brains, rather than simply hemisphere (or brain region) size (Rosen, 1996).

In addition to differences in the gross anatomy and at the cellular level, hemispheric lateralization is also observed in the functional organization of the brain. One of the earliest observations of this was the left hemispheric dominance for language, which was first noted in the XIX century by Broca (1861) and Wernicke (1874) who observed that language was more severely impaired after a LH than a RH lesion. Similarly, clinical studies in patients with brain lesions and decades of neuropsychological testing in split-brain patients have led to the notion that visuospatial cognition is a function that depends predominantly on the right hemisphere (Sperry, 1974; Mesulam, 1981). This hemispheric dominance for both visuospatial cognition (right) and language (left) has been linked to asymmetries in structural connectivity. Using diffusion-weighted magnetic resonance imaging (MRI) and a probabilistic tractography approach (Kucyi et al., 2012) compared the strength of white matter connections emanating from the right versus left temporoparietal junction (TPJ), a key component of the attention network (Corbetta and Shulman, 2002). Consistent with the lateralization of language pathways, the authors found greater connectivity between the TPJ and inferior frontal gyrus in the left than the right hemisphere. Similarly, consistent with a right hemispheric dominance for visuospatial cognition, they found greater TPJ-insula connectivity in the right than the left hemisphere. Thiebaut de Schotten and collaborators (2011) also investigated the possible anatomical bases for this right hemispheric dominance in visuospatial cognition. Using diffusion tensor imaging (DTI) they found asymmetries in the white matter anatomical parallel pathways that connect the parietal and frontal cortices (the fronto-parietal network) (Schmahmann and Pandya, 2009), which are involved in visuospatial attention in both humans (Corbetta and Shulman, 2002) and non-human primates (Buschman and Miller, 2007). Namely, the authors reported the first evidence in humans for a larger diameter for the parieto-frontal connections fibers in the right than left hemisphere (this concerns in particular the second and the third branches of the Superior Longitudinal Fasciculus SFL II and III), and for the SFL II a significant correlation between the degree of anatomical lateralization and asymmetry of performance on visuospatial tasks such as line bisection (Thiebaut de Schotten et al., 2011).

From the reported literature, we see that asymmetries are not only present at the anatomical level but also at the structural and functional levels. However, how

asymmetries in structural organization translate into asymmetries of visuospatial functions is still debated. In attempt to contribute to this understanding the present thesis investigated visuospatial cognition in healthy individuals using both behavioral and physiological approaches.

1.2 VISUOSPATIAL COGNITION AND ITS ASYMMETRY

Visuospatial cognition refers to perception of the spatial relationships among objects within the field of vision. Controlling visuospatial abilities has been largely demonstrated to predominantly rely on the RH, and especially on right parietal cortex (Newcombe, 1969; Mesulam, 1981; De Renzi et al., 1982; Kinsbourne, 1987; McCarthy and Warrington, 1990), from both studies of neurological patients and with deficits such as neglect or extinction (Mesulam, 1981; Weintraub and Mesulam, 1987; Posner and Petersen, 1990; Desimone and Duncan, 1995; Vallar, 1998; Kastner and Ungerleider, 2000; Schintu et al., 2014a) as well as by a number of neuroimaging studies in normal subjects (Nobre et al., 1997; Corbetta et al., 2000; Rushworth et al., 2001; Corbetta and Shulman, 2002).

Based on the fact that the similarities concerning perception of space, time and quantities present in the literature may be indicative of common processing rooted in our need for information about the spatial and temporal structure of the external world, the perception of these three domains has been unified by a recent theory; A Theory Of Magnitude (ATOM; Walsh, 2003a). The ATOM theory proposes that space, time, and quantity are all part of a generalized magnitude system and posits the existence of a common metric system that is assumed to be inherently spatial and to have its neural substrate in the right inferior parietal cortex (Walsh, 2003a; Buetti and Walsh, 2009). This theory assumes that the brain has developed an economical fashion to process and measure all quantity-related features, that is learnt through, and useful for, interacting with the environment (Walsh, 2003a). In this context time (perception) is spatially represented on a hypothetical *mental temporal line* which ascends from left to right similar to the *mental number line* (Dehaene et al., 1993) in which smaller numbers are typically represented on the left side of space and larger numbers on the right side of space (for a review see Hubbard et al., 2005; Umiltà et al., 2009).

Visuospatial cognition is mediated by attention that, as neuropsychological studies in humans have long suggested, it is a gateway between perceptual selection and behavior in the widest sense of the word (Mesulam, 1999). Attention is the cognitive mechanism by which salient or behaviorally relevant sensory information is selected for perception and awareness (Desimone and Duncan, 1995), and that determines which sensory signals control behavior constraining the rate of information processing (Cohen and Maunsell, 2009). Visual attention can be primarily allocated to either the structure of the object (object-based selection (e.g. Duncan, 1984; Behrmann et al., 1998) or to where an object is in space (space-based selection (e.g. Posner, 1980). Object-based and space-based attention share common neural mechanisms in the parietal lobes, in addition to task specific mechanisms in early visual processing areas of temporal and occipital cortices (Fink et al., 1997). The allocation of attention can be automatically controlled by stimulus-driven (bottom-up) factors that reflect sensory stimulation, or by voluntary (top-down) processes such as knowledge, expectation and current goals. The dynamic interaction of these factors controls where, how, and to what, we pay attention in the visual environment (Corbetta and Shulman, 2002). A right hemispheric specialization has also been suggested for attention in general, and spatial attention in particular.

Visuospatial cognition can be both pathologically and inherently asymmetric; unilateral spatial neglect and pseudoneglect are two manifestations of its asymmetry.

1.2.1 UNILATERAL SPATIAL NEGLECT - USN

“Though not suffering from a loss of topographical memory or an inability to describe familiar routes, they nevertheless got lost in going from one room to another in their own homes, always making the same error of choosing a right turning instead of a left, or a door on the right instead of one on the left. In each case there was a massive lesion in the right parieto-occipital region, and it is suggested that this ... resulted in an inattention to or neglect of the left half of external space. The patient who is thus cut off from the sensations which are necessary for the construction of a body scheme may react to the situation in several different ways. He may remember that the limbs on his left side are still there, or he may periodically forget them until reminded of their presence. He may have an illusion of their absence, i.e. they may ‘feel absent’ although he knows that they are there; he may believe that they are absent but allow himself to be convinced by evidence to the contrary; or, finally, his belief in their absence may be unamenable to reason and evidence to the contrary and so constitute a delusion.” W. R. Brain, 1941 (Brain 64: pp. 257 and 264)

USN is a multi-component syndrome that includes failures to report or respond to stimuli that are located on the contralesional side of space when this failure cannot be attributed to either primary sensory or motor deficits (Vallar, 1993). It is as if these patients were not taking into account information coming from the left side of space (Vallar, 2001). For example, they may have difficulty performing complex but overlearned motor tasks on the neglected side including dressing themselves, reaching for objects, writing, drawing, and orienting to sounds. They may shave or apply make-up only on the non-neglected ipsilesional side of their face, eat from only the right side of a plate, include only details appearing on the ipsilesional side when copying drawings, write on the right side of a page, omit left side targets in visual search tasks, and deviate rightward when bisecting horizontal lines. When presented with bilateral stimuli, they may immediately look toward the rightmost stimulus, as if their attention were “magnetically” attracted by this stimulus (Gainotti et al., 1991). USN can also alter the spatial organization of the dream setting and the way the dreamer deploys attention to the dream scene (Doricchi et al., 2007). The symptoms of USN may reflect the interaction of a variety of spatially lateralized and non-lateralized impairments, not all of which are present in all patients (Milner and McIntosh, 2005). USN is a highly heterogeneous disorder (e.g. Chatterjee, 1998; Stone et al., 1998), and several dissociations have been observed, such as patients neglect the *left-side* in near but not far space (Halligan and Marshall, 1991a) and vice versa (Covey et al., 1994) or show USN in some tests but not in others (Halligan and Marshall, 1992). Finally, these patients may also suffer associated deficits they are unaware of, being for example anosognosic for the frequently comorbid hemiplegia (Vallar and Ronchi, 2006), or show delusionals such as somatoparaphrenia (Vallar and Ronchi, 2009) in which patients disown their own left limbs, making the rehabilitation path even more arduous. This inability to attend to objects and/or even one’s own body in the contralesional portion of space makes USN a highly debilitating syndrome that affects up to 82% of individuals after a RH stroke (Stone et al., 1993). Not only does USN reduce the functional independence of these RH patients, leading to difficulties in everyday activities (Luauté et al., 2006a), but it is also associated with worse rehabilitation outcomes compared to RH lesioned patients without USN (Jehkonen et al., 2006) and its severity even predicts the quality of the functional outcome after acute inpatient rehabilitation (Di Monaco et al., 2011). The need of effective rehabilitation methods stands clear from the high incidence and

relevant repercussion that USN has on the recovery of functions and thus the general well being of these patients.

Although USN was already observed at the end of the XIX and beginning of the XX century (Oppenheimer, 1885; Bálint, 1909; Holmes, 1918; Riddoch, 1935), the relevance and implications of the syndrome in terms of ‘higher’ functions were strongly debated. Dr. Brain (1941; 1945) was the first to discuss it as a syndrome - ‘an inattention to, or neglect of the left half of visual space’. However, the idea of an isolated neglect syndrome as a specific disorder of space perception was not shared by the German neurologist Bay who claimed that all so-called ‘higher’ perceptual disorders were secondary to sensory impairment, general intellectual loss, or language disturbance; reducing most of the agnosia cases reported in the German literature at that time to mere sensory and intellectual impairments (Bay, 1950). USN was explained by him as resulting from restricted visual fields and generally slow and clumsy behavior (translated from Bay, 1950 p.140 in Harvey, 2004). Although other investigators have vigorously argued against this view of USN as arising from sensory deficits (Ettlenger, 1956; Ettlenger et al., 1957) the classification of USN as a *higher order syndrome* was only confirmed in the seventies thanks to the ingenious and now classic experiment designed by (Bisiach and Luzzatti, 1978). In this experiment USN patients omitted left-sided details in describing from memory a highly familiar scene, such as the Duomo square in Milan, depending on the perspective taken. The authors thus demonstrated the presence of USN on purely imaginable tasks, i.e. tasks that could be solved without any sensory input (i.e. it was already available in the memory of the patients before the injury).

Despite years of research, and given the heterogeneous profile of this syndrome, a unitary explanation of USN, as well as agreement concerning its causal mechanisms has not been found yet, however some possible explication has been excluded on the base of clinical evidence or dissociation of symptoms. The possibility of elementary sensory impairment as a cause of USN has been excluded on the base of dissociation between patients with hemianopia (decreased vision or blindness in half the visual field) and neglect patients (McFie et al., 1950; Gainotti, 1968), such as the fact that hemianopic patients (without USN) try to compensate for their deficit (Barton and Black, 1998) whereas USN patients keep deviating ipsilesionally. Also the possibility that USN is caused by a representational deficit has been excluded,

given the fact that USN is not restricted to the visual modality but is also seen in auditory (Bisiach et al., 1984; De Renzi et al., 1989), tactile (Chedru, 1976; Bisiach et al., 1985) and imagined space (Bisiach and Luzzatti, 1978; Bisiach et al., 1981), and that a dissociation between imaginative and visuospatial tasks has been shown (Behrmann et al., 1992; Bartolomeo et al., 1994). Another possible cause of USN was attributed to a dysfunctional (left sided) mental representation of space (distorted and not destroyed (Gainotti and Tiacci, 1971), characterized by a horizontal anisometry, refers to a distortion of a cognitive representation of space with spatial coordinates progressively relaxing from the right to the left. The mental representation of space would lose its (relative) symmetry in neglect patients because the distances between space coordinates would no longer be uniform for the whole space, but would progressively increase from the right to the left (Bisiach et al., 1996, 1998, 1999) or alternatively because of a *compression* of left-sided spatial coordinates (Halligan and Marshall, 1991b). However, the possibility of an horizontal anisometry as casual to USN has been excluded since the generality of the anisometry is limited by findings showing that actually neglect patients without visual field defect reproduced equivalent distances contralesionally and ipsilesionally of an imagined line, instead of overextend (or underextend) the distance contralesionally as it would have been expected to equalize the amount of perceived spatial extent (Doricchi and Angelelli, 1999a). The possibility that USN is caused by a displacement of the egocentric coordinates, consequent to an asymmetric pattern of activity after the right hemisphere lesion, has also been ruled out given the absence of correlation between USN symptoms and the presence (or the side) of a deviation of the egocentric reference position as recorded by a straight-ahead pointing task (Chokron and Bartolomeo, 1997; Farnè et al., 1998).

It is important to consider that an event on the right side is more likely to attract a patient's attention than an event occurring on the left, that left visual stimuli are usually extinguished in neglect patients (Gainotti et al., 1991), and this *extinction* may persist after clinical signs of neglect have subsided (Karnath, 1988). Given that putting stimuli in competition is a powerful mean of eliciting signs of spatial bias (Di Pellegrino and De Renzi, 1995) and attention is considered the basic mechanism used to deal with multiple competing stimuli, it follows that USN may be the expression of an attentional bias (Bartolomeo and Chokron, 2001).

1.2.1.2 *Attentional theoretical Models of USN*

Different attentional theories have been proposed to explain the high occurrence of USN following a RH. Four main models have emerged and they respectively define USN as: i) a deficit in orienting attention to the left contralesional hemisphere; ii) a pathological rightward attentional bias due to a release of interhemispheric inhibition - the rivalry theory (Kinsbourne, 1977, 1993); iii) a deficit in disengaging attention from the right side to reorient it to the left side (Posner and Petersen, 1990); and iv) a pathological functional imbalance due to a release of interhemispheric inhibition but specifically between the dorsal parts of the attentional network due to damage of the ventral network (Corbetta et al., 2005). (The proposed anatomical correlates will be illustrated in section 1.3.1)

Heilman and Van Den Abell (1980), and Mesulam, (1981, 1999) proposed that the RH directs attention to both visual hemifields, whereas the LH directs attention solely to the right visual field (RVF). Thus, although the RH can compensate for LH damage, such compensation is not possible after RH damage, thereby resulting in more frequent neglect of the left visual field (LVF) after RH damage than of the right visual field after LH damage. Similarly, the unequal distribution of spatial attention between the hemispaces is thought to arise because the right parietal cortex orients attention to both halves of space, whereas the left hemisphere orients attention primarily to the right. Therefore, left parietal lesions would tend to be compensated for by the intact right hemisphere, whereas when the right parietal cortex is damaged, there would be little or no compensatory capacity in the left hemisphere to orient attention to the left side of space.

Kinsbourne (1977, 1993) proposed a different model of spatial attention based on an interhemispheric competition mechanism, postulating that each hemisphere directs attention toward the contralateral visual field/hemisphere, and that the two hemispheres remain balanced through reciprocal inhibition. The hemispheric rivalry theory conceives USN as the result of an imbalanced system after damage to one *processor*, which induces the release of the intact hemisphere from inhibition, and thus produces a pathologically imbalanced attentional vector, i.e. a bias toward the ipsilesional visual field. Following the logic of this proposal, recovery from USN could be driven by a restoration of the balance between hemispheres. This model of

neglect proposes that the lack of attention to the contralesional space after unilateral brain damage is partly due to a sort of disinhibition of the unaffected hemisphere, implicating the involvement of an imbalance of the excitatory and inhibitory properties of attentional neurons in both the affected and unaffected hemispheres of brain-damaged patients in USN.

Posner and Petersen (1990) theorized that the orienting of attention could be organized in three distinct stages. They argue that to orient attention to a new location, the brain first has to disengage, that is take attention away from the current focus, then to move attention elsewhere, finally to engage, or anchor on a new target. Spatial orienting of attention thus includes a disengagement and re-engagement mechanism plus a shifting mechanism. In this framework, USN was conceptualized as a deficit in disengaging attention from the right side to reorient it to the left side (Posner et al., 1984).

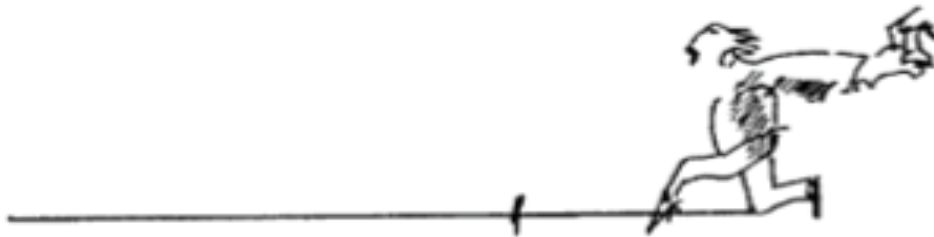
Corbetta and Shulman (2002) more recently proposed another a model of USN that integrates some elements of the previous theories. They subdivided the cortical centers for spatial attention into a dorsal and a ventral attention network. The ventral attention network, located predominantly in inferior parietal and frontal regions of the RH, is specialized for target detection, particularly when they are salient or unexpected, and the dorsal attention network, including bilaterally the SPL, intra-parietal sulcus (IPS) and the frontal eye field, is activated by directional cues and is involved in attention orientation: preparing and applying goal-directed selection for stimuli and responses. The ventral attention network acts as a circuit breaker of ongoing cognitive activity when a behaviorally relevant stimulus is detected and the current attentional set needs to change on the basis of the incoming stimulus. Lesions of the ventral network can thus provoke a dysfunction in the structurally intact dorsal network in the right hemisphere, resulting in a functional imbalance between the left (hyperactive) and right (hypoactive) dorsal attention networks (Corbetta et al., 2005).

All these models are grounded to some extent on the notion of interhemispheric rivalry, that not only has been largely influential to explain USN etiology, but over the last 40 years continues to gather support from investigations in both pathological and healthy populations (e.g. Sparing et al., 2009), and recently showed to account for individual visuospatial behavior in healthy subjects

(Szczepanski and Kastner, 2013) (see Discussion section 5.2.1). Studies thus support the hypothesis that after a natural or an experimental (reversible) virtual lesion of the right PPC, the release of interhemispheric inhibition on the LH from the RH may produce an imbalance in which the LH is disinhibited, thus directing pathologically ‘strong’ attention to the right side (Oliveri et al., 1999; Fierro et al., 2000, 2001; Brighina et al., 2002; Koch et al., 2008; Nyffeler et al., 2008; Sparing et al., 2009). The reduction of the rightward bias might thus correlate with a restoration or rebalancing of interhemispheric interactions. The interhemispheric re-balancing hypothesis is also supported by a number of fMRI studies that directly investigated changes in brain activity during USN recovery from the acute to the chronic stage. These studies showed that neglect amelioration correlated with the reinstatement of a functional balance between the regions of the dorsal attentional network of both hemispheres (Corbetta et al., 2005; He et al., 2007). Corbetta and colleagues showed that in both the acute and chronic stages the parietal imbalance correlated with the degree of the rightward attentional bias as measured by reaction (RT) time in Posner task. Support for this view also stems from animal studies, which by reversibly deactivating (cooling) focal brain areas in cats showed not only that the unilateral deactivation of the PPC results in contralateral visuospatial neglect, but also that it could be reversed by subsequent deactivation of the same region in the opposite hemisphere (Lynch and McLaren, 1989; Lomber and Payne, 1996; Lomber et al., 2002; Payne et al., 2003). One assumption of the hemispheric balance theory is that a second lesion in the homologous contralateral area would cancel the effect of the previous lesion: the Sprague effect (Sprague, 1966). A single case study of a patient who showed severe USN following a first right-sided parietal infarct supports this idea as this patient recovered from neglect 10 days later, when she suffered from a second infarct in the dorsolateral frontal cortex of the left hemisphere (Vuilleumier et al., 1996). Even if the rivalry model does fit with much recent evidence on neglect recovery, Bartolomeo, Thiebaut de Schotten and Doricchi (2007) based on a review of animal and patient studies proposes that neglect can be the result of a intra- and or interhemispheric disconnection and thus, suggest that inter-hemispheric cooperation (e.g. Wilke et al., 2012), rather than competition, can be crucial for recovery from neglect as well as other neuropsychological deficits.

Finally, The concept of a pathological hyperactivity of contralesional brain areas as being part of the central pathophysiological mechanism in USN is supported by recent fMRI data in patients. Focal brain lesions in the RH have been shown to affect the functioning of the attentional network in the ipsi- and contralesional hemispheres, causing a relative hyperactivity in the left, undamaged hemisphere (Corbetta et al., 2005). Whether the possible LH hyper-excitability, a consequence of the release of interhemispheric inhibition after a lesion in the RH, can be the cause for USN is questioned (Umarova et al., 2011; Ricci et al., 2012).

1.2.2 LINE BISECTION - A METHOD TO QUANTIFY VISUOSPATIAL ASYMMETRY



Federico Fellini's performance.
(From Cantagallo & Della Sala, 1998)

The line bisection task has become an invaluable tool to gain a better understanding of the functional processes involved when responding to different stimulus conditions, such as spatial location, line length, spatial cueing, and is one of the most classical neuropsychological tests employed to detect the presence of USN. The most typical line-bisection task consists of a *paper and pencil task* in which subjects are asked to mark, with a pen, where they think the middle of the line is; USN patients usually place the mark on the right side of the true center.

Line bisection can be categorized into *visual* and *non-visual* variants; the latter ones are also called representational line bisection tasks.

Visual line bisection tasks includes:

- Manual line bisection task is the first task used and standardized, and consists of a *paper and pencil task* in which subjects are asked to mark, with a pen, where they think the middle of the line is. A displacement of the bisection mark towards the side of the brain lesion is interpreted as a symptom of USN; the fact that some patients bisect the line far to the right of the veridical midpoint suggests that their attentional bias has shifted toward the right visual field (RVF) (Schenkenberg et al., 1980; Bisiach et al., 1983).
- Perceptual line bisection task is the perceptual version of the manual bisection task. It is often used to assess spatial biases in healthy subjects independently on motor biases or abilities (Milner et al., 1992; McCourt and Olafson, 1997; McCourt and Jewell, 1999). Instead of marking the center of a line, subjects are asked to judge whether the transector of a pre-bisected line is to the right or left of the true center (Milner et al., 1992).

Representational line bisection tasks require the subjects to either explore a stimulus using touch in the complete absence of direct visuospatial processing or to mentally represent the stimulus.

Representational bisection tasks include:

- Haptic manual line bisection tasks ask the subject to manually explore a rod with either the left or the right hand, and to locate the center of the rod using tactile and/or kinesthetic feedback. To minimize tactile information, and bias the task toward the use of kinesthetic cues, some studies make subjects bisect an aluminum rod by moving a cursor within a channel running along its length.
- Mental alphabet line bisection task, subject are presented with letter strings (e.g. C_H_P) and asked to estimate whether the letter length is greater on the left or right side of the inner-letter (Nicholls and Loftus, 2007).

With the perspective that information concerning time would also share, along with other magnitudes, the same spatial system of encoding, with ascending order from left to right, representational line bisection tasks also include:

- Time line bisection task (TL), which ask the subject to judge or reproduce the duration of a sound, thus involving the representation of time (Magnani et al.,

2011). There are different versions of task that has been used to assess time perception. The auditory-verbal modality consists of the verbal classification of auditory stimuli of different duration, with respect to previously acquired pair of reference durations (“short” or “long”) (Wearden, 1991; Wearden and Ferrara, 1995). The auditory stimuli, can also be presented on different spatial location with respect to the participant’ midline, and participants can be asked to judge the tone duration either when the tone is delivered from a specific location ignoring its pitch (spatial condition), when the tone is of a specific pitch, ignoring its location in space (tonal condition) (Magnani et al., 2012). In the visuomotor modality (time bisection task) participants, after having seen a stimulus (circle) presented on a screen for a variable duration, are required to judge by pressing a button when they think that the duration of the second visually presented stimulus corresponding to half the duration of the previous stimulus has elapsed or participants can instead be asked to reproduce, by pressing a key, the whole duration of the stimuli presented on the screen (Frassinetti et al., 2009).

- Mental number line bisection task (MNL), asks the subject to “bisect” the mental number line by estimating (without calculating) the number halfway between two others (e.g., 2_9; 12_19) (Zorzi et al., 2002; Longo and Lourenco, 2007), and involves the mental representation of small and large numbers.

Line bisection has been investigated, in both pathological and healthy population, also in a vertical orientation. However the focus of this thesis will be on the horizontal line bisection task.

Patients with right-hemisphere damage and left unilateral neglect typically bisect horizontal lines to the right of the true midpoint (Schenkenberg et al., 1980). Contralesional line bisection errors in hemianopic patients were already reported in the early German literature (Axenfeld, 1894; Liepmann and Kalmus, 1900). The relationship between ipsilesional line bisection errors and USN was already observed a century ago, but it was interpreted as a “variant” of hemianopia (Best, 1910) since at that time USN was unheard of (Kerkhoff and Bucher, 2008). Investigations of spatial

perception neglected the line bisection task until its rediscovery in the seventies, as a tool to assess USN, when with the birth of cognitive psychology and the rapid development of cognitive neuropsychology and neuroscience, theoretical concepts such as spatial attention became the object of research. Even though line bisection was reintroduced as a method for evaluating neglect patients in 1976 (Bisiach et al., 1976), only in 1980 Schenkenberg and collaborators formally did evaluate this method and show that this quick and simple test has the statistical power to discriminate, under certain conditions, between patients with RH lesions and patients with diffuse lesions, patients with LH lesions, and hospital controls (Schenkenberg et al., 1980). Ipsilesional errors in line bisection are now well known to be one of the hallmarks of USN (Halligan and Marshall, 1988, 1991c).

Several factors influence patient performance in line bisection task, i.e. the amount of rightward deviation (Bartolomeo and Chokron, 2001). First, the longer the line the more the patient will bisect it rightward (Bisiach et al., 1983; Nichelli et al., 1989), and this relationship is described as a linear function (Riddoch and Humphreys, 1983). For very short lines a paradoxical leftward deviation effect has been observed - the “crossover effect”, in which patients even reverse their rightward bias (Halligan and Marshall, 1988), as well as for the mental number line (Dehaene et al., 1993). Second, the line’s position in space, with respect to the patient’s trunk midline also influences performance; when lines are located in the left hemispace the rightward deviation increases, whereas when lines are located in the right hemispace it decreases (Heilman and Valenstein, 1979; Schenkenberg et al., 1980; Nichelli et al., 1989). The “cross- over” effect can also arise via the manipulation of spatial position, so that some patients make leftward errors for lines presented in right hemispace, though erring rightwards when lines of a similar length are presented at other locations (Mennemeier et al., 2001). Third, the direction in which the line is explored has been shown to influence line bisection performance: in a passive version of the task (i.e. patients have to observe a cursor moving along the line and to say “stop” when it crossed the perceived middle), the amount of rightward shift decreases with a left-to-right movement of the cursor, and increased when the cursor was moved from right-to-left (Reuter-Lorenz and Posner, 1990; Mattingley et al., 1994; Chokron et al., 1998).

A body of evidence indicates that the ipsilesional error in line bisection

performance cannot be completely explained by elementary sensory deficits (Barton and Black, 1998), or by deficits in programming hand movements towards the left side (Milner et al., 1993), although such additional factors may well contribute to the patients' final performance (Bisiach et al., 1990; Doricchi and Angelelli, 1999a). Several possible explanations have been proposed to account for the rightward bias of USN patients in line bisection and provide different accounts of this pattern of performance.

Marshall and Halligan (1989) proposed that line bisection errors reflect the direction of attentional approach to the subjective midpoint, and that cross-over bisections is associated with a reversal of the patients' normal right-to-left scanning patterns scantrack model. Instead Ishiai et al. (2006) reported that the eye movements of four USN patients, that were asked to bisect lines of three different lengths were no predictive of the relationship between direction of final scan and direction of bisection error, and that there was any evidence that right-to-left overt scans predominate amongst neglect patients making bisection responses. The authors suggest that the direction of approach might influence the deviation of the subjective midpoint on the attended segment of the line. Some version of the scantrack model might thus be applicable, though it would need to be a radical modification of the original model (McIntosh, 2006). The perceptual competition hypothesis (Marshall and Halligan, 1990; Anderson, 1996) refers, to a biased competition between the two halves of the line with the right part being subjectively perceived as longer than the left part. The competition hypothesis predicts greater rightward displacements under perceptual than imagery conditions in neglect patients. This perceptual asymmetry might be related to a bias in attentional orienting, favoring rightward movements of attention, impairing leftward orienting, or both (see Bartolomeo and Chokron, 2002 for review). Such a rightward attentional bias might increase the perceptual salience of the right portion relative to the left portion of the line (Anderson, 1996; Bultitude and Aimola Davies, 2006). Thus, in line bisection the right and the left portions of the line would compete with each other until the point of subjective equality is reached. In USN, competition would be biased thus causing the length of the right portion to be overestimated with respect to the left portion, which would in turn bias the patient's response rightward. The crucial difference between the competition hypothesis and the anisometry hypothesis (Bisiach et al., 1996) that was described in section 1.2.1 is

the contribution of the right portion of the line to the final performance. According to the competition hypothesis, the right portion of the (virtual or physical) line has an obvious importance in shaping performance, which is based on a perceptual comparison between the two subjective portions of the line, whereas for the anisometry hypothesis the presence or absence of the right portion should not influence the performance, which results from a distortion of the relative spatial coordinates (e.g. Ishiai et al., 2000). Urbanski and Bartolomeo (2008), have provided evidence that right overestimations are highly dependent on competition between horizontal segments on the two sides of space; the authors concluded that the right-sided portion of the line is of crucial importance in determining rightward deviations in patients in line bisection, consistent with the biased competition hypothesis and with neurocognitive models of attentional orienting.

Kinsbourne (1993) proposed that USN may limit the capacity to attend simultaneously to locations on both sides of space, rendering the patient incapable of making a normal bisection judgment. He accounted both rightward and leftward errors as due to the inability of the patients to sustain a concurrent awareness of both ends of the line, and thereby judge its length, a rightward or leftward error could result depending on how far left the patient moves before placing their transection (Ishiai et al., 2001). Koyama and collaborators have suggested that severe neglect patients strategically transect at a constant distance from the right endpoint of the line and entertained the possibility that the left and right endpoints of the line have differential influences on neglect behavior (Koyama et al., 1997). McIntosh and collaborators (2005) introduced a novel framework for describing and understanding line bisection behavior, the endpoint weightings approach, which does not rely on the assumption that the subjects perform the task by estimating the midpoint. The endpoint weightings analysis is an accurate quantitative model of bisection behavior, but as the authors acknowledge it does not explain more than the previous models having the errors as dependent variable. However, it is thought to be more parsimonious than the standard description as the latter use directional error as its dependent variable, and thus assumes that the bisection response is made at the subjective midpoint of the line. McIntosh and collaborators (2005) data show that it is possible to consider the two endpoints of the line as having independent influences upon the placement of the response. This can be expressed in terms of a weighting for

each endpoint — the proportion of the change in endpoint location that is reflected in the response. Within this new framework, some patients with left visual neglect appear to be entirely uninfluenced by the location of the left endpoint of the line, responding exclusively with reference to the right endpoint. In less severe cases, the left endpoint does have a reliable influence, but this is almost always less than that of the right. An index of the asymmetry between the weightings was found to distinguish neglect patients reliably from healthy controls, as well as being sensitive to a slight leftward bias amongst controls. The endpoint weightings approach provides a unified explanation for the effects of line length and spatial position using the single explanatory entity of an endpoint weighting. McIntosh and collaborators' (2005) study shows that it is possible to develop a quantitative description of neglect performance in which line bisection data can be modeled accurately without assuming that the subject maintains any overview of the bisection stimulus or necessarily perceives a subjective midpoint, consistent with Koyama et al.'s claim that patients with severe neglect bisect without regard to the left endpoint (Koyama et al., 1997).

More Recently, Charras and Lupiáñez (2010) by using a line extension task, in which a vertical line was centrally displayed on a sheet of paper, and by asking participants to trace a horizontal segment, perpendicular to the vertical (L shape) either on the left or right side, showed that performance of USN patients was biased on the left side, consistent with a left underestimation, but identical to controls on the right side. With this novel methodological approach the authors showed that it was possible to dissociate the relative roles of left underestimation and right overestimation in the left-right imbalance characteristic of neglect. However, even though the ipsilesional visual field is sometimes considered as being “intact”, it is important to underline that right-sided stimuli are not correctly or normally processed, but can rather be over-enhanced or over-prioritized (Kinsbourne, 1993; Bartolomeo and Chokron, 1999; Bartolomeo et al., 1999; Snow and Mattingley, 2006), and it has been shown that the right half (Urbanski and Bartolomeo, 2008) is relevant in determining the bias in USN patients when the two segments are in competition. Charras et al., (2012) using the same approach of previous study (Charras and Lupiáñez, 2010) aimed to dissociate the relative contribution of the left and right biases. To do so, in addition to Ls configurations, they introduced configurations in which there was a *competition* between the stimuli (e.g Ts and Xs configurations in

which the vertical line remained centrally presented but horizontal lines were bisected, either symmetrically or asymmetrically such that one part falls in the left side of space and the other in the right side)¹. The authors were also able to test the role of left-right competition in the case of vertical emphasis (with the T configurations), or of horizontal emphasis (in the X configurations). Indeed, previous studies in normal participants had revealed that vertical lines are slightly overestimated as compared to horizontal lines in the left and right Ts, whereas horizontal lines are overestimated as compared to vertical lines in the left and right Xs (Charras and Lupiáñez, 2009, 2010). The participants of the 2012 study were asked to compare a vertical segment to a horizontal segment in each of the 3 configurations (L, T and X). Their results showed that across all three configurations, left-sided lines were under-estimated. Concerning the other component, i.e. the over-estimation of the right-sided lines, the pattern was different depending on the configuration because for the T configurations the vertical overestimation prevented the left-right horizontal integration, while for the X configurations, that involved a left-right horizontal competition and integration, the data showed right overestimation. The authors concluded that this right over-estimation contributes to patients' biased performance. Indeed, it seems that in patients, the left-right competition weakened the left bias (the horizontal underestimation in the left X configuration is smaller than in the left T or L configurations), but produced a right over-emphasis (the horizontal line is largely overestimated in the right X). Taken together their results showed that each side of the line could reflect opposite biases (underestimation and overestimation) and that those depend on opposite hemispheres. Their results indicate that, in contrast to the right distortion, the left distortion occurs independently of left-right competition. The authors propose distinct neural bases for right overestimation, resulting from the activity of an isolated left hemisphere, and left underestimation, dependent on impaired functioning of right-hemisphere attentional networks.

From the evidence reviewed above a common denominator is the relevance of the *right side* (McIntosh et al., 2005; Urbanski and Bartolomeo, 2008) in determining the rightward bias in line bisection in USN patients.

¹ Please note that what is defined "X configuration" does not match with the actual shape that resembles a "+".

We can see that despite the popularity and apparent simplicity of this task the reason for this pathological rightward error in line bisection is far from being simple. It has even been debated whether pathological bisection errors should be considered as part of the neglect syndrome at all, given its poor correlation with other typical tests as target cancellation (Halligan and Marshall, 1992; Ferber and Karnath, 2001) and drawing tasks (Bisiach et al., 1976; Schenkenberg et al., 1980). However, the line bisection task has been largely employed not only in pathological populations but also in healthy individuals mostly with the initial aim of providing a control group for USN patients. Studies of line bisection in healthy individuals have led to the knowledge that visuospatial cognition is inherently asymmetric in a direction that is opposite to the rightward bias exhibited by USN patients. This leftward asymmetry in healthy individuals has been termed pseudoneglect.

1.2.3 PSEUDONEGLECT

Healthy subjects show a bias towards the left side when judging the midpoint of a horizontal line (Bowers and Heilman, 1980). The first observation of this phenomenon what we today know as “pseudoneglect” was probably made at the beginning of the last century when Liepmann and Kalmus (1900) observed that healthy subjects systematically misjudged the center of a line if they assessed it monocularly. The leftward bias exhibited by healthy subjects is of a much smaller magnitude than the rightward bias shown by USN patients, millimeters in healthy and up to a few centimeters in patients, but it is nevertheless a robust and consistent phenomenon that can be behaviorally quantified (Turnbull and McGeorge, 1998). When it was first defined, researchers used the term pseudoneglect to describe leftward biases on line bisection and other visuospatial judgment tasks (Nicholls et al., 1999). Nowadays, the term pseudoneglect refers to the general tendency in healthy people to preferentially attend to the left side of space (Hatin et al., 2012). Interestingly the presence of pseudoneglect is not limited to humans, as it has also been shown for example in chickens (Regolin, 2006) and pigeons (Diekamp et al., 2005), but it has not been proven in non-human primates yet.

Pseudoneglect has also been shown at a representational level, i.e. mentally representing a stimulus or exploring a stimulus using touch in the complete absence of

direct visuospatial processing (see Brooks et al., 2014 for a review). Similar to the famous study in USN patients (Bisiach and Luzzatti, 1978), McGeorge and colleagues (2007) asked healthy participants living in Milan (Italy) to imagine the Piazza del Duomo and describe the landmarks on each side of the square from two opposite viewing perspectives. They found that more landmarks were reported from the left side of the image than from the right, irrespective of the participants' viewpoint. Similarly, other authors documented a significant tendency (Friedman et al., 2012) or non-significant trend (Bourlon et al., 2011) to report more elements from the left-hand side when healthy participants mentally described landmarks on a map. Bowers and Heilman (1980) were among the first to demonstrate that young participants bisected wooden rods in the absence of vision significantly leftward of the true center when using the index finger of either hand. Further evidence for a purely representational form of pseudoneglect comes from the fact that early blind participants also display leftward biases on the tactile rod bisection task (Cattaneo et al., 2011b). Pseudoneglect is also present for the *mental number line* task, which involves the mental representation of small and large numbers (Longo and Lourenco, 2007), and for mental alphabet lines (Nicholls and Loftus, 2007). Empirical observations have indicated that smaller numbers are typically represented on the left side of space and larger numbers on the right side of space (for a review see Hubbard et al., 2005; Umiltà et al., 2009; but also Gevers et al., 2010).

As well as for neglect patients, these inherent horizontal asymmetries in healthy subjects, as measured by line bisection task, interact with several factors like stimulus length and azimuthal stimulus placement, even if different studies show contradictory results. We can say that with left hemispace presentation leftward error or larger leftward errors were reported as compared with center or right hemispace presentation (Reuter-Lorenz et al., 1990; Milner et al., 1992; McCourt and Jewell, 1999). Manning and collaborators (1990a) reported that leftward error magnitude increases as a function of line length, and McCourt and Jewell (1999) found rightward errors with short lines and leftward errors with medium and long length lines. Halligan and collaborators (1991) found that their subjects erred leftward when bisecting with the left hand and erred rightward when bisecting with the right hand, with the error increasing as a function of line length. Line length has also been shown to interact with the position where the line is presented since the error magnitude

increased with line length, but to a greater degree in left hemispace presentations than in right hemispace presentations (i.e. in the left and right hemispace conditions, but not in the midline condition, leftward error increased with line length) and Nichelli and collaborators (1989) reported errors in the direction opposite to the hemispace of line presentation, with the error magnitude increasing as a function of line length. However other studies failed in showing significant modulation of performance based on line length and/or report no effects of lateralized spatial presentation (see Jewell and McCourt, 2000 for a review). Sampaio and Chokron (1992) found no significant effects of stimulus length in a kinesthetic task or in a tactile task when subjects used their left hand, but an effect was found in the tactile task when subjects used their right hand. When subjects used their right hand they tended to err to the right of veridical center and this effect increased as a function of line length, and Laeng and collaborators (1996) found that subjects erred rightward with very short rods, but erred leftwards when bisecting long rods.

Other variables, as mostly shown by line bisection performance, modulate pseudoneglect in its magnitude and presence (Jewell and McCourt, 2000). There are a number of factors known to affect how neurologically healthy individuals perform line bisection tasks. For example, cuing the left side of the line with a letter that must be attended to induce a leftward bias, whereas rightward cueing induces a rightward bias, and reduces pseudoneglect (Milner et al., 1992). Scanning direction also modulates rod bisection: starting to explore the line from the right-hand side, significantly enhances pseudoneglect and again the bias interacts with age (see Brooks et al., 2014 for a review on representational pseudoneglect). Performing the task with the left hand leads to a greater leftward bias, whereas completing the task with the right hand reduces it (see Jewell and McCourt, 2000 for a review). The typical tendency to bisect or judge the center of a line to the left of center also becomes less manifest, or disappears, with age (Jewell and McCourt, 2000; Failla et al., 2003; Schmitz and Peigneux, 2011). Sex differences have not been unanimously shown to play a role in line bisection; for example, two studies that did report gender effects produced opposite results: Wolfe (1923) found that females erred more to the left than males, whereas Roig and Cicero (1994) found the reverse. Concerning the rod bisection, in young participants there was not a significant pseudoneglect bias, but there was a significant effect of gender with females showing a greater leftward bias

than males (Brooks et al., 2014). Also time has been shown to modulate line bisection performance. Continuing to do a task, e.g. for 60 minutes, diminishes (or even reverses) pseudoneglect on a perceptual line bisection task – time on task effect (Dufour et al., 2007; Benwell et al., 2014). Pseudoneglect is thus attenuated, or shifted rightward, with decreasing alertness or increasing fatigue over time (Dodds et al., 2008, 2009; Newman et al., 2013). Consistently, the left spatial bias exhibited by healthy subjects is also modulated by sleep deprivation as shown by a rightward modulation in perceptual line bisection performance (Manly et al., 2005). Also motor activation can modulate cognition, such a pointing task in an asymmetric part of space (mimicking the optical displacement while wearing prisms) has been shown to modulate performance on both manual and perceptual line bisection (Dupierrix et al., 2008). Similarly Herlihey and collaborators (2013) showed that 5min of lateralized pointing modulates performance on the hierarchical figures task (Navon task) as a function of pointing direction (interference from irrelevant global information increased after pointing to left side of space and decreased after pointing to the right side of space). Tapping in the left side of space increases pseudoneglect in mental number line, and tapping to the right reduces this bias (Cattaneo et al., 2011a), but not free-viewing perceptual asymmetry without action (Nicholls et al., 2001). To sum up, these modulations suggest that visuospatial biases are influenced by tasks that affect the relative level of activation of the hemispheres.

Importantly, significant individual differences have been noted in a majority of line bisection studies (see Jewell and McCourt, 2000 for a review). Manning and colleagues (1990b) specifically examined the issue of individual differences and reported that some subjects erred rightward while others leftward, with between-subject variability in error magnitude being quite large. If some subjects make consistent leftward while others consistent rightward bisection errors, the proportion of these so-called 'left-shifters' and 'right-shifters' in a particular experiment could potentially affect the results. A recent study has shown that, depending on an initial pseudoneglect bias, participants directionally modulated their performance over time; i.e. participants with an initial leftward bias in a landmark task showed a significant rightward shift over the course of the experimental session, whereas participants with an initial rightward bias shifted leftward (Benwell et al., 2014). The authors argued that this asymmetry in shifts induced by time-on task effect along with the differences

in initial biases (pseudoneglect presence or absence) could reflect different observer subtypes, with diverging behavioral patterns and possibly driven by differences in brain organization and/or lateralization (Benwell et al., 2014), although one subsequent study has casted some doubts about the authors' conclusion (see Discussion section 5.2.2).

From the reported evidence we clearly see that both the pseudoneglect phenomena and USN are characterized by an important variability of performance in both populations. Nevertheless, the presence of pseudoneglect is a well-established phenomenon in healthy subjects. It is a consistent visuospatial bias shown by a healthy population that not only interests researchers for the understanding of basic visuospatial cognition, but also because it can possibly represent the opposite expression of the rightward bisection bias typical of USN. Understanding visuospatial function and its modulation in intact brains may thus help to shed light on the USN pathology *per se*.

1.2.3.1 *The theoretical origin of pseudoneglect*

Possible candidates for explaining the origins of visuospatial lateral biases such as those described so far have been traced back to some culturally inherited habits such as scanning direction and reading direction. The scanning hypothesis, put forward by Manning and collaborators (1990b), who investigated the variability in line bisection in healthy participants, proposes that the direction in which an individual scans visual space biases attention to the side of space on which the scan originated. Although some studies of line bisection support the scanning direction hypothesis (Chokron and Imbert, 1993; Brodie and Pettigrew, 1996; Chokron et al., 1998), others have failed to find an effect of scanning direction on line bisection and free-viewing perceptual asymmetries, another putative measure of pseudoneglect; (McCourt and Olafson, 1997; McCourt and Jewell, 1999; Nicholls and Roberts, 2002). Roman and colleagues (2013) showed that the direction of reading of a language determined the direction of recall in bilingual Arabic-Spanish speakers - Spanish reproduced aural-verbal arrays in a left-right order and Arabic in a right-left direction. Although reading direction can have an impact on visual line bisection (Chokron and Imbert, 1993; Zivotofsky, 2004), experiments that directly tested this issue report evidence of a leftward bias

even when scanning behavior and preferred reading direction are directly controlled (Nicholls and Roberts, 2002). Also the impact of the strategy used on visual bisection tasks has been directly tested. In the ‘greyscales’ task Nicholls and collaborators (2005) failed to report a specific effect of the strategy used, similar to Varnava and Halligan’s (2009) study, in which the strategies used by 140 participants in a line bisection task were reported, and revealed that participants deviated leftward regardless of their strategy.

It seems, therefore, that the orienting of attention towards the left side of a stimulus is an automatic and involuntary process; neither scan direction, nor reading direction, nor strategy fully account for the leftward lateral bias.

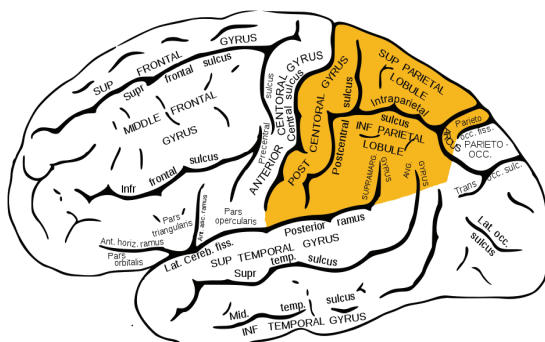
An hypothesis accounting for data on the visual line bisection task is the activation orientation theory (Reuter-Lorenz et al., 1990). The activation orientation theory posits that more attention is given to the side of space contralateral to the more activated hemisphere (Reuter-Lorenz et al., 1990; Kinsbourne, 1993; Bultitude and Aimola Davies, 2006), implying that the leftward attentional biases of pseudoneglect are related to stronger activation of the right hemisphere (RH). The first critical assumption of the activation orientation theory is that the RH controls the orienting of attention toward the left visual field, and thus pseudoneglect is thought to result from the strong contralateral attentional orienting exerted by the right hemisphere specifically in this part of visual space. Accordingly, as Reuter-Lorenz and collaborators (1990) reported, the presentation of lines within the left visual field induced pseudoneglect whereas right visual field presentation attenuated or reversed the bias. The second critical assumption is that the leftward orienting of attention by the RH leads to the perception of the left portion of a stimulus as being longer than the right portion. There is some evidence supporting this assumption, as lateral cueing to the left or right end of a line, prior to the bisection, leads to left- and right-ward shifts in the perceived mid point, respectively, suggesting that the cue biases attention towards one portion of the line, which then results in that portion being perceived as longer (Bultitude and Aimola Davies, 2006). The activation-orientation hypothesis explains pseudoneglect in line bisection as resulting from an uneven distribution of attention; more attention is given to the left side of space than to the right side because the (visuospatial) nature of the task itself makes the RH more active than the LH. Indeed, completion of the line bisection task appears to consistently involve activation

of the right inferior parietal (IPL) cortex (Fink et al., 2000a; Foxe et al., 2003; Billingsley et al., 2004). This theory can also account for modulation of performance by factors such as cuing and hand use, factors that can affect which hemisphere is most active (Jewell and McCourt, 2000), such as using the right hand to bisect a line would increase LH activity, resulting in drawing more attention to the right side of space and therefore reducing pseudoneglect.

1.3 THE NEURAL UNDERPINNING

1.3.1 VISUOSPATIAL COGNITION

The parietal cortex is situated at the intersection of visual, auditory, and tactile cortices at the ‘crossroads of the brain’ (Critchley, 1953), and has a crucial role in transforming sensory inputs into motor outputs. In the course of doing so, a host of cognitive computations are engaged including spatial representation and updating, attention, coordinate transformation, as well as motor planning (Culham, 2002). The involvement of the right parietal cortex in visuospatial cognition is supported by an abundant literature from classical and modern neuropsychological approaches in neglect patients (e.g. Heilman and Van Den Abell, 1980; Vallar and Perani, 1986; Mort et al., 2003; Buxbaum et al., 2004; Farnè et al., 2004), as well as virtual lesion approaches with transcranial magnetic stimulation (TMS) (Fierro et al., 2000; Hilgetag et al., 2001; Brighina et al., 2002; Müri et al., 2002; Valero-Cabré et al., 2006; Rounis et al., 2007).



(Lewis and Gray, 1918)

Figure 1: The most anterior part of the parietal lobe is the postcentral gyrus (Brodmann area, BA 3) i.e. the primary somatosensory cortical area, which is separated from the posterior parietal cortex by the postcentral sulcus. The posterior parietal cortex is subdivided into the superior parietal lobule (SPL) (BA 5, 7) and the inferior parietal lobule (IPL) (BA 39, 40), and those are separated by the intraparietal sulcus (IPS).

Much less is known about human parietal cortex than that of homologous

monkey cortex, but recent studies, employing neuroimaging and neuropsychological methods, have begun to elucidate increasingly its fine-grained functional and structural distinctions (Behrmann et al., 2004; Shomstein, 2012).

As I describe in section 1.2 Walsh (2003a) proposed that the organization of the inferior parietal cortex reflects the common need for space, time and quantity information. The fact that number selective neurons ('numerons') have been shown to exist in the cat (Thompson et al., 1970) and monkey (Sawamura et al., 2002) brain anatomically supports his hypothesis. Indeed, the presence of neurons selective for numerical quantity has been reported by recordings in the upper bank of the IPS and the superior parietal lobule in the macaque (Nieder et al., 2002; Sawamura et al., 2002), and in the prefrontal cortex (Nieder et al., 2002; Walsh, 2003b). As well as temporal attention mechanisms have been located in the right and left parietal cortex (Tracy et al., 2000; Rao et al., 2003), the right and left dorsolateral prefrontal cortex, the cingulate cortex, and the visual cortex (Ghose and Maunsell, 2002; Macar et al., 2002).

The right PPC is shown a crucial neural correlate of line bisection tasks. In a series of fMRI experiments in healthy subjects Fink and colleagues (2000a) found that the right superior posterior parietal cortex (BA 7), right inferior parietal cortex (BA 40), cerebellar vermis, left cerebellar hemisphere (irrespective of the hand used to answer), and both bilateral striate and extra striate cortices, were activated in the Landmark task in which the participants were asked to judge whether the line was properly bisected or not (binary choice). In a further study, and consistent with the results of lesion studies (Vallar, 1993), the role of right inferior parietal cortex as a key structure in the line bisection judgment task has been furthered confirmed (Fink et al., 2000b). It can be argued that the left cerebellar hemisphere activation in Fink and colleagues (2000a) may be associated with the right parietal activation simply by reflecting increased neural computations in the right parietal cortex that then "overflow" into (left) cerebellar regions via direct parieto– cerebellar connections (Brodal and Bjaalie, 1997). However, Fink and collaborators (2000a) argued that this explanation is unlikely, since other areas directly connected with the right parietal cortex (e.g., premotor or prefrontal areas (Cavada and Goldman-Rakic, 1989)) did not show a corresponding (lateralized) activation. The authors propose that activation of

the left cerebellar hemisphere during the Landmark task may rather reflect a role of the left cerebellar hemisphere in visuospatial functions.

Fink and collaborators have also investigated the possible influence of (different) task instructions, i.e. of the cognitive strategies used to perform the task, and showed that instructions can have a modulatory effect on the neural mechanisms underlying task performance (Fink et al., 2002). They compared brain activation in healthy volunteers who were asked whether a) segments on either side of the transection mark were of equal length (instruction stressing line length comparisons) versus (b) whether the transection mark was in the center of the line (instruction stressing centrality judgments). The authors found activity in the inferior parietal lobes bilaterally and the right temporo-occipital cortex for both strategies, whereas explicit length comparisons differentially activated left superior posterior parietal cortex with a tendency toward activation of the equivalent area on the right; suggesting that explicit comparisons of spatial extent were implicated in this strategy. The differential activation of bilateral occipital cortex following center judgments suggests that the center of a line is extracted at an early stage of visual processing. The bilateral activation of superior parietal cortex when participants received instruction to compare the lengths of two ‘objects’ (the extent to the left and to the right of the transection mark) was explained by the authors as a demand of endogenous (voluntary) attentional shifts between the two lines (Corbetta et al., 1993; Fink et al., 1997; Corbetta and Shulman, 1998). The reverse comparison in which the instruction stressed whether the transection mark is centrally placed, instead shows significantly increased activity in the lingual gyrus bilaterally (relative to the line length comparison condition) and this activation in early visual processing areas suggest that the strategy involved may emphasize some kind of relatively primitive judgment of ‘balance’ (Bingham and Muchisky, 1993) or symmetry (Driver et al., 1992; Marshall and Halligan, 1995).

In a more recent fMRI study, Çiçek and colleagues found that RH-lateralized processes are predominantly engaged during both perceptual and manual line bisection tasks in normal subjects; the intra-parietal sulcus and lateral peristriate cortex metabolic activity (BOLD) was lateralized to the right during both tasks (Çiçek et al., 2009). In another study, Foxe and colleagues used high-density event-related potentials (ERP) to investigate the neural processes involved when healthy subjects

perform the perceptual line bisection task and recorded a robust net negative potential (from 170–400 ms post-stimulus presentation) that correlated with line-bisection judgments (Foxy et al., 2003). The topographical mapping showed three distinct phases of negativity; in the first phase (170–190 ms) this negative potential was exclusively distributed over the right parieto-occipital and lateral occipital scalp, in the second phase (190–240 ms) a second negative focus emerges in the right central parietal scalp, consistent with subsequent involvement of right superior parietal cortices, and in the third phase (240–400 ms) the topography became dominated by this right central parietal negativity. Furthermore the inverse source modeling confirmed that RH lateral occipital, inferior parietal, and superior parietal regions were the likeliest generators of this activity. Further evidence of the right parietal cortex as a crucial structure for line bisection tasks come from TMS studies in which stimulation/disruption of the right inferior parietal cortex only modulated line bisection judgments in healthy subjects (Fierro et al., 2000; Brighina et al., 2002). Furthermore, intraoperative electrical stimulation of the right inferior parietal lobule or the caudal superior temporal gyrus, but not of its rostral portion, can induce rightward deviations on line bisection (Thiebaut de Schotten et al., 2005).

Doricchi and collaborators (2005) have shown a dissociation between mental number line and physical line bisection in neglect patients with a lesion overlap approach. Their data show that comparative judgments of numeric quantities activate bilaterally the horizontal segment of the intraparietal sulcus, the left precentral gyrus, and, depending on task, prefrontal areas (Dehaene et al., 2003, 2004; Walsh, 2003a), while clinical (Doricchi and Angelelli, 1999b), imaging (Fink et al., 2000a) and TMS (Fierro et al. 2000) data demonstrate that physical line bisection depends on the striate, and extrastriate visual cortex, the inferior and superior parietal lobes, with marked lateralization in the right hemisphere.

1.3.2 VISUOSPATIAL ATTENTION

A network of areas in the posterior parietal cortex (PPC) and prefrontal cortex (PFC) has been implicated in the control of both spatial and nonspatial deployments of visual attention) (Corbetta et al., 1991; Kastner and Ungerleider, 2000; Vandenberghe et al., 2001; Corbetta and Shulman, 2002; Yantis et al., 2002; Giesbrecht et al., 2003;

Serences et al., 2004). The PPC is crucial for visually guided behavior (Andersen and Buneo, 2002) and in mediating shifts of spatial attention (Corbetta et al., 1991; Vandenberghe et al., 2001; Yantis et al., 2002; Bisley and Goldberg, 2003).

Corbetta and Shulman (2002) propose a model that includes and updates elements of previous models: the parietal and frontal cores of the attention network of Mesulam's model (1999), the 'orienting' function of Posner's posterior attention system (Posner and Petersen, 1990), and the hemispheric model competition proposed by Kinsbourne (1993). Corbetta and Shulman model hypothesizes that the neural sources of spatial attention are controlled by two partially segregated but interacting neural systems: the dorsal and ventral fronto-parietal networks. The dorsal fronto-parietal network, which is centered in the dorsal posterior parietal (SPL) and frontal cortices, is involved in the cognitive selection of sensory information, whereas the ventral fronto-parietal network, which is largely lateralized to the RH and is centered in the temporo-parietal and ventral frontal cortices, is recruited during the detection of behaviorally relevant sensory events, particularly when they are salient or unattended (Corbetta and Shulman, 2002). The ventral network may serve as an alerting system that detects behaviorally relevant stimuli in the environment, and once a relevant stimulus is detected, its precise localization depends on the dorsal system. A related hypothesis is that the ventral system acts as a circuit breaker of ongoing cognitive activity when a behaviorally relevant stimulus is detected. When subjects detect a low-frequency or unexpected event, they must break the current attentional set and adopt a new one on the basis of this incoming stimulus.

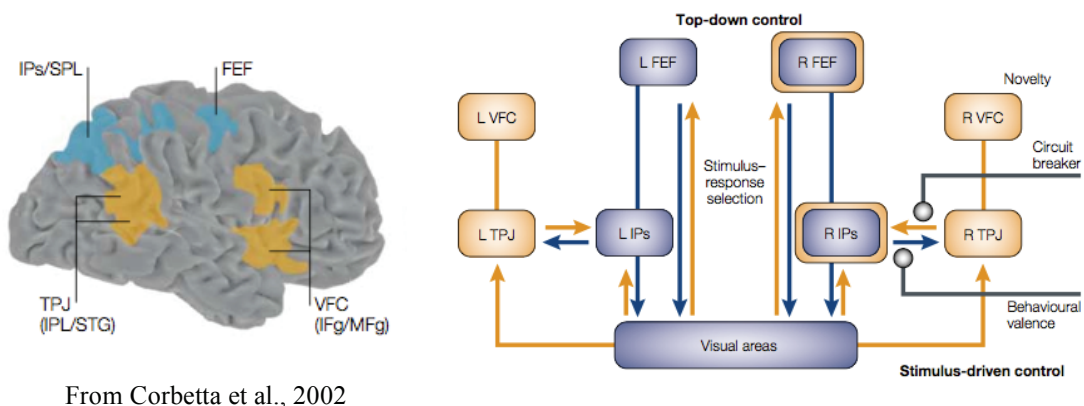


Figure 2: Dorsal and ventral fronto-parietal networks.

The dorsal fronto-parietal network (Areas in blue) includes frontal eye field (FEF) and intraparietal sulcus/superior parietal lobule (IPs/SPL). The stimulus-driven ventral fronto-parietal network (Areas in orange) includes the temporo-parietal junction (TPJ), inferior parietal lobule/superior temporal gyrus (IPL/STG), ventral frontal cortex (VFC) and inferior frontal gyrus/middle frontal gyrus (IFG/MFG). The anatomical model of top-down and stimulus-driven control suggests that the IPs–FEF network is involved in the top-down control of visual processing (blue arrows). The TPJ–VFC network is involved in stimulus-driven control (orange arrows). The IPs and FEF are also modulated by stimulus-driven control. Connections between the TPJ and IPs interrupt ongoing top-down control when unattended stimuli are detected. Behavioral relevance is mediated by direct or indirect (not shown) connections between the IPs and TPJ. The VFC might be involved in novelty detection. (From Corbetta and Shulman, 2002).

Functional magnetic resonance imaging (fMRI) studies have documented that bottom-up attentional capture, if mediated by stimulus salience and/or relevance, is subserved by the temporo-parietal junction (TPJ), when the stimulus change occurs in the modality that is relevant to the current behavior and in response to potentially novel (unexpected or infrequent) stimuli, and when engaged in a neutral behavioral context (i.e. not performing a specific task) (Downar et al., 2001, 2002). Given the multisensory attentional role played by the TPJ, this activation is modality independent (auditory, tactile, visual) (Behrmann et al., 2004). The superior parietal lobule (SPL) and the precuneus (PC) are instead engaged when the attention is deployed in a top-down or goal-directed (Yantis et al., 2002; Yantis and Serences, 2003). In a typical task, individuals are shown two streams of input presented peripherally to the left and right of fixation and are initially instructed to monitor one stream for a cue (a digit among the stream of letters). The identity of the cue indicates to the subject whether they should maintain attention on the current stream or shift attention to the other stream. An increase in activation in extra striate cortex was observed when attention was shifted to the contralateral visual field, as compared to when attention was maintained on the contralateral visual field. Similarly, activity in extra striate cortex decreased following a shift of attention to the ipsilateral visual field and remained relatively low when attention was maintained on the ipsilateral target (Yantis et al., 2002; Yantis and Serences, 2003). The same authors (Yantis et al., 2002; Yantis and Serences, 2003) showed that both the right SPL and inferior parietal lobule (IPL) were transiently active when attention was shifted between spatial locations, as compared to the condition in which subjects remained focused, suggesting that the SPL is not the source of a continuous signal to actively maintain

the attentive state but the source of a brief attentional control signal to shift attentive states. Moreover, SPL is reported activated not only on shifting between spatial location but also between any two dimensions of the input (for example, shifts between superimposed houses and faces, two different features of an object, or two different sensory modalities), whereas non-spatial shifts are specifically accompanied by increased activity in the precuneus region (which is the continuation of the SPL on the medial side of the parietal lobe) (see Behrmann et al., 2004 for a review).

1.3.3 USN

Even though the first lesion localization reports of patients affected by USN date to the second half of the 1800's (Pick, 1898), it was only in the half of the 1900's that USN was systematically associated with right parietal damage. The 1941 description of the British neurologist Dr. Brain, who reported three patients with unilateral

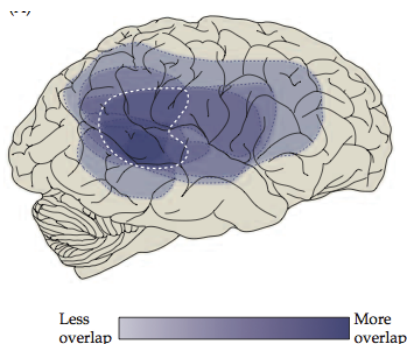


Figure 3 Composite of the location of the underlying lesions in 8 USN patients. The site of damage was ascertained from CT scans (see Box B in Chapter 1). While the lesions include parietal cortical areas, frontal areas, and the temporal lobe of the right hemisphere, the region of the right parietal lobe indicated by the dashed line is most often affected. (From Purves, 2004).

parietal lobe lesions affected by varying degrees of attentional deficits, is generally considered to be the first explicit link between parietal lobe lesions and deficits in attention or perceptual awareness - USN.

USN is most commonly thought to follow lesions to the right inferior parietal lobe (IPL) (Friedrich et al., 1998; Vallar, 1998; Bartolomeo and Chokron, 2002; Halligan et al., 2003). However, Karnath and collaborators (2004) have argued that the right superior temporal gyrus (STG) is the cortical area most associated with USN, and also argued that subcortical sites such as the putamen and the caudate nucleus

within the basal ganglia, the pulvinar within the thalamus, are relevant for neglect. However, since these subcortical areas have connections with many cortical regions, including the parietal and occipital lobes, this does not unequivocally support the STG as the natural cortical component of the neural network involved in neglect

(Behrmann et al., 2004). This idea is supported by Mort and collaborators who showed with a MRI study that 14 out of 14 USN patients, and only one control, had a lesion to the angular gyrus (Mort et al., 2003); thus reinforcing the idea that lesions to IPL are crucial in causing USN.

As we understand, the precise localization of the critical lesions causing USN still remains controversial. USN patients often have relatively large lesions of the right hemisphere, which are likely to disrupt several functional modules of a large-scale network rather than cortical modules, as demonstrated by the diverse nature of their symptoms (Bartolomeo, 2007). Doricchi and Tomaiuolo (2003) identified the superior longitudinal fasciculus (SLF) as the region of maximum overlap in a group of 10 USN patients (without visual field defect) and, in patients without subcortical lesions the rostral part of the supramarginal gyrus within the IPL was an additional region of maximum overlap. Thiebaut de Schotten, Bartolomeo, Doricchi and colleagues have emphasized the need to understand USN in terms of dysfunctional brain networks, and not solely in terms of the specialized functions of damaged tissue local to the stroke, suggesting that USN occurs when damage affects the anatomical connections and thus disrupts the functional interactions between parietal and frontal cortex (Thiebaut de Schotten et al., 2005; Bartolomeo, 2007). To date at least two tracts of the fronto-parietal network, that when damaged give rise to neglect symptoms, have been identified: a superior pathway inter-linking dorsal regions of parietal and frontal cortex, and a more inferior pathway connecting ventral parietal-frontal regions (Thiebaut de Schotten et al., 2005; He et al., 2007).

1.3.4 PSEUDONEGLECT

Multiple studies have shown a greater right versus left hemispheric activation during line bisection tasks (Cıçek et al., 2003, 2007, 2009). However, the idea that people with pseudoneglect over-attend to the left half of space because of an overall higher right-hemispheric activation as compared to the left, has only recently found empirical support from study by Simon-Dack and collaborators (2013) that investigated the relationships between resting interhemispheric brain activity (i.e. not during a task) and the presence of pseudoneglect. The authors showed a general

greater right middle frontal resting activation (across theta, beta, and gamma bands) in individuals with pseudoneglect on a perceptual line bisection task.

The results of a recent physiological study suggest that the right PPC does have a stronger inhibitory influence toward the contralateral homologous area in healthy subjects than vice versa (Koch et al., 2011), consistent with the idea of a default inter-hemispheric imbalance. They also found that the amount of inhibition exerted by the right PPC over the left PPC correlated with the amount of pseudoneglect (see also He et al., 2013).

However, a recent elegant multimodal approach study provides compelling evidence *for a control through competitive interactions between hemispheres, rather than a dominant RH in the intact human brain* (Szczepanski and Kastner, 2013 p.5411). Their data show how individual differences in the strengths of the fronto-parietal attentional weights in each hemisphere predicted subjects' respective behavioral preferences when allocating spatial attention, as measured by a landmark task (Szczepanski and Kastner, 2013).

Finally Benwell et al., (2014) using EEG technique investigated the neural correlates of line-length effect in healthy subjects. Their data showed that pseudoneglect was present during long line but not during short line bisection performance, and that the effect of line-length was associated with stronger right parieto- occipital responses as compared to short lines in an early time window (100–200 ms) post-stimulus onset. Given that this early differential activation for long as compared to short lines was task-independent (present even in a non-spatial control task not requiring line bisection but just the judgment of whether the line was bisected or not), the authors suggested that it may reflect a reflexive attentional response to long lines. Indeed the source-localizing analysis of the line-length effect was located in the right temporo-parietal junction (TPJ), and there was a positive correlation between the strength of this effect and the magnitude by which the long lines (compared to short ones) elicited the leftward bias across individuals. The authors concluded that left bisection bias is stimulus-driven and is associated with increased right hemispheric engagement of areas of the ventral attention network, therefore implicating that the level of activity of this network has a key role in the genesis of leftward spatial bias. Their data also show a later event localized in the right superior

parietal cortex, that this time was task-dependent (i.e. in spatial and not in no spatial control task) but irrespective of stimulus properties (line length) and uncorrelated with performance in line bisection; the authors related the involvement of SPL to the later decisional stage of task performance. Since these two distinct sources were both localized in the RH but differently located, the authors concluded that this dissociation might reflect different stages in task processing.

It is clear that visuospatial cognition is asymmetric as well as its neural correlates, with a clear dominance of the right hemisphere for spatial attention, reason why RH damage so frequently results in USN, but the link between higher activity in the RH during visuo-spatial tasks and pseudoneglect remains debated, as well as the causal link between the hyper-activity of the LH and USN.

1.5 TOOLS TO MODULATE AND INVESTIGATE VISUOSPATIAL COGNITION

Several methods have been used to alleviate USN, and a few of these have also been applied to healthy subjects with the aim of better understanding the functioning of the intact brain and in the hope of gaining insights into the possible neural origins and mechanisms of USN. The rehabilitation techniques or approaches that have been implemented to reduce USN symptoms can be classified as top-down (interventions that encourage awareness of the disability and potential compensatory strategies) or 'bottom-up' (interventions that do not require awareness). Despite the large body of research investigating treatment techniques for neglect (see Luaute et al., 2006 for a review), a recent evidence-based review including 23 randomized control trials demonstrated a lack of efficacy of existing rehabilitation approaches, with no consensus regarding the most effective technique (Bowen et al., 2013). The methods reviewed in Luaute and collaborators (2006) are summarized in **Figure 4**.

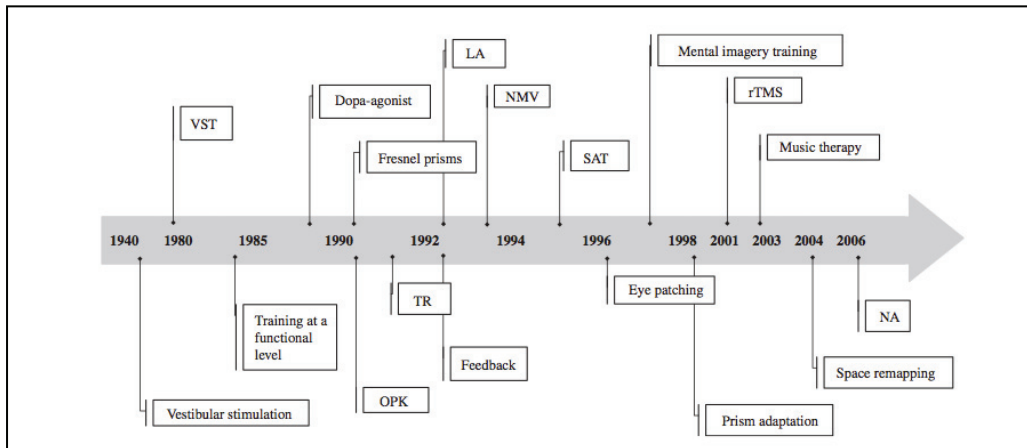


Figure 4: Time line of the first publication of the different attempts to remediate USN (from Luaute et al., 2006). Abbreviations: VST: visual scanning training; LA: limb activation; rTMS: repetitive transcranial magnetic stimulation; SAT: sustained attention training; OPK: optokinetic; NMV: neck muscle vibration; TR: trunk rotation; NA: noradrenergic agonist.

Top-down techniques include training on visual scanning tasks (VST) (Weinberg et al., 1977, 1979) and mental imagery training (Smania et al., 1997). However if we recall the fact that one of the hallmarks of USN is unawareness of the deficit (Vallar et al., 2003) it is maybe not surprising that these methods, which requiring a substantial commitment from the patient and awareness of the disability, are not very effective. Indeed, they rely on leftward voluntary orienting of attention using top-down (goal-driven/descending) strategies to enrich visual perception and monitoring (Pisella et al., 2006), functions that are only partially spared in most patients. It may even appear illogical to build a rehabilitation procedure around awareness and intention for patients with a deficit in consciousness: *‘The first step in the treatment of hemi-inattention is to make the patient aware of the problem. This is particularly difficult in hemi-inattention since this failure in awareness appears to be at the heart of the patient’s difficulty’*. This paradox was already identified in 1977 by Diller and Weinberg (1977 p.67; in Pisella et al., 2006). However since it is known that anosognosia contributes to poor outcome in USN patients, it has also been suggested that this problem needs to be addressed before implementing any training procedures (McGlynn and Schacter, 1989). With this in mind, feedback-training procedures, involving a bottom-up mechanism to produce the feedback (i.e. aimed at restoring self awareness) and a top-down mechanism to compensate for neglect behavior were developed (Ramachandran et al., 1999; Harvey et al., 2003). As argued by Harvey and collaborators (2003), all these approaches require the patients to voluntarily initiate

and maintain attention oriented to the left side, a demanding task on its own, as many patients find it difficult to do so in everyday life. To act on higher-level cognition and bypass the impaired conscious awareness and intention one should, at least in principle, find another entry route into space representation systems. One possible route is via bottom up techniques that aim to enhance automatic orientation toward left space without requiring language-mediated attentive orienting.

There are many different bottom up techniques; caloric vestibular stimulation (CVS), galvanic-vestibular stimulation (GVS) (see Utz et al., 2010 for review), vestibular stimulation (Ferrè et al., 2011a, 2011b, 2013), optokinetic stimulation (OKS) (Mattingley et al., 1994; Vicario et al., 2007), neck-muscle vibration (NMV) and trans-cutaneous electrical stimulation (TENS) (Karnath, 1995), trunk rotation (TR) (Schindler and Kerkhoff, 1997), limb activation (LA) (Wilson et al., 2000), and sustained attention training (SAT) (Robertson et al., 1995). Other bottom-up interventions involving vision have also been developed using Fresnel prisms (Rossi et al., 1990), eye patching (Barrett and Burkholder, 2006) and half-field patching (Beis et al., 1999; Zeloni et al., 2002).

Modulation of alertness has also been shown to affect pathological visuospatial biases (Robertson et al., 1998; Finke et al., 2012) and pharmacological treatments have been used in rehabilitation of USN, including a noradrenergic agonist (Malhotra et al., 2006), the efficacy of which is being still investigated and dopamine-agonists which ameliorate some classical signs of USN (Fleet et al., 1987; Gorgoraptis et al., 2012). USN is also temporarily improved by psychostimulants drugs and exacerbated by sedatives (Malhotra et al., 2006). While there is currently no consensus about the most effective treatment for USN the potential benefits of repetitive sessions and the combination of more than one of these techniques appear promising (Kerkhoff et al., 1992; Antonucci et al., 1995; Schröder et al., 2008; Thimm et al., 2009).

Two additional techniques used to modulate and investigate visuospatial cognition are prism adaptation (PA) and non-invasive brain stimulation (NIBS). These are explained in detail in the following paragraphs, as both are tools adopted in the present thesis to investigate intact visuospatial cognition.

1.5.1 NON-INVASIVE BRAIN STIMULATION TECHNIQUES - NIBS

Non-invasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) have recently received much attention (e.g., Miniussi and Vallar, 2011), and beyond being an invaluable research tool have emerged as potentially interesting rehabilitation tools (for a review see Fasotti and Van Kessel, 2013).

TMS is a non-invasive and painless technique for the investigation of cognitive functions and is based on Faraday's principles of electromagnetic induction discovered in 1831, (see Wassermann, 1998; Rossi et al., 2009; Lefaucheur et al., 2014 for general application guidelines). The stimulator delivers a large current in a short period of time; the current flowing in the TMS coil produces a magnetic field that lasts for less than a millisecond. This rapid magnetic field penetrates the scalp and induces an electrical field (current) sufficient to stimulate neuronal activity and change the stimulus dynamics of neuronal firing in the stimulated region.

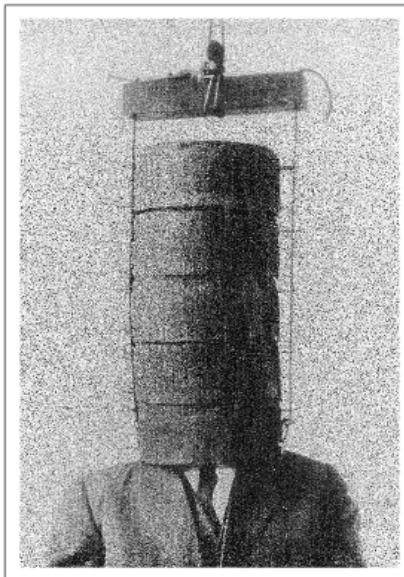


Figure 5: Example of early coil used by Magnusson and Stevens, 1911. (Form Walsh and Pascual-Leone, 2003)

Since the first successful experiment in 1985, when Barker and colleagues were able to elicit involuntary finger movements by stimulating the motor cortex, TMS has become a mainstay of cognitive neuroscience. It offers an approach that goes beyond the correlational description of the relationship between brain and behavior that is offered by different neuroimaging techniques (see Sandrini et al., 2011 for review). TMS allows the inference of causal relations between specific brain regions and individual cognitive functions (Robertson et al., 2003), whereas other imaging techniques provide correlational maps of cognitive processes in the brain with varying levels of temporal and spatial resolution (Walsh and Cowey, 2000).

Oliveri and colleagues (2001) were the first to demonstrate the reduction of the possible left hemisphere hyper-excitability in USN patients. They applied rTMS over the contralesional PPC (P5 or P6 position of the 10-20 EEG system - 400msec

trains of 10 stimuli at 25Hz) to seven USN patients (five with right brain damage and two with left brain damage). They delivered rTMS while pre-bisected lines appeared on the computer screen placed in front of the patients and found that, compared with both baseline and sham measurements, the stimulation of the unaffected/spared hemisphere transiently (i.e. during the stimulation) reduced errors in line bisection judgments (i.e. the magnitude of USN) in both right and left lesioned patients. After a single session of low-frequency 1Hz rTMS Koch and colleagues (2008) reported an improvement in the naming of chimeric figures for 12 right brain-damaged patients stimulated over the left PPC (P3 position of the 10-20 EEG system). Although the effects of rTMS seem to outlast the stimulation period, these effects are only transient and their therapeutic benefits seem limited. In animal research, long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength have been obtained with theta burst stimulation (TBS), which is a high- frequency stimulation that mimics the theta wave, a spontaneous 5–7 Hz neural rhythm (Abraham, 2003). This stimulation protocol was introduced to NIBS in an attempt to improve the duration of the after-effects. Several trains of TBS on the left PPC in 11 neglect patients increased the number of perceived left visual targets up to 32 h after the end of the stimulation (Nyffeler et al., 2009). A couple of years after the first study applying contralesional parietal rTMS to alleviate USN, Brighina and colleagues (2003) investigated whether repetitive sessions of rTMS could induce a long lasting amelioration of USN. They delivered seven sessions of low-frequency 1 Hz rTMS (900 pulses) over 14 days to the left PPC (P5 position on the 10-20 EEG system) of three right brain damaged USN patients. The strong rightward bias exhibited by these patients on the line bisection task was reduced immediately after the stimulation and the beneficial effect was still present 15 but not 30 days after the end of the treatment. Several other studies have followed, one example is a pilot study of two USN patients (Shindo et al., 2006) in which six sessions of rTMS delivered to the left PPC (P5 position of the 10-20 EEG system) over two weeks improved performance in two right hemisphere-damaged patients on several subtests of the Behavioral Inattention Test (BIT) up to 6 weeks after treatment. Another study Song and colleagues (2009) in seven USN patients showed that repetitive sessions of low-frequency rTMS (2 sessions of 15 minutes a day at 0.5 Hz on over two weeks -P3 position of the 10-20 EEG system) improved both line bisection and line cancellation and that this improvement lasted for two weeks. Interestingly, there was no decrease in performance between the end of

the treatment and two weeks after the end of the stimulation sessions. Finally, in another pilot study (Lim et al., 2010) the experimenters delivered 1 Hz trains of 900 pulses for 5 days a week for 2 weeks on the left PPC (P5 position of the 10-20 EEG system) of seven right brain damaged patients and found an improvement in line bisection but no gain in line cancellation. More recently it has been reported that 10 sessions of continuous TBS over a 2-week period on the left PPC of 18 neglect patients in the sub-acute stage improved BIT scores immediately after the stimulation and at 1 month follow-up (Koch et al., 2012). In a double-blind, sham-controlled experiment Cazzoli and colleagues applied four trains of TBS to the left PPC of 16 neglect patients over two consecutive days and reported improvement in spontaneous everyday USN symptoms and behaviors as measured by the Catherine Bergego Scale up to 3 weeks after stimulation. In contrast, the eight no-treatment (sham-stimulation) USN patients showed no change in the severity of their symptoms over a similar time period (Cazzoli et al., 2012). Agosta and colleagues tested six chronic patients using contralesional rTMS over the PPC (P3) and found that this relieved visual extinction in these chronic stroke patients (Agosta et al., 2014)

Despite studies showing that multiple stimulation sessions could bring promising and encouraging results, much more research is needed to establish the longer-term effects and generalization of the different treatments. It is also necessary to establish a unique method for quantifying the induced-amelioration in daily life (Fasotti and Van Kessel, 2013), and to fully consider the economic (and other factors) that may be decisive for introducing rTMS as a therapeutic option (Wassermann and Zimmermann, 2012).

So far the majority of NIBS studies targeting USN have aimed to inhibit the left hemisphere. However, a few study have tried to ameliorate USN by stimulating the lesioned (right) hemisphere. in a double blind, cross-over, sham-controlled experiment Ko and colleagues stimulated fifteen sub-acute stroke USN patients with anodal (positive stimulation) and sham tDCS stimulation in a counterbalanced and randomized order, with a 48-h interval between the two stimulation sessions (Ko et al., 2008). The results showed that Anodal tDCS applied to the right PPC (P4 in the international 10–20 EEG system) significantly improved performance in a figure cancellation and manual line bisection task immediately after stimulation. In a similar study, Sparing and colleagues stimulated ten USN patients over the PPC (P3 or P4 of

the 10–20 EEG system) with four different tDCS stimulation conditions each lasting ten minutes. They found that manual line bisection was the only task modified by the tDCS, and that patients improved on this task following both the cathodal (inhibitory) tDCS applied over the intact left PPC and anodal (facilitatory) tDCS applied over the lesioned right PPC (Sparing et al., 2009).

It has been demonstrated that single-pulse TMS in healthy brains can induce a transient disruptive effect in many cognitive tasks depending on the stimulated brain region. For example, interfering with the neural activity of the parietal cortex modulates the perception of contralateral tactile stimuli (Seyal et al., 1995; Oliveri et al., 1999). Using an interference approach, i.e. transiently disrupting cortical activity, several studies have tested the contribution of the intact posterior parietal cortex in spatial tasks. Right parietal (P6) rTMS (trains of 10 stimuli at 25Hz for 400 msec) synchronously triggered with the visual stimuli (line bisection task) presented on a computer screen induced a significant rightward bias in symmetry judgments, as compared with sham trains that were intermixed with the real stimulation to control for non-specific effects (Fierro et al., 2000). This study showed for the first time that transient disruption of right parietal cortex induced by focal rTMS induces a contralateral visuospatial ‘deficit’ in normal subjects tested with a perceptual line bisection task. Using an identical TMS protocol Brighina and colleagues disrupted activity in right frontal (F4) and right parietal areas (P4 of the 10–20 EEG system), (Brighina et al., 2002) and showed that rTMS applied synchronously with visual stimuli over both frontal and parietal areas induced neglect-like behavior. Since rTMS applied synchronously with visual stimuli over both areas induced significant perceptual biases (i.e. subjects made opposite errors in the two response conditions) and failed to elicit any response biases (i.e. the tendency to name the same side of the line in the two response conditions as happens in USN patients) this study highlights both the contribution of the frontal cortex to the induction of neglect-like behavior, thus its possible role in USN, as well as the predominant role of sensory perceptual factors in parietal and frontal areas. Taken together, these studies clearly show that focal rTMS over the right parietal and frontal areas of normal humans transiently disrupts cortical functions as captured by a perceptual line bisection task. The same group also used a single pulse approach to investigate the exact timing in which a TMS pulse modulated visuospatial cognition as measured by a perceptual line

bisection task (Fierro et al., 2001). A transitory rightward bias was observed when online single-pulse TMS was delivered on the right parietal but not frontal area (F4 P4 of the 10–20 EEG system), and this visuospatial modulation was present only when the stimulation was delivered 150 ms following the stimulus presentation, and not 225 ms or 300 ms after visual stimulus onset. With a similar approach Pourtois and colleagues (2001) interfered with performance on a visuospatial task (a landmark task), and showed a processing cost for ipsilateral targets when online single-pulse TMS was applied over the right PPC 50 ms post-stimulus. Similarly, by delivering TMS over the right parietal cortex some authors have found not only an *impairment* of performance contralateral to the stimulated hemisphere, such as a decrease of pseudoneglect, but also an enhanced performance ipsilateral to the induced “virtual lesion” in a task involving detection of either visual (Hilgetag et al., 2001) or tactile stimuli (Seyal et al., 1995).

NIBS techniques have also been shown to modulate behavior in healthy subjects for the representational modality. Indeed, similar to the study of Oliveri and collaborators in 2004 in which rTMS over the right parietal region (P4) counteracted the typical leftward mental number line bias in healthy individuals, Göbel and colleagues (2006) reported that online rTMS (5Hz for 1000 msec) applied over the right parietal (angular gyrus/adjacent posterior part of the intraparietal sulcus), but not occipital lobe, modulated the mental number line rightward – i.e. a bias towards larger numbers with the perceived numerical midpoint shifted right - consistent with ‘neglect-like’ behavior. Similarly, Cattaneo and colleagues (2009) showed that by stimulating the right, but not left, angular gyrus the priming of attention towards smaller numbers on the left side of the mental number line is disrupted.

TMS not only allows the investigation of the relationship between selective regions and behavior, but it also has the advantage of being able to trace the time at which activity in a particular cortical region contributes to a given task, and to “map” the functional connectivity between brain regions (Pascual-Leone et al., 2000). TMS has indeed been used successfully to study the functional interactions between two or more connected brain areas. The dual-site paired-pulse protocol for example allows the investigation of functional cortical interactions between interconnected areas. A first pulse (conditioning pulse (CS)) is used to activate putative pathways to the motor cortex from the stimulation site, while a second pulse (test stimulus (TS)) is delivered

over M1 a few milliseconds later to probe for changes in excitability that are produced by the CS. This dual-site paired-pulse paradigm has been used to test the hypothesis of LH (parietal) hyper-activation in neglect patients (Kinsbourne, 1977). Koch and collaborators revealed an hyper-excitability within the left parietal-motor interactions (PPC-M1) in neglect patients, and showed that applying rTMS over the spared PPC both down-regulated the PPC-M1 connectivity and ameliorated neglect symptoms (Koch et al., 2008). With a similar approach but increasing the number of conditioning pulses prior to the test pulse, the same research group investigated interhemispheric (parietal-to-parietal) interactions using a triple-pulse TMS approach: they investigated the interhemispheric influence of PPC over the contralateral PPC as measured by its influence on the contralateral PPC-M1 functional connectivity (Koch et al., 2011). The authors show that a conditioning pulse over the right PPC, as compared to a conditioning pulse delivered on the left PPC, induces a stronger inhibitory interhemispheric (parietal-to-parietal) connection as measured by parieto-motor interaction, i.e. stronger right-to-left than left-to-right interhemispheric inhibition, revealing an asymmetry in the interhemispheric connectivity.

NIBS methods have been shown to successfully modulate visuospatial cognition; alleviating USN symptoms by inhibiting the left or exciting the right parietal cortex, and inducing neglect-like behavior in healthy subject by mostly inhibiting or disrupting activity in the right parietal cortex. Another technique that has shown similar behavioral effects in both patients and healthy individuals is Prismatic Adaptation.

1.5.2 PRISMATIC ADAPTATION

Prism adaptation (PA) is a simple and quick way of producing not only low-level modifications of visuomotor correspondences, measurable as the post-exposure aftereffects (sensorimotor aftereffect), but also of alleviating higher cognitive deficits such as USN (Rossetti et al., 1998). Rossetti and colleagues not only found a significant reduction in neglect symptoms after adaptation to rightward shifting prisms, but also that the prism-induced amelioration lasted and even increased over the 2 hours after adaptation (Rossetti et al., 1998). This procedure has attracted much research interest in recent years, including many studies of prism adaptation in

healthy subjects. Nowadays it is considered a promising rehabilitation technique for USN (Luauté et al., 2006a), although more rigorous translational research is needed to address the knowledge gap that presently blocks the implementation of inpatient prism adaptation. Some randomized controlled studies have failed to demonstrate the reliability of PA-induced improvements but various groups have conducted randomized controlled studies (Barrett et al., 2012) and single-case studies that show positive effects of PA on USN.

Prism adaptation consists of adaptation to wedge prisms (usually mounted on goggles) that redirect the light passing through the prisms (based on the wedge angle) and thereby deviate vision. Wedge prisms deviate the beam without affecting other beam parameters. Figure 6 shows a schematic representation of the beam deviation induced by wedge prisms along with an example of what the displaced vision looks like (Note that this is only an example and does not match the deviation used in our experiments).

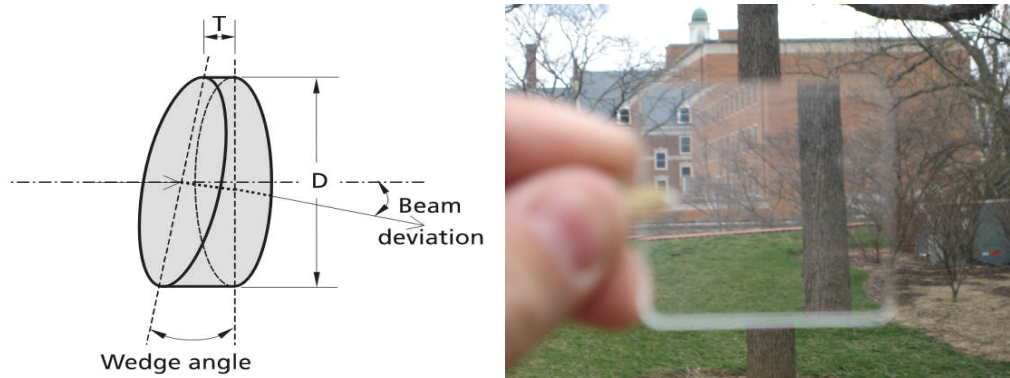


Figure 6: a) The drawing above depicts a single wedge prism, an incident beam of light and the resulting beam deviation; b) Example of displacement induced by the prism.

PA was first introduced by Hermann von Helmholtz in the late 19th-century to support his perceptual learning theory (Helmholtz, 1867), and since then this technique has been extensively investigated (Stratton, 1896; Hein and Held, 1962; Held and Freedman, 1963; Held and Mikaelian, 1964; Hay et al., 1971; see Redding and Wallace, 2006 for a review). PA is a form of sensorimotor training that involves (1) pre-exposure baseline measurements - usually consisting of pointing movements toward a target without feedback - the sensorimotor performance that is the hallmark of PA, (2) active exposure to prismatic displacement and pointing while wearing the

prisms to produce adaptation and, (3) a post-exposure measure - usually consisting of pointing movements without feedback toward the same target used to assess the baseline measurement (Figure 7). The difference between the pre- and post- exposure measures is called the *after-effect* and is used to quantify the sensorimotor effect of PA.

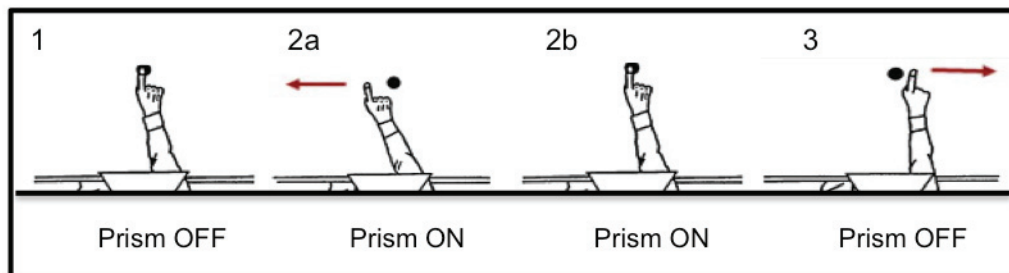


Figure 7: Schematic of the adaptation procedure to left deviating prisms (LPA). 1) Pre-exposure (*baseline measurement*); 2) Active exposure to left prismatic displacement a) early pointing phase (*direct effect*) b) late pointing phase (*recalibration*) 3) Post-exposure (*after-effect*). (Note that the amount of both direct effects and after-effects is purely schematic).

Right-shifting prisms (RPA) shift vision toward the right, lead to a leftward aftereffect, and are typically used in patients to alleviate USN symptoms. In contrast, left-shifting prisms (LPA) shift vision toward the left, lead to a rightward aftereffect, and are typically used in healthy subjects to induce neglect-like behavior. When subjects execute the first pointing movements toward the perceived (i.e. displaced) target while wearing the prismatic glasses they are usually (with the exception of USN patients) aware of a mismatch between the expected and obtained movement outcome. This is called the *direct effect* of PA and is in the same direction as the prismatic displacement. In the case of LPA, for example, participants notice that their right index finger ends up to the left of the real target location (versus the perceived one), and while continuing to point, by means of the online feedback, they correct this error (*recalibration*) and achieve more accurate pointing movements over time (*alignment*). This spatial remapping is related to the displacement of the visual field induced by the prism and occurs by changing the constants that relate the various coordinate systems (Redding and Wallace, 2006). After several pointing movements (the actual number usually depends on the protocol but in general more pointing movements are performed by healthy subjects than patients, e.g. 150 versus 50) the

glasses are removed. The pointing movements the subjects perform in the post-exposure condition are shifted in the direction opposite to the prismatic displacement. Thus, in case of LPA, they will be to the right of the target (*after-effect*). The fact that during the exposure phase the *direct effect* quickly disappears, whereas the *after-effect* slowly increases, suggests that at least two adaptive processes are operating during prism exposure: rapid recalibration of target position to quickly reduce performance error, and slowly developing realignment to bring the coordinate system origins into correspondence (see Redding et al., 2005; Redding and Wallace, 2006 for review). The realignment process is thought to be an unconscious process triggered by spatial discordance between perceived position and the position actually achieved and not merely by the direct error *per se*; and it is thought to represent “true adaptation”. The reason for this is that after-effects can occur even in the absence of a detectable pointing error, as for example is the case in the multi-step PA procedure in which the subject is not aware that the deviation is gradually increased (e.g. Michel et al., 2007). Realignment only occurs when at least the initial third of the movement is occluded (Redding and Wallace, 2006), whereas recalibration, also known as the strategic component, occurs regardless of whether the movement path during pointing is entirely or partially visible. Prism adaptation is not efficient if the hand is visible at the start of the pointing movements since the movement can then be fully planned using a consistent visuo-visual comparison of the hand and target positions through the prisms.

In USN patients RPA improves performance on the line bisection task (Rossetti et al., 1998; Pisella et al., 2002) and on other visuospatial tasks such as copy drawing copying. However, PA’s beneficial effects are not solely restricted to visuomotor tasks, as it also ameliorates purely visuo-perceptual symptoms, e.g. global/local processing (Bultitude et al., 2009). Farnè and colleagues examined the effects of prism adaptation in six USN patients and found that both visuomotor (bell/line/letter cancellation and line bisection), and visuo-verbal tasks (verbal description and naming of objects) simultaneously improved, and that this improvement lasted at least 24 hours (Farnè et al., 2002). Performance in non-visual tasks like haptic exploration (McIntosh et al., 2002) and tactile and auditory extinction (Maravita et al., 2003; Jacquin-Courtois et al., 2010) are also improved by RPA. RPA has been also shown to ameliorate visual imagery, as USN patients who initially could

not evoke city names on the western half of the imagined map of France clearly improved on this task after RPA (Rode et al., 1998, 2001). It also produces generalizable effects in the wider sensorimotor domain as it affects non-trained tasks such as wheel-chair navigation (Jacquin-Courtois et al., 2008) and postural control (Tilikete et al., 2001). RPA in USN patients has also been shown to induce a leftward shift on the mental number bisection test (Rossetti et al., 2004a) and on temporal order judgments (Berberovic et al., 2004), and biases time perception toward an underestimation of time duration (Magnani et al., 2011; Oliveri et al., 2013).

PA in healthy subjects has been investigated over the last 15 years. After the original discovery that LPA biases performance rightward on the perceptual line bisection task in healthy subjects (Colent et al., 2000) many other studies have shown that LPA modulates visuospatial cognition in healthy participants. Beyond several studies reporting behavioral changes on visuospatial tasks like line bisection and greyscale displays (Colent et al., 2000; Jackson and Newport, 2001; Berberovic and Mattingley, 2003; Michel et al., 2003; Loftus et al., 2008, 2009), a single session of LPA has also been reported to modulate haptic exploration (Girardi et al., 2004), global/local processing (Bultitude and Woods, 2010; Reed and Dassonville, 2014), spatial remapping (Bultitude et al., 2013), and perception of time duration (Magnani et al., 2012). Taken together, these studies allow us to conclude that left PA, which produces a rightward sensorimotor after-effect, induces neglect-like symptoms in healthy subjects at the level of spatial cognition.

As we can see from the findings summarized above, there are similarities in PA-induced modulations between neglect patients and healthy individuals. It is worth acknowledging, however, that the effects of PA on defective/damaged visuospatial abilities go well beyond the parameters usually affected in normal subjects, and that patients show a larger aftereffect than healthy subjects. Both these differences could be related to the fact that patients are probably less aware of the displacement of the prismatic displacement as USN patients do not notice the alteration resulting from the optical deviation (Jakobson and Goodale, 1989) and healthy subjects exhibit larger adaptive after-effects when the prismatic deviation is not noticeable (multiple-step (unaware) exposure compared to a single-step exposure (Michel et al., 2007)).

The effectiveness of PA in affecting spatial cognition has also been shown to be unidirectional in both pathological and healthy populations: only RPA has been shown to act on USN symptoms (Luauté et al., 2012), and only LPA has been so far reported to be effective in healthy. Indeed, most of the studies investigating PA in healthy subjects did not find any significant effect of RPA on cognition. Except for the modulation the estimated duration of auditory stimuli, which has been shown to be modulated by both PA directions (Magnani et al., 2012) only one study (to my knowledge) has so far shown a significant leftward shift in line bisection after RPA in healthy subjects. Goedert and colleagues (2010) reported a significant modulation of manual line bisection performance when they looked at the interaction between the PA direction and the bias participants showed before PA (i.e. the presence or absence of pseudoneglect) (Goedert et al., 2010). Specifically, they reported that LPA significantly and directionally modulated performance in subjects with pseudoneglect, whereas RPA significantly modulated it in subjects with an initial rightward bias (i.e. no pseudoneglect). On the basis of these results it seems possible that PA might interact with the *baseline state of the system* as expressed by the presence or absence of pseudoneglect (Goedert et al., 2010).

The duration of PA-induced modulations is a crucial feature for both clinical and fundamental research. A group of patients showed a sustained improvement 24h after the training session (Farnè et al., 2002) but individual cases may exhibit even longer-lasting amelioration of neglect, up to 1 week (e.g. McIntosh et al., 2002; Pisella et al., 2002). It also appears that repetitive RPA can produce significantly longer-term benefits. Four RPA sessions have been shown to produce short- but not long-term benefits (Nys et al., 2008), whereas protocols using 10 or more sessions of prism adaptation have reported reliable, generalizable benefits that lasted between 4 and 5 weeks after the end of the therapy (Frassinetti et al., 2002; Serino et al., 2009). Daily PA for ten days has been reported to improve neglect for up to 3 months after treatment (Serino et al., 2006). PA-induced long lasting improvements are not limited to acute USN patients, as visuospatial symptoms in a chronic patient (11 years post stroke) improved for up to 1 year after long-term PA training (Humphreys et al., 2006), and in another chronic patient (almost 6 years post stroke) the detection of stimuli in the contralesional visual field improved up to 24 months after the end of the treatment which consisted of daily exposure to prisms over a three-month period

(Nijboer et al., 2011). Interestingly, RPA-induced cognitive effects in patients are not only immediately present, but also appear to become stronger with increasing time after the adaptation procedure (i.e. 2 h) (Rossetti et al., 1998).

As we have seen, the duration of the PA-induced effects in patients has been extensively investigated at both the sensorimotor and cognitive levels. In contrast, the literature concerning healthy subjects only explicitly reports the duration of the sensorimotor after-effect, which appears to last between 20 and 40 min after a single PA session in healthy subjects (Taub and Goldberg, 1973; Fernández-Ruiz et al., 2004). In one study, however, a significant aftereffect was reported at a much later time (24 h) (Lackner and Lobovits, 1977). Longer lasting sensorimotor aftereffects, from several days to up to two weeks have only been reported following ‘potentiated’ adaptation protocols (such as incremental exposure to the prismatic deviation, adaptation training spaced by breaks, and protracted pointing during the sensorimotor training) (Choe and Welch, 1974; Klapp et al., 1974; Yin and Kitazawa, 2001; Hatada et al., 2006; Michel et al., 2007). Until now the duration of the PA-induced cognitive effects in healthy individuals has never been explicitly reported and can only be inferred from the duration of the task used to quantify it (when such information is available).

1.5.2.1 PA – An anatomo-functional model

Despite all the evidence that prism adaptation can successfully ameliorate the signs of neglect, the underlying mechanisms by which low-level visuomotor adaptation produces recovery of high-order visuospatial representations are still under investigation.

A review of the literature reveals that the anatomical correlates of PA appear to involve two main structures: the cerebellum and the posterior parietal cortex (PPC). The posterior parietal cortices have been shown to be targets of the cerebellar outputs via a neuronal loop that also include the dentate nucleus and subcortical structures such as the thalamus and the globus pallidus (Middleton and Strick, 2000; Clower et al., 2001). The cerebellum’s involvement in PA is further supported by lesion-studies in both human (Weiner et al., 1983; Martin et al., 1996; Pisella et al., 2005) and non-human primates (Baizer et al., 1999; Kurata and Hoshi, 1999), and typical aftereffects

are dramatically reduced in cerebellar patients compared to controls (Weiner et al., 1983). A patient with a left cerebellar lesion (including the superior part of the dentate nucleus and most of the anterior lobe of the left cerebellar hemisphere) was successfully adapted to a rightward (but not leftward) prism deviation, independently of the hand used during the adaptation procedure (Pisella et al., 2005). This visual lateralization of the prism adaptation network was already suggested by a study in monkeys in which Kurata and Hoshi (1999) observed deficits in PA after the inactivation of the ventral premotor cortical area only when vision was shifted contralateral to the inactivated cortical area (i.e. LH - RPA or RH - LPA). Given that the connections between the cerebellum and the cerebral cortex are crossed (Schmahmann and Pandya, 1997), this finding supports a lateralized cerebro-cerebellar network for the computation and integration of the directional visual error in prism adaptation. The implication of such a lateralized cerebello-cerebral network in the functional anatomy of the therapeutic effects of prism adaptation on USN was confirmed by a functional neuroimaging study in neglect patients (Luauté et al., 2006b). This Positron Emission Tomography (PET) study of five USN patients showed that RPA increased activity in the left temporal-occipital junction, thalamus, globus pallidus and right cerebellum. Furthermore, there was a decrease in the activity of the right PPC which correlated with significant improvements on two subtests of the Behavioral Inattention Test battery (BIT) requiring visual search. The right cerebellar hemisphere and the right dentate nucleus were both significantly activated in the positive covariation analysis between the prism adaptation-induced changes in regional cerebral blood flow and neuropsychological performance (Luauté et al., 2006b).

Based on these anatomical and behavioral data, Pisella and collaborators proposed a simple model that involves the cerebellum and the PPC (Pisella et al., 2006). The clinical effect of RPA in USN is hypothesized to rely on a network in which the error signal generated by RPA is initially processed in the left occipital cortex, the information is then transferred to the right cerebellum, where the visuomotor realignment takes place (i.e. ‘true adaptation’) and then via a bottom-up signal from the cerebellum modulates the parietal cerebral areas in the left hemisphere (Michel et al., 2003; Rode et al., 2003; Pisella et al., 2005) reducing the pathological interhemispheric imbalance (Figure 8).

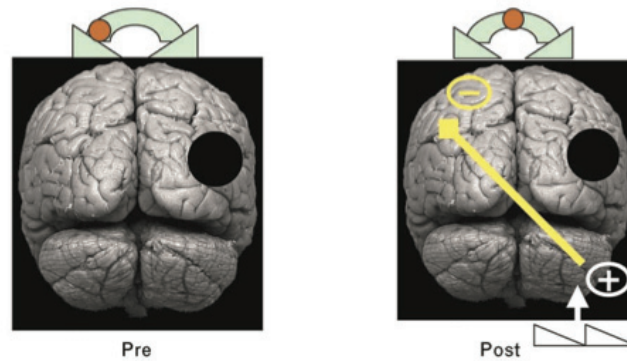


Figure 8 The anatomo-functional model. (From Pisella et al 2006)

In contrast, LPA may induce neglect-like behavior in healthy subjects via the inhibition of the function of the right parietal lobe, thanks to inputs from the left cerebellar cortex. By adding a single cerebello-parietal mechanism into the framework of the interhemispheric rivalry theory this model could readily account for both the PA-induced rightward (neglect-like) visuospatial bias in healthy subjects and the therapeutic effects in neglect patients. Members of our group have suggested that the effects of PA on spatial cognition could be modulated by the cerebello-parietal connections and that RPA might primarily modulate cortical activity via correction signals from the right cerebellum to the left SPL/IPS (Luauté et al., 2006b; Pisella et al., 2006, Striemer et al. 2008). The leftward realignment, and therefore USN symptom amelioration, might occur by callosal connections from left to right SPL via which signals processed in left parietal cortex would be transmitted to right hemispheric dorsal areas that are normally responsible for leftward orienting (Striemer et al. 2008, Striemer and Danckert, 2010) and that are hypo-activated as a consequence of the ventral network damage (Corbetta et al., 2005).

Different imaging studies that have been published have not provided consistent results between each other and with respect to the proposed models. However, this interhemispheric communication via SPL is supported by imaging data in healthy subjects (Danckert et al., 2008; Luauté et al., 2009; Chapman et al., 2010) in which both the bilateral superior parietal lobule (SPL) and right cerebellum are activated during the adaptation phase with LPA. It is also supported by the fact that lesions to SPL/IPS eliminate all cognitive aftereffects of PA (Striemer et al., 2008) but do not prevent sensorimotor adaptation (Pisella et al., 2004).

The results of few imaging studies in healthy participants support the hypothesis that PA might modulate the activity of cortical areas implicated in spatial cognition through a bottom-up signal generated in the cerebellum by showing that PA in the early phase (error detection and correction) activates a parieto-cerebellar network – right cerebellum and either left or right aIPL according to the prismatic deviation (Clower et al., 1996; Danckert et al., 2008; Chapman et al., 2010). In an event-related fMRI study Luauté and colleagues showed that during the earliest phase of LPA left anterior intraparietal sulcus was primarily implicated in error detection, whereas left parieto-occipital sulcus was implicated in error correction. Activation in right intraparietal cortex was also observed during the early exposure phase, which, given the dominant role of right PPC in visuospatial processing and attention, may implicate a visuospatial component in the initial error signal generated by prism exposure (Luauté et al., 2009). Importantly, the authors also found that for RPA the right cerebellar activity progressively increased during prism exposure, in accordance with a key role for this structure in spatial realignment. This suggests that the cerebellum might be responsible for the neural changes in the superior temporal cortices, which were activated during the later phase of prism exposure (when the deviation was fully compensated and the error completely abolished) and thus could mediate the effects of prism adaptation on cognitive spatial representations. Even though anatomical connections between the temporal cortex and the cerebellum remain poorly understood they might participate in cognitive functions associated with the cerebellum (Ramnani, 2006). A recent fMRI study in seven neglect patients showed that RPA increased activation of both hemispheres, namely in bilateral parietal, frontal, and occipital cortices, and that these increases were associated with a significant behavioral improvement in USN symptoms as measured by line bisection and visual search. The authors concluded that this bilateral fronto-parietal network recruitment might be responsible for counteracting the pathological biases produced by unilateral right hemisphere damage (Saj et al., 2013). Another just-published fMRI study investigated the effects of RPA in healthy participants by comparing the activation patterns before and after PA on the visual detection task. In this study they found a significant increase in the ipsilateral field representation in the left inferior parietal lobule and a significant decrease in the right inferior parietal lobule (Crottaz-Herbette et al., 2014). From this, the authors concluded that a brief exposure to PA

differentially modulates left and right parietal activation during visual detection (Crottaz-Herbette et al., 2014).

An fMRI study published this year aimed to investigate the neural basis of PA in time perception in healthy individuals and to test the possible stability of this effect over time (as late as 30 minutes after adaptation) and thus its possible maintenance (Magnani et al., 2014). The contrast of the time reproduction performance after PA as compared to baseline revealed increased brain activation in the time-task relative to the control task (i.e. in the contrast/difference between the experimental-task that required temporal encoding of a visual stimulus and the control-task that required detection of the appearance of a visual stimulus). This increased activity was located in the anterior part of the left insula and in the left superior frontal gyrus in the immediate post- compared to pre-PA session, and in the left middle frontal gyrus in the late post session (30 minutes after PA).

An alternative to Pisella's model (2006) of PA's mechanism of action proposes that PA produces a resetting of ocular scanning behavior, which facilitates the exploration of the neglected visual field (Angeli et al., 2004; Serino et al., 2006). Several dissociations have, however, been documented between oculomotor change and the amelioration of visuospatial behavioral performance (Dijkerman et al., 2003; Ferber et al., 2003) and evidence suggests that the improvement in the detection of stimuli in the contralesional visual field to 24 months after PA measured by perimetry (a well-controlled and commonly-used method to carefully map primary visual and/or attentional deficits in the visual field), is unlikely due to compensatory eye movements (Nijboer et al., 2011). In any case, the anatomo-functional model proposed by Pisella and collaborators (2006) is still compatible with the possible role of a realignment of the oculomotor system in the PA-induced amelioration, in that by reducing the rightward scanning bias it may facilitate exploration of the left, neglected side of space (Angeli et al., 2004; Malhotra et al., 2006; Serino et al., 2006).

The anatomical and functional complexity of the cerebellum and the lack of clear behavioral criteria to identify the transition from one process (strategic control) to the other (spatial realignment) make the understanding of PA mechanism of action a difficult and problematic endeavor (Newport and Schenk, 2012). It is still necessary to build up a coherent framework integrating one century of PA investigations with

the recent body of patient and healthy subject literature (Redding and Wallace, 2006). As a step in this direction, the aim of my thesis work has been to test the anatomofunctional model proposed by Pisella and colleagues (2006).

2. PRISM ADAPTATION IN THE HEALTHY BRAIN: THE SHIFT IN
LINE BISECTION JUDGMENTS IS LONG LASTING AND
FLUCTUATES

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Since the duration of the induced visuospatial modulation in healthy individuals has never being investigated we addressed this question in a first study in which we investigated the duration and dynamic of PA-induced sensorimotor and visuospatial modulations in healthy participants by repeatedly measuring modulations induced by LPA and RPA for 40 minutes.

Abstract

Rightward prism adaptation has been shown to ameliorate visuospatial biases in right brain-damaged patients with neglect, and a single session of prism adaptation can lead to improvements that last up to several hours. Leftward prism adaptation in neurologically healthy individuals induces neglect-like biases in visuospatial tasks. The duration of these effects in healthy individuals, typically assumed to be ephemeral, has never been investigated. Here we assessed the time-course of the adaptation-induced modifications in a classical perceptual line bisection task that was repeatedly administered for approximately 40 minutes after a single session of adaptation to either a leftward or rightward prismatic deviation. Consistent with previous reports, only adaptation to leftward-deviating prisms induced a visuospatial shift on perceptual line bisection judgments. The typical pattern of pseudoneglect was counteracted by a rightward shift in midline judgments, which became significant between 5 and 10 minutes after adaptation, fluctuated between being significant or not several times in the 40 minutes following adaptation, and was present as late as 35 minutes. In contrast, the sensorimotor aftereffect was present immediately after adaptation to both rightward and leftward deviating prisms, decayed initially then remained stable until 40 minutes. These results demonstrate that both the sensorimotor and visuospatial effects last for at least 35 minutes, but that the visuospatial shift needs time to fully develop and fluctuates. By showing that the effects of prism adaptation in the undamaged brain are not ephemeral, these findings reveal the presence of another, so-far neglected dimension in the domain of the cognitive effects induced by prism adaptation, namely time. The prolonged duration of the induced visuospatial shift, previously considered to be a feature of prism adaptation unique to brain-damaged subjects, also applies to the normal brain.

Introduction

Prism Adaptation (PA) is a classic technique for reversibly modifying sensorimotor correspondences and has been extensively investigated (Helmholtz, 1867; Stratton, 1896; Hein and Held, 1962; Held and Freedman, 1963; Held and Mikaelian, 1964; Hay et al., 1971; for review see Redding and Wallace, 2006). Wedge prisms produce a lateral shift of the visual field, and adaptation of hand pointing movements to displaced vision is now considered to be one of the most promising techniques for treating neglect symptoms (Milner and McIntosh, 2005; Luauté et al., 2006a; Newport and Schenk, 2012). Indeed, since the original demonstration of its efficacy in ameliorating performance on standard neuropsychological tests of neglect (copying a drawing, drawing from memory, reading) (Rossetti et al., 1998) PA has been shown to promote the resetting of the oculo-motor system (Serino et al., 2006) and to improve performance on a range of tasks that tap into visuospatial cognition like line bisection (Pisella et al., 2002), global/local processing (Bultitude et al., 2009), haptic exploration (McIntosh et al., 2002), wheel-chair navigation (Jacquin-Courtois et al., 2008), and visual imagery (Rode et al., 2001), possibly by acting mainly on the dorsal stream (Striemer and Danckert, 2010b; Fortis et al., 2011). PA also improves performance on non-visual tasks like tactile and auditory extinction (Maravita et al., 2003; Jacquin-Courtois et al., 2010).

In addition to its ability to reduce neglect symptoms in patient populations, a remarkable feature of PA is its ability to induce neglect-like behavior in healthy subjects. For example, PA changes behavior on visuospatial tasks like line bisection, greyscales, global/local processing, and haptic exploration (Colent et al., 2000; Jackson and Newport, 2001; Berberovic and Mattingley, 2003; Michel et al., 2003; Girardi et al., 2004; Loftus et al., 2009; Bultitude and Woods, 2010). It also alters spatial remapping (Bultitude et al., 2013) and the estimated duration of auditory stimuli (Magnani et al., 2012). In this respect, PA is similar to some brain-modulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), which can alleviate neglect symptoms in patients (Oliveri et al., 2001; Brighina et al., 2002; Koch et al., 2008; Sparing et al., 2009) and induce neglect-like behavior in healthy participants (Fierro et al., 2000; Sparing et al., 2009; Giglia et al., 2011; Romei et al., 2011).

It is important to note that the direction of the prismatic displacement is pivotal for improving neglect in patients or inducing neglect-like behavior in healthy subjects. Neglect symptoms in patients improve only after adaptation to rightward-deviating prisms (Luauté et al., 2012) and visuospatial performance in healthy subjects is shifted only after adaptation to leftward-deviating prisms (Colent et al., 2000; Berberovic and Mattingley, 2003; Michel et al., 2003; Nijboer et al., 2010). In addition to differing in terms of the direction of the prismatic displacement required to induce visuospatial adaptation effects, neglect patients and healthy subjects also differ with respect to the duration of these effects. For example, a single session of PA in neglect patients can significantly improve neglect symptoms for at least two hours (Rossetti et al., 1998) and in some patients for up to several days (Farnè et al., 2002; Pisella et al., 2002). Two-weeks of treatment can produce positive effects for one to six months (Frassinetti et al., 2002; Serino et al., 2007), and a single patient treated daily for three months still had improved detection of contralesional visual stimuli two years after the prism treatment (Nijboer et al., 2011). In healthy subjects, perceptual changes are assumed to last only a few minutes, but this idea appears to come from the fact that almost all studies examined visuospatial effects only in the few minutes following adaptation, and not from data showing that these effects disappear at later times.

In this study we examined sensorimotor and visuospatial aftereffects in healthy participants multiple times after prism adaptation. Accuracy in open-loop pointing was used to measure the sensorimotor aftereffects and line bisection judgments measured the visuospatial aftereffect. Young participants typically make midline judgments to the left of the true center (Bowers and Heilman, 1980; Jewell and McCourt, 2000; Toba et al., 2011). This left bias is termed pseudoneglect, and there is a large body of evidence showing that adaptation to leftward-deviating prisms causes participants to shift their midline judgments to the right, thus reducing (Loftus et al., 2009; Nijboer et al., 2010), or cancelling (Colent et al., 2000; Berberovic and Mattingley, 2003; Michel et al., 2003) their pseudoneglect. Since we were particularly interested in the time course of visuospatial aftereffects produced by PA we designed a pre/multiple-posts experiment in which we assessed pointing accuracy and midline judgments every 5 minutes for 40 minutes after a single session of PA.

Methods

Participants

Forty healthy volunteers participated in the study. First, twenty participants (10 males, mean age = 20.8, standard error of the mean (SEM) = 0.46) underwent adaptation to leftward-deviating prisms and then another twenty participants (8 males, mean age = 20.8 SEM = 0.31) were adapted using rightward-deviating prisms. All participants had normal or corrected-to-normal vision and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). They all gave informed consent and were paid for their participation in the study. The study was approved by the local ethics committee and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki (last update: Seoul, 2008).

Procedure

Throughout the experiment participants were comfortably seated with their head positioned on a chinrest. The experiment consisted of nine blocks (one before and eight after PA). Each experimental block lasted a maximum of five minutes, and included six open-loop pointing movements with the right index finger towards a central target as well as the Landmark (perceptual line bisection) task. The open-loop pointing movements (which took approximately 30 seconds) were always performed before the Landmark task. Response times during the Landmark task varied across participants (and for a given participant across blocks), resulting in a variable block duration of between 4 and 5 minutes. The experimenter carefully monitored the timing to ensure that each experimental block started at the same time (i.e. 0, 5, 10, 15, 20, 25, 30, 35, and 40 minutes after prism adaptation). The block before adaptation provided baseline measurements of behavior on the open-loop pointing and line bisection tasks. These measures were then compared with those obtained in each of the eight post-adaptation blocks (Fig. 1). In order to reduce the possibility of deadaptation across time participants were instructed to keep their eyes closed and to avoid moving their right hand unless instructed to perform the open-loop pointing movements. An additional series of six open-loop pointing movements was administered after the eighth block to assess whether the sensorimotor aftereffect was still present at the end of the experiment.

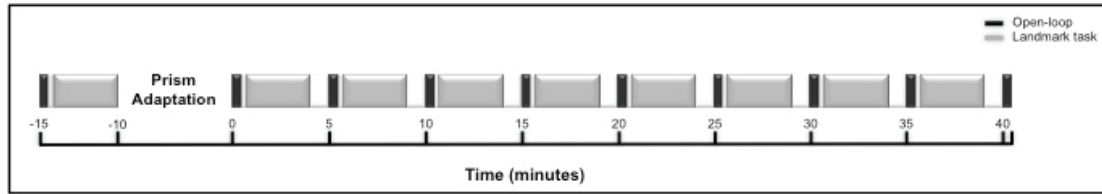


Figure 1. Experimental design The experiment consisted of nine experimental blocks (one before and eight after prism adaptation) plus an open loop pointing measure after the eighth block. For each of the nine experiment blocks open loop pointing was always performed before the Landmark task. Because of variation in response times during the Landmark task the end of one block and the beginning of the next were separated by between 0 and 60 seconds.

Prism adaptation

Participants were fitted with prismatic goggles that deviated their visual field by 15 degrees either leftward ($n=20$) or rightward ($n=20$). They were seated in front of a white horizontal board on which three target dots (5 mm diameter) were positioned at 0, -10 and +10 degrees from their body midline at a distance of 57 cm from their eyes. They performed a total of 150 verbally instructed pointing movements with their right index finger towards the right (+10°) and left (-10°) targets in a pseudorandom order. Before pointing they placed their right index finger on the starting position, which was just in front of their chest. Participants could not see their hand when it was in the starting position and during the first third of the pointing movement. Participants were instructed to point with the index finger extended, to execute a one-shot movement at a fast but comfortable speed, and to return their hand to the starting position only when instructed by the experimenter.

After 150 pointing movements the prismatic goggles were removed and behavior on the sensorimotor and visuospatial tasks was repeatedly measured using open-loop pointing movements to the central target (0°) and the Landmark task.

Open-loop pointing

Open-loop pointing was measured with participants seated in front of the same board as that used during the prism adaptation procedure. Before each pointing movement participants were given verbal instructions. They were told to look at the central target (0°), close their eyes, point to the target with their right index finger while keeping their eyes closed, and then return their hand to the starting position. The delay

between participants closing their eyes and pointing to the central target was always between 1 and 2 seconds. To ensure that participants had no visual feedback regarding their movement vision of the arm was occluded during pointing. Pointing error was visually tracked and recorded by the experimenter as the distance between the fingertip and the central target (to the nearest 0.5 cm), with positive values representing errors to the right of the target and negative values errors to the left. Each of the ten open-loop pointing measures was the average of six pointing movements.

Landmark task

For each of the nine Landmark task measurements participants had to judge whether the line that appeared on the computer screen positioned in front of them was bisected toward the right or the left of the line's true center. They were instructed to inspect the whole line and judge whether "the mark (transector) was closer to the left or right end of the line". In this two alternative forced-choice paradigm participants answered by pressing a pedal with their left foot if the transector was perceived as being closer to the left end of the line and with their right foot if they thought it was closer to the right end of the line. They were instructed to respond accurately and quickly. Ten practice trials were given prior to the experiment to ensure that participants understood the instructions. The stimuli were white lines (350 mm x 3mm) and were displayed on a black screen positioned 35 cm from the participant's eyes. Lines bisected at the true center and at 2, 4, 6, 8, and 10 mm toward the left and right of the true center were presented six times in a pseudo random order, yielding a total of 66 trials, which took approximately three minutes to complete. Each pre-bisected line was displayed for a maximum of five seconds or until a response was made, and was then replaced by a black-and-white patterned mask which stayed on the screen for one second before the next bisected line was displayed. For each participant the percentage of right responses was plotted as a function of the position of the transector. These data were then fitted with a sigmoid function and the value on the x-axis corresponding to the point at which the participant responded 'right' 50% of the time was taken as that participant's point of subjective equality (PSE).

Presentation software (Neurobehavioral Systems, Inc, USA) was used to generate the stimuli, record responses, and control the timing of stimulus presentation throughout the task.

Results

Open-loop pointing accuracy was used to assess whether participants adapted to prisms and how long they remained adapted. Since the sign of the error depends upon the direction of the prisms, to assess whether the amount of sensorimotor adaptation was similar for the two groups we performed a repeated measures ANOVA on the absolute value of the difference between the pre- and post-adaptation landing positions (sensorimotor shift) with group (leftward versus rightward) as a between-subject factor and time (Post 1 to Post 9) as a within-subject factor. This analysis revealed a main effect of time but no main effect of group and no time by group interaction (time $[F(8, 304) = 106.02, p < .001]$; group $[F(1, 38) = .22, p = .642]$; time \times group $[F(8, 304) = 1.85, p = .066]$). To assess the effect of prism direction on line bisection judgments we performed a repeated measures ANOVA on the line bisection judgment data with group (leftward versus rightward) as a between-subject factor and time (Post 1 to Post 8) as a within-subject factor. This analysis revealed no main effects or interactions (time $[F(7, 266) = .54, p = .799]$; group $[F(1, 38) = .80, p = .376]$; time \times group $[F(7, 266) = 1.18, p = .311]$).

Since data from the leftward and rightward deviating prisms were collected sequentially, and since visual inspection of the PSE data after leftward deviating prisms revealed an unstable rightward shift in line bisection judgments, subsequent analyses were performed separately for leftward and rightward deviating prisms. Specifically, for each PA group (leftward and rightward) pointing error and PSE were submitted to separate repeated measures ANOVAs with time as a within-subject factor. Statistical significance was set at 0.05 (two-tailed), and p-values were corrected using either Dunnett (pre versus post comparisons) or Bonferroni (multiple comparisons). Means are presented with standard error of the mean in parentheses.

Leftward-deviating PA

Open-loop pointing

Fig. 2 (left panel) shows the average pointing error for all ten open-loop pointing measurements. In the pre-adaptation block participants pointed on average 0.56 cm (0.28) to the left of the target and pointing errors after adaptation decreased across time. The one-way repeated measures ANOVA revealed a significant effect of time

[$F(9, 171) = 81.55, p < .001$]. Post-hoc tests comparing the baseline measurement with each of the post-adaptation measurements revealed that open-loop pointing at baseline differed significantly from each of the nine post-adaptation measurements (all p s $< .001$, Dunnett corrected), showing that participants were significantly adapted until the end of the experiment.

Landmark Task

Fig. 3 (top panel) shows the average PSE for all nine Landmark measurements. Before adaptation to leftward deviating prisms the average PSE was 2.30 mm (0.51) towards the left of the true midpoint. After adaptation the PSE shifted toward the right (values became less negative). A one-way repeated measures ANOVA with time as a within-subject factor revealed a significant effect of time [$F(8, 152) 2.59, p = .011$]. Post-hoc tests comparing the baseline block with each of the eight post-adaptation blocks revealed that the baseline midline judgment differed significantly from judgments at posts 2, 4, 5 and 7 (all p s $\leq .028$, Dunnett corrected). That is, midline judgments shifted significantly to the right approximately 10, 20, 25, and 35 minutes after removal of the prismatic goggles.

To assess whether there was any correlation between an individual participant's shift in open-loop pointing and his/her PSE shift we computed a Pearson product moment correlation between open-loop shift and PSE shift for each of the eight post-adaptation blocks. None of these correlations were significant (all r s $\leq -.365$, all p s $\geq .114$).

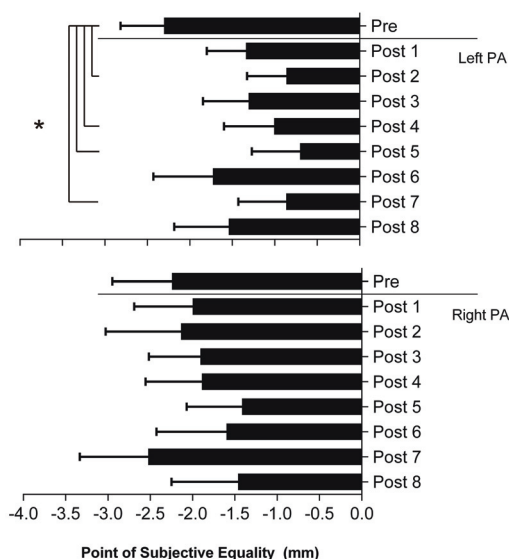


Figure 2. Point of Subjective Equality Judgment (Visuospatial Aftereffect). Average behavior of all 40 subjects (20 in each group) on the Landmark task before (above the solid horizontal line) and after adaptation to leftward- (Top panel) and rightward-deviating prisms (Bottom panel). PA; prism adaptation. Bars represent the average point of subjective equality for midline judgments. Zero represents the line's true center. Negative values represent judgments to the left of the line's true center. Error bars represent 1 SEM. * $p < .05$.

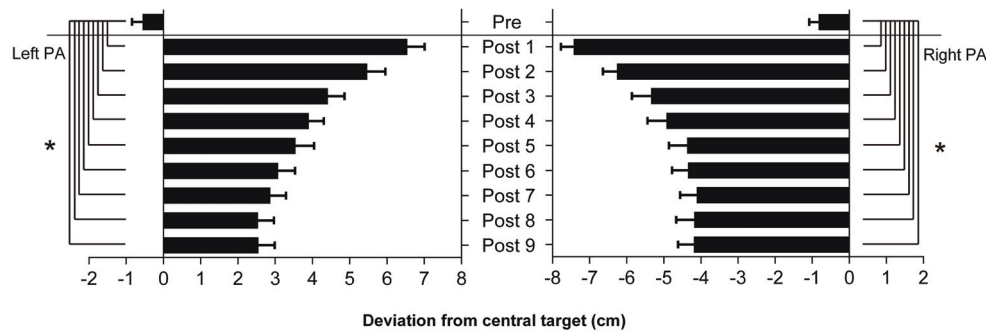


Figure 3. Open-loop Pointing Error (Sensorimotor Aftereffect). Average behavior of all 40 subjects (20 in each group) on the sensorimotor task before (above the solid horizontal line) and after adaptation to leftward (Left panel) and rightward-deviating prisms (Right panel). PA; prism adaptation. Bars represent the average pointing error when participants pointed to the midline target. Zero represents no deviation from the central target. Negative and positive values represent errors to the left and right of the target. Error bars represent 1 SEM. * $p < .001$.

In order to assess whether the pattern of visuospatial behavior observed after adaptation to leftward deviating prisms was specific to the direction of the prismatic deviation we performed a second identical experiment using rightward-deviating prisms.

Rightward-deviating PA

Open-loop pointing

Fig. 2 (right panel) shows the average pointing error for all ten open-loop pointing measurements. In the pre-adaptation block participants pointed on average 0.82 cm (0.25) to the left of the target and pointing errors after adaptation decreased across time. The one-way repeated measures ANOVA revealed a significant effect of time [$F(9, 171) = 80.30, p < .001$]. Post-hoc tests comparing the baseline measurement with each of the post-adaptation measurements revealed that open-loop pointing at baseline differed significantly from each of the nine post-adaptation measurements (all $ps < .001$, Dunnett corrected), showing that participants were significantly adapted until the end of the experiment.

Landmark task

Fig. 3 (bottom panel) shows that, similar to the leftward deviating prisms group, the average PSE before PA was 2.24 mm (0.70) towards the left of the true midpoint. Unlike for the leftward deviating prisms, however, adaptation to rightward deviating prisms did not change midline judgments across time [$F(8, 152) = 0.63, p = .750$]. There was no correlation between an individual participant's shift in open-loop pointing and his/her PSE shift at any of the eight post-adaptation blocks (all $r_s \leq -.253$, all $p_s \geq .281$).

Discussion

The aim of this study was to investigate the time course and duration of the visuospatial aftereffect produced by leftward-deviating prisms in healthy participants. As expected, adaptation to both leftward and rightward-deviating prisms induced a significant aftereffect in open-loop pointing, while only leftward-deviating prisms induced a significant (rightward) shift in midline judgments. The sensorimotor shift was significantly different from baseline for both prismatic deviations at all post-adaptation blocks, whereas in the leftward deviating prism group the visuospatial shift significantly differed from baseline only at post-adaptation blocks 2, 4, 5, and 7. In addition to demonstrating that adaptation to leftward-deviating prisms induces rightward shifts on both a sensorimotor and a visuospatial task that last for at least half an hour, we found that the time course of the visuospatial aftereffect differs from that of the sensorimotor aftereffect in that it takes some time to develop and does not decrease systematically across time.

The visuospatial shift develops over time

By examining the visuospatial aftereffect on a five minute time scale we were able to observe that the effect was not fully established immediately after removal of the goggles, but needed some time to set in. Previous studies found a significant rightward shift immediately after adaptation (Colent et al., 2000; Berberovic and Mattingley, 2003; Michel et al., 2003; Nijboer et al., 2010; Striemer and Danckert, 2010a), whereas the shift in our experiment was significant at post 2 (between 5 and 10 minutes after adaptation) and not in the first five minutes after adaptation. This

discrepancy might be due to the length of the tasks used to assess visuospatial changes after PA, although the exact duration is not always reported. Indeed, if the effect develops over the first 5 to 10 minutes after removal of the goggles then studies that use longer tasks will be more likely to report a significant visuospatial aftereffect in their first post-test, whereas a short task like ours will not necessarily reveal a significant shift immediately after adaptation.

The delay between the end of adaptation and the appearance of a significant visuospatial aftereffect in healthy subjects resembles (albeit on different time scale) the temporal development of the beneficial effects of a single session of PA reported in neglect patients. The first study to report the efficacy of rightward-deviating prisms in ameliorating neglect symptoms observed that neglect symptoms were less severe two hours after adaptation than immediately after removal of the goggles (Rossetti et al., 1998). Although further studies are necessary in order to make a strict comparison between the time courses of aftereffects in the two populations, the present findings suggest that, as in patients, the physiological mechanisms responsible for visuospatial aftereffects in the healthy brain might require some time after the end of adaptation before they significantly affect visuospatial behavior.

The visuospatial shift lasts longer than expected

Here we show for the first time that the visuospatial aftereffect of a single session of leftward deviating prisms lasts more than half an hour. We found a significant rightward shift at four post-adaptation blocks, the latest of which corresponded to approximately 35 minutes after removal of the goggles. The observation that a cognitive effect in healthy subjects can last this long after a single session of PA has never been reported previously. Indeed, very few studies have even assessed the time course of the robust sensorimotor aftereffect, let alone the visuospatial aftereffect. Of the studies that did look at the sensorimotor aftereffect over time the duration of the aftereffect after a single (not potentiated) adaptation session appears to be similar to what we observed (between 20 and 40 minutes) (Taub and Goldberg, 1973; Fernández-Ruiz et al., 2004), and only one study reported a significant aftereffect at a later time (24 hours) (Lackner and Lobovits, 1977). Sensorimotor aftereffects lasting several days or up to two weeks have been reported, but only following ‘potentiated’ adaptation protocols (such as incremental exposure to the prismatic deviation,

adaptation training spaced by breaks, and protracted pointing during the sensorimotor training) (Choe and Welch, 1974; Klapp et al., 1974; Yin and Kitazawa, 2001; Hatada et al., 2006; Michel et al., 2007).

The time courses of the sensorimotor and visuospatial aftereffects were quite different. First, the sensorimotor aftereffect was significant and maximal immediately after adaptation, while the visuospatial shift was first significant between 5 and 10 minutes after adaptation. Second, the sensorimotor aftereffect decayed in the initial period after adaptation and then plateaued for the remainder of the post-adaptation blocks, while the visuospatial shift fluctuated because, compared to pre-adaptation, bisection judgments were only significantly modified at post-adaptation blocks 2, 4, 5, and 7. It is important to note that while these timings emerged at the group level the majority of participants showed rightward shifts at these blocks (18, 16, 13 and 15 out of 20 participants, respectively) and that shifts were induced by adaptation to leftward-, but not rightward-deviating prisms. As in previous studies (Frassinetti et al., 2002; Pisella et al., 2002; Berberovic and Mattingley, 2003; Girardi et al., 2004) we found no linear correlation between the sensorimotor and visuospatial aftereffects either immediately after adaptation or at later times.

These findings suggest that the slow development and long duration of visuospatial aftereffects might not be limited to neglect patients, and may instead be a general characteristic of the effects of sensorimotor adaptation on spatial cognition.

The visuospatial shift fluctuates

One intriguing result of this study was the instability of the visuospatial shift. In the rightward deviating prism group adaptation did not alter judgments on the Landmark task: the visuospatial aftereffect was never different from the pre-adaptation midline judgment. In contrast, adaptation to leftward deviating prisms induced a significant visuospatial shift in four non-consecutive post-adaptation blocks. This contrasts sharply with the sensorimotor aftereffect, which always differed significantly from the pre-adaptation measure of open-loop pointing.

These visuospatial shift fluctuations may be relevant within the framework of both neglect pathology and its recovery. After a right hemisphere lesion the lateralized (rightward) bias in neglect may be caused by a left hemisphere orienting

mechanism that becomes hyperactive, and neglect recovery may be related to the restoration of hemispheric/attentional equilibrium. Amelioration of neglect symptoms following either spontaneous recovery or PA correlates with activation of both hemispheres (Corbetta et al., 2005; Luauté et al., 2006b; Saj et al., 2013). The hypothesized hemispheric rebalancing in neglect recovery is supported by studies showing 1) that a second lesion in the spared hemisphere can improve neglect symptoms (Vuilleumier et al., 1996), 2) that inhibitory repetitive transcranial magnetic stimulation (rTMS) to the left parietal cortex transiently ameliorates neglect symptoms (Oliveri et al., 2001; Koch et al., 2008, 2012; Oliveri, 2011), and 3) that spontaneous neglect recovery is associated with an interhemispheric push-pull pattern of activity in the parietal cortices whereby the right parietal cortex is reactivated, and the left is less active in the chronic than the acute phase (Corbetta et al., 2005). Complementary evidence of inter-hemispheric interactions comes from studies in healthy participants (e.g., Koch et al., 2011). It is therefore possible that PA ameliorates neglect symptoms or induces neglect-like behavior by reestablishing or perturbing the hemispheric equilibrium. Since a parieto-cerebellar network has been shown to be involved in PA, changes in hemispheric equilibrium might be induced by bottom up signals from the cerebellum to the parietal cortex (Pisella et al., 2006).

Visuospatial shift fluctuations could also be due to a local modulation of activity within the right inferior parietal lobule (IPL). Right IPL is known to be involved in midline judgments in healthy participants (Fink et al., 2000; Cavézian et al., 2012), and inhibitory rTMS on the right IPL but not its left counterpart induces a significant rightward shift in the landmark line bisection task (Fierro et al., 2000). These fluctuations in visuospatial shift were an unexpected result, and future work is needed to clarify their origin.

Concluding remarks

This is the first study investigating the time course of the visuospatial shift after adaptation to leftward deviating prisms in healthy individuals. The rightward shift in midline judgments that we observed developed across time, lasted for at least 35 minutes after removal of the goggles, and its presence fluctuated across time. We limited our testing period to 40 minutes because we expected the visuospatial shift to decay across time and to disappear within this time period. As such, further studies

are required in order to establish how long visuospatial shifts last in the neurologically healthy brain.

It would be interesting to test neglect patients at a number of closely-spaced time intervals to see whether the degree of improvement in neglect symptoms also fluctuates after a single session of adaptation to rightward shifting prisms.

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3. TIME MATTERS: BOTH RIGHTWARD AND LEFTWARD PRISM
ADAPTATION BIAS LINE BISECTION BUT WITH DIFFERENT
TEMPORAL DYNAMICS

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In the first study solely LPA induced a significant modulation of the perceived center of the line. Thus, we wondered whether RPA failed to modulate line bisection judgments within the explored time window (i.e. 40 minutes) because its effects require more time to become significant. Indeed, if the prediction of the anatomo-functional model (Pisella et al., 2006) is correct, in healthy individuals we should observe a leftward modulation on visuospatial tasks after RPA. We tested this prediction with a second behavioral experiment in which we assessed PA after-effects following both right and left PA over a longer period of time (up to three days).

Abstract

Rightward prismatic adaptation (RPA) can reduce neglect symptoms in patients whereas adaptation to leftward deviating prisms (LPA) can induce neglect-like behavior in healthy subjects. The anatomo-functional model of PA postulates that both directions of PA should affect visuospatial perception in healthy subjects by hypo-activating the parietal cortex contralateral to the direction of the prismatic deviation and thus modulating interhemispheric balance. However, changes in visuospatial perception after RPA in healthy subjects have seldom been reported. Recent evidence that the LPA-induced visuospatial bias requires some time after adaptation to develop fully led us to hypothesize that any RPA-induced visuospatial bias might require more time and display different dynamics from that of LPA. We administered a perceptual line bisection task repeatedly over three days after LPA or RPA. In line with our prediction the results showed that both deviations induced a shift on the line bisection task in the direction opposite to the prismatic deviation. Crucially, while LPA induced a rapid rightward shift, after RPA the shift was gradual and became significant only 6 hours after adaptation. In sharp contrast, the temporal dynamics of the sensorimotor after-effects were comparable across both PA directions. By providing evidence that RPA in healthy subjects biases line bisection leftward our findings support the proposal that a single cerebello-parietal mechanism accounts for both reduction and induction of neglect(-like) behavior. We suggest that the different dynamics of left and right PA are produced by directional asymmetries in interhemispheric communication.

Introduction

Hemispheric rivalry is a widely acknowledged model for orienting spatial attention. Its main tenet is that spatial attention results from the balancing of two competitive and contralaterally-directed hemispheric vectors, whose weights depend on the activation level of each hemisphere (Kinsbourne, 1977). This theory, accounting for neglect as the result of a breakdown of the interhemispheric equilibrium, has gathered increasing support as it can explain both spontaneous (Corbetta et al., 2005) and stimulation-induced (Oliveri et al., 2001; Brighina et al., 2003; Koch et al., 2008; Sparing et al., 2009) neglect recovery, as well as visuospatial orienting biases in healthy subjects (Szczepanski and Kastner, 2013). Rightward prismatic adaptation (RPA), one of the most promising treatments for neglect to date (Farnè et al., 2002; Luauté et al., 2006; Serino et al., 2009; Nijboer et al., 2011; Kerkhoff and Schenk, 2012; Newport and Schenk, 2012; Jacquin-Courtois et al., 2013), is thought to restore the interhemispheric equilibrium, as supported by neuroimaging evidence suggesting the bilateral involvement of the dorsal attentional network (Saj et al., 2013). The anatomo-functional model proposed to explain the neurobiology of PA hypothesizes that both RPA and left prismatic adaptation (LPA) modulate the activity of the contralateral posterior parietal cortex (PPC) via bottom up signals from the cerebellum ipsilateral to the prismatic deviation (Pisella et al., 2005), thus possibly re-balancing the biased interhemispheric rivalry (Pisella et al., 2006; Striemer and Danckert, 2010; Newport and Schenk, 2012). This model provides a solid theoretical framework for understanding the functioning of PA because it evokes the same mechanism to explain both RPA's therapeutic effects in neglect (Rossetti et al., 1998) and the induction of rightward (neglect-like) biases following LPA in healthy subjects (e.g. Colent et al., 2000). Even though this model predicts that in healthy subjects LPA and RPA should produce opposite effects on visuospatial cognition, reports of significant changes in visuospatial perception after RPA in healthy subjects are so rare that RPA has become the gold-standard control for the effects of LPA. Indeed, not only do most studies showing a significant visuospatial modulation following LPA report no modulation after RPA (Colent et al., 2000; Michel et al., 2003; Loftus et al., 2009; Bultitude et al., 2013; Reed and Dassonville, 2014; Schintu et al., 2014), but the two studies reporting RPA-induced visuospatial modulation found it either in the unexpected direction (Berberovic and Mattingley, 2003), or in only a sub-population

(Goedert et al., 2010). This has resulted in the somewhat paradoxical situation wherein the current model of PA is not supported by the majority of PA studies.

Here we investigated whether the answer to this paradox might lie in our recent finding of a “temporal dimension” in PA whereby the rightward shift in perceptual line bisection after LPA requires some time after adaptation to develop fully, persists for at least 35 minutes, and within this time fluctuates rather than decreases systematically (Schintu et al., 2014). We hypothesized that changes in visuospatial cognition in healthy subjects take longer to significantly appear after RPA than LPA and tested this by investigating the after-effects of a single session of left or right PA over 3 days.

Materials and Methods

Participants

Sixteen healthy volunteers participated in the study. Given that our hypothesis stemmed out from our previous study in which the sample showed pseudoneglect in the perceptual line bisection task (Schintu et al., 2014), we included only participants who perceived the middle of the horizontal line to the left of the true center. Participants were randomly assigned to either the LPA group (n=8, 5 females, mean age = 23 standard error of the mean (SEM) = 0.7) or RPA group (n=8, 7 females, mean age = 23.2 SEM = 0.9). All participants had normal or corrected-to-normal vision and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). They gave informed consent and were paid for their participation in the experiment. The study was approved by the local ethics committee and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki (last update: Seoul, 2008).

Procedure

The experiment consisted of eleven blocks: one before and ten after PA (see Figure 1). The pre-adaptation block occurred before PA and the post adaptation blocks were administered 2 minutes, 1, 2, 4, 6, and 8 hours (T0 to T8) after PA on the same day as the PA (D1), and again at T0 and T8 on the following two days (D2T0, D2T8, D3T0, D3T8). In the time elapsing between sessions participants were not restrained in any

activity and free to carry whatever activity they liked (such as writing, reading, sleeping...etc.).

Each experimental block included four different tasks, which measured four different parameters:

- Perceptual line bisection (LB) – visuospatial shift;
- Open-loop pointing (OL) – sensorimotor shift;
- Straight-ahead pointing (SA) – proprioceptive shift;
- Visual judgment (VJ) – visual shift.

The four tasks were presented in one of two sequences (A and B) and participants were randomly assigned to one of the two sequences (Sequence A: SA - VJ - LB – OL; Sequence B: OL - SA - VJ- LB). Based upon the previous study from our group showing that the visuospatial shift was not significant until 5 minutes after LPA (Schintu et al., 2014), the perceptual line bisection task was always administered in the second half of each block - between 5 and 10 minutes after the onset of the block. Care was taken to ensure that each experimental block started at the correct time after PA, but since response times during each task varied slightly across participants (and for a given participant across blocks), block duration ranged between 10 and 12 minutes. For each task the block before adaptation provided a baseline measurement, which was then compared with those obtained in each of the ten post-adaptation blocks (Fig. 1).

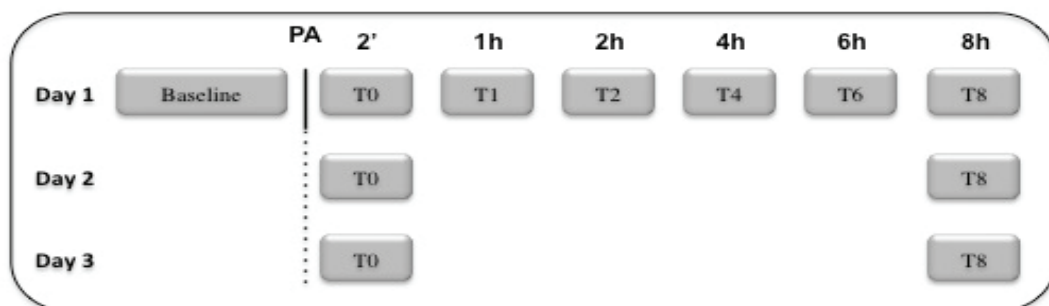


Figure 1. Experimental design. The experiment consisted of eleven experimental blocks (one before and ten after prism adaptation). PA: prism adaptation to leftward or rightward prism depending on the experimental group. Each block consisted of four tasks: Perceptual line bisection, Open-loop pointing, Straight-ahead pointing, Visual judgment.

Apparatus

The same experimental setup was used throughout the whole experiment (baseline measurement, prism adaptation, and post-adaptation measurements). Participants were comfortably seated with their head positioned on a chinrest in front of a horizontal board that measured the landing position of the finger during the open-loop and straight-ahead pointing tasks with an accuracy of 1 degree (similar to Rossetti et al., 1998), and on which three target dots (8 mm diameter) were positioned at 0, -10 and +10 degrees from their body midline and at approximately 57 cm from their nasion. During both these tasks and the adaptation procedure, participants rested their left hand on their left thigh and pointed with their right index finger perpendicular to the board while wearing a thimble-mounted sensor which permitted the position of the index finger to be measured in angular degrees from the mid-sagittal axis. The right index finger's (unseen) starting position was marked by a home-pad close to the chest aligned with the body's mid-sagittal axis. Participants were instructed to point at a fast but comfortable speed during PA procedure, and as uniformly as possible throughout the experiment in terms of speed and distance from their chest. During both visual judgment and perceptual line bisection tasks a computer screen (22 inches, resolution 1680x1050, refresh rate 60 HZ) was positioned 35 cm from the participants' eyes with its center aligned to the participant's mid-sagittal axis. During these tasks, participants placed their hands on their lap beneath the table.

Prism adaptation

Participants were fitted with prismatic goggles that deviated their visual field by 15 degrees either leftward (n=8) or rightward (n=8). They were seated in front of the board and performed a total of 150 verbally instructed pointing movements with their right index finger towards the right (+10°) and left (-10°) targets in a pseudorandom order. Before pointing they placed their right index finger on the starting position. Participants could not see their hand when it was at the starting position and during the first third of the pointing movement. They were instructed to point with the index finger perpendicular to the board, to execute a one-shot movement at fast but comfortable speed, and to return their hand to the starting position when instructed by the experimenter. After 150 pointing movements the prismatic goggles were removed

and performance on the four tasks mentioned above and described in detail below was measured ten times at the time-points illustrated in Fig. 1.

Experimental tasks

Perceptual line bisection to measure visuospatial shift

Perceptual line bisection task was used as a measure of the visuospatial shift induced by PA; it consisted in a series of pre-bisected line that appeared centrally displayed on the computer screen. Participants were instructed to fully inspect each pre-bisected line and judge whether the mark (transector) was closer to the left or right end of the line. In this two-alternative forced-choice paradigm participants answered by pressing the pedal under their left foot if the transector was perceived as being closer to the left end and under their right foot if they thought it was closer to the right end. Bilateral responses were used to avoid any asymmetry in hemispheric activation that may be associated with unilateral or verbal responses (Kinsbourne, 1975, 1993). They were instructed to respond accurately and quickly. Prior to the baseline measure, at least ten practice trials were given to ensure that participants properly understood the instructions and were confident answering with the pedals. The stimuli were white lines (350 mm x ~2 mm) and were displayed on a black screen positioned 35 cm from the participant's eyes. Lines were transected at the true center and at 2, 4, 6, 8, and 10 mm toward the left and right of the true center. Each of the 11 different pre-bisected lines was presented six times in a random order, yielding a total of 66 trials, which took approximately three minutes to complete. Each pre-bisected line was displayed for a maximum of five seconds or until a response was made, and was then replaced by a black-and-white patterned mask which stayed on the screen for one second before the next pre-bisected line was displayed. Presentation software (Neurobehavioral Systems, Inc., USA) was used to generate the stimuli, record responses, and control the timing of stimulus presentation throughout the task. For each participant the percentage of 'right' responses was plotted as a function of the position of the transector. These data were then fitted with a sigmoid function and the value on the x-axis corresponding to the point at which the participant responded 'right' 50% of the time was taken as that participant's point of subjective equality (PSE).

Open-loop pointing to measure sensorimotor shift

Open-loop pointing task was used as a measure of sensorimotor shift induced by PA. Participants performed six pointing movements to the central target (0°) without visual feedback. Before each of the six pointing movements participants were instructed to look at the central target (0°), close their eyes, point to the target with their right index finger while keeping their eyes closed, and then return their hand to the starting position. The delay between participants closing their eyes and pointing to the central target ranged between 1 and 2 seconds. To ensure that participants had no visual feedback regarding either their movement or their landing position, vision of the arm and hand was occluded before onset of the pointing movement. The sensorimotor shift was measured as the average of the six pointing movements to the central target.

Straight-ahead pointing to measure proprioceptive shift

Straight-ahead pointing task was used as a measure of proprioceptive shift induced by PA. Participants performed six pointing movements to their perceived midline. Before each movement, they were verbally instructed to close their eyes and imagine a line splitting their body in half, to project this line onto the board in front of them, to point to the line while keeping their eyes closed, and then return their hand to the starting position. As for the open-loop task described above, the delay between participants closing their eyes and pointing to the central target was always between 1 and 2 seconds, and vision of the arm and hand was occluded before onset of the pointing movement.

Visual judgment of body midline to measure visual shift

Visual Judgment task was used as a measure of the visual shift induced by PA. Participants had to judge whether a white dot (0.3° of diameter) that appeared on the computer screen was on the right or left side of their body's midline. In this two-alternative forced-choice paradigm the experimenter recorded the participants' verbal responses. The dot was displayed on a black screen positioned 35 cm from the participant's eyes in total darkness and remained on the screen until a response was made. We used a simple staircase method with adaptive step size of the horizontal dot position, and the step size gradually decreased during the course of the experiment

based on the responses of the subject. At the beginning of the experiment the first stimulus was positioned within a range of 40 degrees centered on the subject's midsagittal axis: between -20° (to the left) and $+20^\circ$ (to the right). The left/right side of the dot's initial position was alternated across blocks to avoid biases related to the starting position. After each response, the horizontal space was split in half, and the half space that included the positive response was selected for the next stimulus presentation. The iterative process ended when the difference between the two values (maximum and minimum) was smaller than the step resolution (0.6°) and each measurement was the average of six repetitions. Presentation software (Neurobehavioral Systems, Inc, USA) was used to generate the stimuli, record responses, and control the timing of stimulus presentation throughout the task. This task took approximately 5 minutes to complete.

Results

Statistical analyses were carried out using the software Statistica 10 (Statsoft Inc. 2011). Significance was set at .05 (two-tailed) and means are presented with the standard error of the mean (SEM) in parentheses.

Each of the four measures indexing sensorimotor (OL, SA, VJ) and visuospatial (LB) effects of PA was submitted to a repeated measure ANOVA with Time (11 levels) as a within-subject factor and Group (LPA or RPA) as a between-subject factor. Since we were interested in comparing each post-adaptation session to the baseline for a given direction of PA, planned comparisons (two-tailed paired t-tests, Bonferroni corrected) were carried out independently for each PA direction.

Visuospatial shift

Figure 2a shows the average PSE for each of the eleven perceptual line bisection measurements for both the LPA and RPA groups. Before adaptation, the average PSE was -2.6 mm (0.7) in the LPA group and -2.4 (0.8) in the RPA group (i.e. both leftward biased). The repeated measures ANOVA on the PSE data revealed a main effect of Time [$F(10, 140) = 2.26, p = .017$], a non-significant trend for a main effect of Group [$F(1, 14) = 4.08, p = .063$], and a significant Time by Group interaction [$F(10, 140) = 2.45, p = .010$]. Planned comparisons revealed that, compared to baseline, bisection judgments in the LPA group were significantly shifted rightward at

T0, T4, and T8 (all $p_s \leq .043$). In contrast, in the RPA group, line bisection judgments were significantly shifted leftward at T6 only ($p = .008$).

Sensorimotor shift

Figure 2b shows the average landing position for the eleven open-loop pointing measurements. The repeated measures ANOVA on these data revealed a main effect of Group [$F(1, 14) = 24.27, p < .001$], no main effect of Time [$F(10, 140) = 0.96, p = .483$], and a Time by Group interaction [$F(10, 140) = 23.11, p < .001$]. Planned comparisons revealed that for both LPA and RPA groups several post-adaptation measurements differed significantly from the baseline measurement. This was the case for the LPA group at T0, T1, T2, T4, T8, and D3T0 (all $p_s \leq .039$) and for the RPA group at T0, T1, T6, and D2T0 (all $p_s \leq .024$).

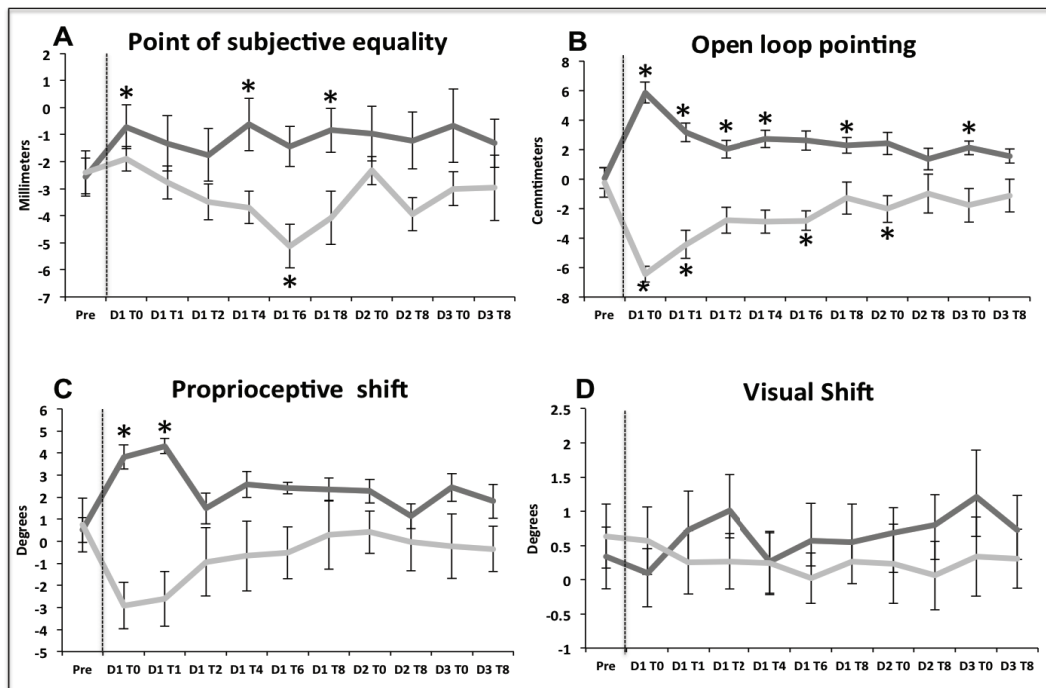


Figure 2. A) Point of subjective equality judgment; B) Open-loop pointing error; C) Straight-ahead pointing; D) Visual judgment of body midline. Average performance of all 16 subjects (8 in each group) on each task before (left of the dotted vertical line) and after adaptation to leftward and rightward-deviating prisms. Negative and positive values represent leftward or rightward errors/deviation in both PSE judgments and open loop pointing. Error bars represent 1 SEM. * $p < .05$. The LPA group is shown in black and the RPA group in grey.

To assess whether there was any correlation between an individual participant's shift in PSE and sensorimotor after-effect as measured by the open-loop

pointing error for each of the ten post-adaptation blocks we computed separate Pearson product moment correlations between the absolute value of the two shifts. None of these correlations were significant ($r_s \leq .211$, $p_s \geq .432$).

Proprioceptive shift

The repeated measures ANOVA on the straight ahead pointing revealed a main effect of Group [$F(1, 14) = 7.20$, $p = .018$], no main effect of Time [$F(10, 140) = 0.52$, $p = .877$], and a Time by Group interaction [$F(10, 140) = 5.01$, $p < .001$]. Planned comparisons revealed that in the LPA group, straight ahead pointing was significantly shifted rightward at T0 and T1 ($p_s \leq .023$), whereas in the RPA group there was a leftward shift at these same times that did not survive Bonferroni correction ($p_s > .05$).

Visual shift

The repeated measures ANOVA on the visual shift data revealed no main effect of Group [$F(1, 14) = 0.32$, $p = .583$] or Time [$F(10, 140) = 0.87$, $p = .565$] and a tendency for Time by Group interaction [$F(10, 140) = 1.81$, $p = .065$].

Discussion

It is well established that LPA induces a significant rightward shift in line bisection judgments. In line with this, our results showed a significant rightward shift in midline perception 5-10 minutes following LPA and again 4 and 8 hours after adaptation. In contrast to the large number of previously reported null results regarding the effects of RPA in healthy subjects (Colent et al., 2000; Michel et al., 2003; Loftus et al., 2009; Bultitude et al., 2013; Reed and Dassonville, 2014; Schintu et al., 2014), but consistent with the predictions of the anatomo-functional model of PA (Pisella et al., 2006; Striemer and Danckert, 2010; Jacquin-Courtois et al., 2013), we also observed a leftward shift of midline perception after RPA, which reached significance 6 hours after adaptation.

In the absence of any data examining LPA's effect on visuospatial cognition across time it was implicitly assumed to follow the same time course as the sensorimotor aftereffect. Namely, it was supposed to be maximal immediately after PA and to decrease across time (Schintu et al., 2014). We recently showed that during the 40 minutes following a single session of LPA the visuospatial shift was not

observed until a few minutes after PA, and instead of decreasing gradually, fluctuated across time (Schintu et al., 2014). Besides replicating our previous results, the present finding of a significant rightward shift 5 - 10 minutes after LPA which ‘vanishes’ and then reappears 4 hours, and again 8 hours afterwards, clearly indicates that LPA’s effects on visuospatial cognition in healthy subjects last much longer than previously suspected and that their recently discovered fluctuations extend well beyond the timescale of 1 hour. Interestingly, similar fluctuations were not observed after RPA, where line bisection judgments gradually shifted leftward until becoming significant 6 hours after adaptation.

Only two studies have reported some modulation of line bisection performance following RPA in healthy subjects. In one study, the visuospatial modulation was rightward, instead of leftward as it would have been expected (Berberovic and Mattingley, 2003). In the second study, the visuospatial modulation was in the expected direction, but limited to a sub-group of participants who at baseline (i.e., before PA) showed a rightward bias in manual line bisection instead of the more typical pseudoneglect. In contrast, the sub-group of participants with pseudoneglect at baseline was not affected by RPA. The authors of this study (Goedert et al., 2010) proposed that the asymmetrical efficacy of left and right PA in modulating visuospatial cognition may depend upon the bias shown by the participants at baseline. Here, however, we show that in two groups with the same initial leftward bias (pseudoneglect) both left and right PA modulated visuospatial cognition in opposite directions. Furthermore, we demonstrate that left and right PA display quite different time courses, showing that the so-far relatively neglected temporal dimension of PA may actually have rather profound consequences for our understanding of visuospatial cognition and should therefore be incorporated into the anatomo-functional model of the mechanisms of prismatic adaptation.

A previously offered explanation for the absence of an effect of RPA on perceptual line bisection judgments in healthy subjects was that RPA acts on the contralateral (left) PPC whereas line bisection relies mostly on the right PPC (Fierro et al., 2000; Fink et al., 2000, 2002). By postulating that each prismatic direction modulates (probably inhibits) the PPC contralateral to the prismatic deviation, the anatomo-functional model implies that LPA modulates healthy visuospatial cognition by directly modulating the right PPC, whereas RPA inhibits the left PPC which is considered to be pathologically hyperactive in patients (Pisella et al., 2006; Striemer

and Danckert, 2010). However, even if perceptual line bisection may be solved uniquely within the right PPC, in healthy subjects it appears to be influenced by interhemispheric competition (Szczepanski and Kastner, 2013). Indeed, the idea that spatial attention is determined and modulated by activity in a network involving (at least) both parietal cortices and their interhemispheric interactions (Oliveri et al., 2001; Fink et al., 2002; Brighina et al., 2003; Szczepanski and Kastner, 2013) is consistent with the results of neuroimaging studies showing that PA produces bilateral parietal activations (Luauté et al., 2006; Saj et al., 2013; Crottaz-Herbette et al., 2014).

The different time courses of the effects of LPA and RPA cannot be attributed to differences in the strength of the sensorimotor adaptation, as the sensorimotor measure we used as a proxy for PA aftereffects clearly showed that left and right PA-induced open-loop pointing errors were opposite in direction, but comparable in size. Similarly, we can rule out the possible role of fatigue in the significant leftward shift in line bisection following RPA, as this shift increased steadily until reaching its maximum 6 hours after PA, then decreased between 6 and 8 hours on the same day, a temporal profile that is incompatible with fatigue. Instead, if the spatial biases created by PA are triggered by reduced activity in the PPC contralateral to the prismatic deviation, which in turn alters bilateral cortical activity via interhemispheric connections (Pisella et al., 2006; Striemer and Danckert, 2010), then a tentative explanation for the different time courses of the visuospatial shifts might be related to recent findings from Koch and collaborators (2011). Using a triple-pulse TMS approach to investigate interhemispheric (parietal-to-parietal) connectivity, these authors found stronger right-to-left than left-to-right interhemispheric inhibition. Specifically, a conditioning pulse over the right PPC induced a greater decrease in parieto-motor connectivity measured in the left hemisphere than vice versa. They proposed that their results reflect anatomical and physiological asymmetries of interhemispheric connections. One such candidate might be the fibers found in the posterior part of the corpus callosum (the splenium), which are important for interhemispheric communication between visual areas, including occipital and posterior parietal cortices (see Berlucchi, 2014 for a review), and appear to contain more right-to-left than left-to-right connections (Putnam et al., 2010). In addition to this anatomical asymmetry, there is also evidence for a general asymmetry in the speed of interhemispheric communication, with communication being faster from

right-to-left (see van der Knaap and van der Ham, 2011 for a review). These asymmetries in the strength and in the speed of interhemispheric communication could be at the origin of our observations. The gradual leftward shift in midline judgments after RPA would reflect slower and weaker activation of the right PPC from the PA-induced inhibition of the left PPC. The rapid, fluctuating shift after LPA would reflect faster and stronger activation of the left PPC from the PA-induced inhibition of the right PPC. A recent fMRI study reporting significant changes in the BOLD signal of healthy participants immediately after adaptation to RPA, but no significant changes in their behavior on a visual detection task (Crottaz-Herbette et al., 2014), demonstrates that the absence of behavioral changes does not imply the absence of neural changes. Together with our data, this finding suggests that RPA might induce a cascade of neural changes in a network involving both hemispheres that are not reflected by significant behavioral changes until a few hours after adaptation.

The gradual appearance of RPA-induced cognitive effects in healthy subjects can be related to the beneficial effects of RPA in the original paper by Rossetti and collaborators (1998), which showed larger effects in neglect patients two hours after adaptation than immediately after adaptation. If RPA inhibits the left PPC and in turn activates the right hemisphere via interhemispheric communication its effects might occur earlier in patients than in healthy subjects because of the hyper-activation of the left hemisphere (Koch et al., 2008) and because of changes in the strength of interhemispheric connections caused by the right hemisphere lesion.

In conclusion, this is the first report showing that RPA biases visuospatial cognition in healthy subjects in a direction opposite to that of LPA-induced. These results provide strong support for the current anatomo-functional model of PA and clearly indicate that the temporal dimension of PA is important, and maybe even critical, and needs to be taken into account when attempting to understand the plasticity mechanisms induced by PA in healthy and neurological populations.

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4. MODULATIONS OF PPC-M1 FUNCTIONAL CONNECTIVITY
AFTER LPA AND SHIFTS IN LINE BISECTION JUDGMENTS
REFLECT INDIVIDUAL DIFFERENCES IN PSEUDONEGLECT

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In preparation

Since the results of the second behavioral experiment provided evidence in support of the anatomo-functional model proposed by Pisella and colleagues (2006) we went on to investigate the physiology of LPA-induced visuospatial modulations. Using a twin-coil paired-pulse TMS approach we examined the effects of LPA on a perceptual line bisection task in healthy participants and on PPC-M1 connectivity in either the left or right hemisphere. Based on the assumption that PA acts similarly to rTMS (both behaviorally and physiologically) we predicted that LPA would induce a neglect-like bias in the line bisection task by modulating the strength of the PPC-M1 connectivity: decreasing it in the RH and increasing it in the LH due to the LH's release from interhemispheric inhibition.

Abstract

Prism adaptation (PA) is a sensorimotor process that is known to modulate visuospatial cognition. While adaptation to a rightward optical displacement (RPA) can ameliorate neglect symptoms, leftward adaptation (LPA) can induce neglect-like bisection biases in healthy individuals. The mechanism underlying PA's effects on cognition is poorly understood. Since similar bisection biases can be induced by the virtual lesion approaches using repetitive transcranial magnetic stimulation (rTMS) of the right posterior parietal cortex (PPC) one possibility is that LPA may induce neglect-like behavior in healthy individuals by decreasing the excitability of the right hemisphere and/or increasing that of the left hemisphere. In agreement with this hypothesis, Koch and collaborators induced an amelioration in neglect patients by down-regulating parietal-to-motor functional connectivity (PPC-M1) within the left hemisphere, measured using dual-site paired-pulse TMS (Koch et al., 2008b). Here we used a similar approach in healthy participants to examine whether the rightward bias induced by LPA on a perceptual line bisection task is associated with modulations of the PPC-M1 connectivity in either the left or right hemisphere. TMS over the right hemisphere seemed to impede the rightward shift in line bisection judgments typically induced by LPA, and we observed no change in PPC-M1 connectivity in the RH after LPA. In contrast, LPA significantly modulated both line bisection judgments and PPC-M1 connectivity when the left hemisphere was probed by TMS. Moreover, the direction of these modulations depended on individual differences between participants, namely whether they initially judged the center of pre-bisected lines on the left (pseudoneglect) or right of the true center. These findings suggest that LPA-induced changes in line bisection and left-hemisphere PPC-M1 connectivity appear to depend upon the initial spatial bias of the subject and that even very sparsely applied TMS over the right PPC might interfere with the network responsible for line bisection shifts after LPA.

Introduction

Unilateral spatial neglect (USN) frequently occurs after right hemispheric damage and is an invalidating multicomponent syndrome in which perception of the contralesional side of space is compromised (Vallar, 1993; Di Monaco et al., 2011). The rivalry theory (Kinsbourne, 1977) hypothesizes that ‘where’ attention is oriented in the external space results from competition between contralaterally-directed hemispheric vectors and that USN results from an imbalance in the system caused by damage to the right hemisphere (RH), which additionally releases the left hemisphere (LH) from interhemispheric inhibition. This imbalance is thought to result from hypo-activation of the damaged right hemisphere with concurrent hyper-activation of the left hemisphere (Corbetta et al., 2005) which biases patients’ attention toward the right side of space (Snow and Mattingley, 2006). One physiological expression of the LH’s release from inhibition has been documented in terms of hyper-excitability of parietal-motor (PPC-M1) connectivity, observed in the spared LH of neglect patients (Koch et al., 2008b). Indeed, when this hyper-excitability is reduced by inhibitory repetitive transcranial magnetic stimulation (rTMS) of the LH, the severity of USN symptoms decreases (Koch et al., 2008b). When inhibitory rTMS protocols are applied to the RH of healthy individuals they induce neglect-like biases, such as a rightward shift in line bisection (e.g., Fierro et al., 2000). Neglect-like biases in bisection can also be obtained by using a simple sensorimotor procedure, such as adaptation to leftward shifting prisms (LPA) (Colent et al., 2000; Schintu et al., 2014). As opposed to rightward prism adaptation (RPA), which has long been known to decrease the severity of neglect symptoms (Rossetti et al., 1998), LPA has been proposed to hypo-activate the right posterior parietal cortex (PPC), possibly in turn altering activity of the left PPC by modulating the interhemispheric balance (Pisella et al., 2006). To date, however, this hypothesis has not been tested.

The aim of the present study was to investigate the physiological counterpart of the neglect-like visuospatial bias induced by LPA in healthy individuals. To this aim, we assessed participants’ perceptual line bisection performance before and after

LPA. In this bisection task, healthy individuals generally perceive the center of the line slightly to the left of the true center, a phenomenon called “pseudoneglect” (Bowers and Heilman, 1980). Some individuals, however, do not exhibit pseudoneglect (see Jewell and McCourt, 2000 for a review), a factor that may influence the modulation of line bisection performance by LPA (Goedert et al., 2010). To assess the changes induced by LPA at the level of activation of the left and right PPC we adopted the dual-site paired-pulse protocol introduced by Koch and colleagues (2007, 2008a), which allows quantification of the influence of PPC over M1 in each hemisphere and thus provides an index of the strength of parieto-frontal functional connectivity. Based on the assumption that PA acts similar to rTMS both behaviorally and physiologically, we made the prediction that LPA would induce a neglect-like bias in the line bisection task by modulating the strength of the PPC-M1 connectivity, namely by decreasing it in the RH, and increasing it in the LH following the release of interhemispheric inhibition.

Material and Methods

Participants

Twenty-eight volunteers (14 males, mean age = 25.46 years, SEM = 0.78) participated in the study. One participant was excluded because he did not properly adapt to the prisms (see methods). The 27 participants (13 males, mean age = 25.2 years, standard error of the mean (SEM) = 0.8) included in the final analyses were all adapted to prisms that shifted the visual field 15 degrees to the left (LPA) and PPC-M1 connectivity was measured before and after LPA in either the left (n = 13; 4 males, mean age 25.6, SEM 1.2) or right hemisphere (n=14, 9 males, age 24.8, SEM 0.9). All participants had normal or corrected-to-normal vision, were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), gave written informed consent, and received payment for their participation in the study. The study was approved by the local ethics committee and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki (last update: Seoul, 2008).

General procedure

Figure 1 shows a schematic of the experimental protocol, which consisted of perceptual line bisection (Landmark), paired-pulse TMS (ppTMS), and open-loop pointing measures both before and after LPA. The order of administration of the Landmark task and ppTMS was counterbalanced across participants (sequence A: ppTMS – Landmark task, sequence B: Landmark task – ppTMS) and the timing of the open-loop measurements was constant across sequences. Throughout the experiment participants were comfortably seated on an armchair with their head positioned on a neck rest during the ppTMS and on a chinrest during the LPA, Landmark task, and open-loop pointing tasks. In order to reduce the possibility of deadaptation, after LPA participants were instructed to keep their eyes closed and avoid moving their right hand during the small breaks between tasks.

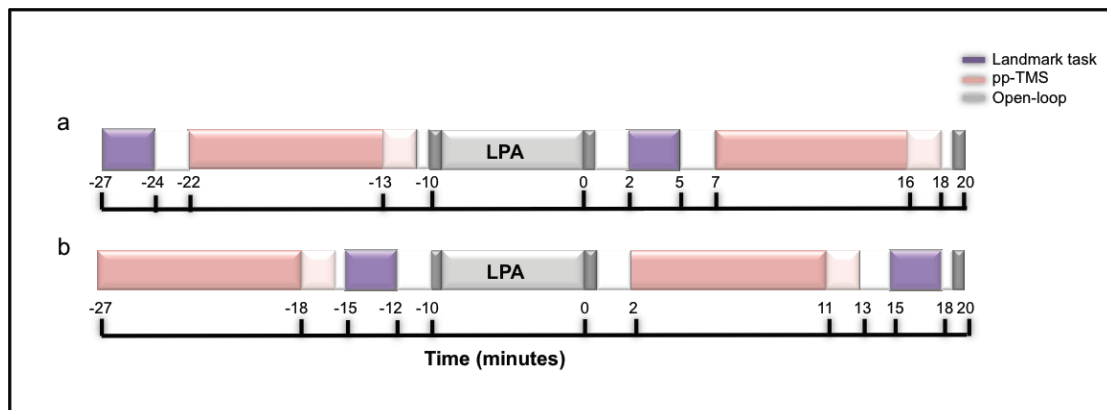


Figure 1. Experiment time course. Sequence a and sequence b both consisted of two blocks (one before and one after prism adaptation); a second open-loop pointing measurement was obtained 20 minutes after leftward prism adaptation (LPA).

Open-loop pointing

Participants were seated in front of white horizontal board on which three target dots (5 mm diameter) were positioned at 0, -10 and +10 degrees from their body midline with the central point 57 cm from their nasion when their head was positioned in the chinrest. Participants performed six pointing movements to the central target (0°)

without visual feedback. Before each of the six pointing movements they were instructed to look at the central target (0°), close their eyes, point to the target with their right index finger while keeping their eyes closed, and then return their hand to the starting position. The delay between participants closing their eyes and pointing to the central target ranged between 1 and 2 seconds. To ensure that participants had no visual feedback regarding either their movement or their landing position, vision of the hand was occluded before onset of the pointing movement. Open-loop pointing performance was calculated as the average of the six pointing movements to the central target. Open-loop pointing is the most reliable measure of the level of adaptation induced by PA and we excluded participants from all analyses if their 20-minute post-PA open-loop measurement was more than 1.96 standard deviations below the group mean (one participant excluded).

Landmark task

A computer screen was positioned in front of the participants who kept their head on the chinrest. A series of pre-bisected lines appeared on the screen and participants were instructed to fully inspect each line and judge whether the mark (transector) was closer to the left or the right end of the line. In this two-alternative forced-choice paradigm participants were instructed to respond accurately and quickly by pressing a pedal with their left foot if the transector was perceived as being closer to the left end of the line or with their right foot if they thought it was closer to the right end. Prior to the pre-LPA measure at least ten practice trials were given to ensure that participants properly understood the instructions and were confident answering with the pedals. Stimuli were white lines (350 mm x ~2 mm) displayed on a black screen positioned 35 cm from the participant's eyes. Lines were transected at the true center and 2, 4, 6, 8, and 10 mm toward either the left or right side of the true center. Each of the 11 different pre-bisected lines was presented six times in a random order, yielding a total of 66 trials, which took approximately three minutes to complete. Each pre-bisected line was displayed for a maximum of five seconds or until a response was made, and was then replaced by a black-and-white patterned mask, which stayed on the screen

for one second before the next pre-bisected line was displayed. Presentation software (Neurobehavioral Systems, Inc., USA) was used to generate the stimuli, record responses, and control the timing of stimulus presentation throughout the task. For each participant the percentage of 'right' responses was plotted as a function of the position of the transector. These data were then fitted with a sigmoid function and the value on the x-axis corresponding to the point at which the participant responded 'right' 50% of the time was taken as that participant's point of subjective equality (PSE).

Prism adaptation

Participants faced the white horizontal board wearing prismatic goggles that deviated their visual field by 15 degrees leftward. They performed a total of 150 verbally-instructed pointing movements with their right index finger towards the right (+10°) and left (-10°) targets in a pseudorandom order. Before pointing they placed their right index finger on the starting position. Participants could not see their hand when it was in the starting position or during the first third of the pointing movement. They were instructed to point with the index finger extended, to execute a one-shot movement at a fast but comfortable speed, and then to return their hand to the starting position. After 150 pointing movements the prismatic goggles were removed and the ppTMS, Landmark, and open-loop pointing measurements were repeated.

Paired-pulse TMS

A twin-coil paired-pulse protocol was used to deliver pulses either to M1 alone (test pulse: TS) or to M1 after a pulse was delivered to the ipsilateral PPC (conditioning pulse: CS). In one group of participants TMS was applied on the left hemisphere (LH-TMS group) whereas in the other group it was applied on the right hemisphere (RH-TMS group).

Electromyographic (EMG) recordings were made from the left (RH-TMS) or right (LH-TMS) first dorsal interosseous (FDI) using Ag-AgCl surface electrodes (Delsys). The active electrodes were placed over the muscle belly and the ground on

the ulnar near the elbow. The EMG signal was sampled at 2000 KHz, digitalized using an analogue-digital converter (Power 1401II, Cambridge Electronics Design, Cambridge, UK) and stored on a personal computer for off-line data analysis using SIGNAL software (Cambridge Electronic Devices, Cambridge, UK). TMS pulses were delivered using two custom-made branding iron figure-of-eight coils (external diameter: 50 mm) each connected to one 200/2 monophasic stimulator (The Magstim Company, Carmarthenshire, Wales), which were custom-synched but operated as two independent stimulators. The coil over M1 was held tangentially to the scalp at an angle of approximately 45 degrees from the midline (Di Lazzaro et al., 1998) while the other coil was positioned over the ipsilateral parietal cortex (over P3/P4 according to the 10-20 EEG system) and was rotated approximately 10° medially in order to induce a posterior-to-anterior directed current in the underlying cortical tissue (Koch et al., 2007). Neuronavigation (Brainsight, Rogue) was used to monitor the position of both coils throughout the experiment.

Participants rested their arm on a pillow placed on their lap or on the armrest of the chair, and leaned their head on a neck-rest. After identifying the FDI hotspot we determined the resting motor threshold (RMT), which was defined as the lowest stimulation intensity that evoked at least five out of ten MEPs of at least 50- μ V peak-to-peak amplitude. We then determined the stimulation intensity necessary to evoke an average MEP of approximately 1 mV in the relaxed FDI when stimulating on the contralateral motor cortex. This was then set at the intensity of the TS while 90% of the resting motor threshold measured over M1 was used as the CS intensity. The inter-stimulus intervals (ISIs) between the CS and TS were 2, 4, 6, and 8 ms (Karabanov et al., 2012). Twenty TS-only trials and twelve TS-CS trials for each ISI were delivered in a fully random sequence, with inter-trial intervals between 5 and 7 seconds. In some participants the TS-only MEP amplitude occasionally decreased substantially below 1 mV. In these cases we delivered a few more trials to make a total of 20 usable TS-only trials. Each ppTMS session lasted between 9 and 11 minutes.

The mean peak-to peak amplitude of the conditioned MEPs (CS-TS trials) was expressed as a percentage of the mean peak-to-peak amplitude of the unconditioned MEPs (TS-only trials) to compute normalized MEP amplitude. Each individual's anatomical MRI was normalized a posteriori onto the Montreal Neurological Institute (MNI) brain template using SPM software.

Data analysis

Statistical analyses on the strength of PPC-M1 connectivity were performed either on the normalized MEP or raw MEP amplitudes. As the aim of our study was to investigate the neural correlates of the well-known right shift in line bisection judgments induced by LPA, we first tested whether the whole group had and remained adapted until the end of the experiment. We then tested for the presence of the expected behavioral effect (a rightward shift in line bisection judgments). Finally, we analyzed the MEP amplitudes in light of the results of the analysis on the behavioral data.

Results

Open-loop pointing

To determine whether participants were significantly adapted immediately after LPA and at the end of the experiment (20 minutes after LPA) we performed a one-way repeated measures ANOVA on the average landing position of the open-loop pointing movements with Time (Pre, Post1, Post2) as the within-subject variable. This analysis revealed a main effect of Time [$F(2,52)=391.82$ $p < 0.001$] (Figure 2). The LSD post hoc tests revealed that the landing position at both Post1 (6.80 cm) and Post2 (3.99 cm) was significantly different from that measured before LPA (0.47 cm value; all $ps < 0.001$), and that Post1 was significantly different from Post2 ($p < 0.001$); This meant that the whole group showed a significant sensorimotor adaptation until the end of the experiment, and that it significantly decayed from the immediate (Post1) to the late (Post2) measurement.

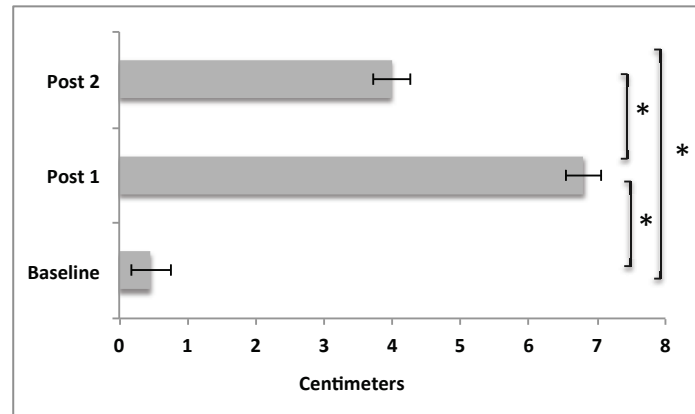


Figure 2 Average landing position for the open-loop pointing measure at baseline, post1 (immediate after LPA) and post2 (20 minutes after LPA) (n=27). Average landing position (x-axis) is represented in centimeters. Bars represent standard error of the mean (SEM).

Landmark task

The average point of subjective equality (PSE) for the whole group was slightly to the left of the true center (0) before LPA (mean -0.77 mm, SEM 0.57mm). After LPA the average PSE shifted even further to the left (mean -1.26 mm, SEM 0.60mm), although a two-tailed t-tests against zero of the change in PSE values after LPA (post minus pre) revealed that this shift was not significant [$t(26) 1.12$ $p= 0.275$]. Thus, not only did LPA apparently fail to induce a significant rightward shift in PSE judgments at the level of the whole group, but overall participants tended to shift in the opposite direction.

In the light of this largely unexpected result, we took a closer look at the factors that could have influenced the otherwise well-established LPA-induced rightward shift in PSE judgments. There is some evidence from a previous study that the perceptual bias of a participant before PA, namely whether they perceive the line's midpoint to the left (i.e., presence of pseudoneglect) or right (i.e., absence of pseudoneglect) of the true center, can interact with the directional effect of PA (Goedert et al., 2010). We then binary split our group of participants- those subjects for whom the PSE value was negative (fourth decimals) were assigned to the pseudoneglect group, whereas those subjects for whom it was positive or equal to zero

(fourth decimals) were assigned to the NO-Pseudoneglect group. Moreover, since the neural substrate of line-bisection is thought to be lateralized in the right parietal cortex (Fierro et al., 2000; Fink et al., 2000), we wondered whether the lack of a rightward shift in bisection could partly be due to the fact that one group received TMS stimulation over the right hemisphere. Another factor we considered was the time after adaptation at which line bisection judgments were administered, as half the participants did the bisection task between 2 and 6 minutes after adaptation while the other half did it between 14 and 18 minutes after adaptation (i.e., after the ppTMS).

To assess whether any of these factors influenced the line bisection performance at baseline we submitted average PSE values at baseline to a factorial ANOVA with Stimulated Hemisphere (LH-TMS group, RH-TMS group), Initial Bias (Pseudoneglect, No-Pseudoneglect) and Sequence (A, B) as between-subject variables. This analysis revealed a significant main effect of Initial Bias [$F(1, 19) = 42.174$ $p < 0.001$] and no other main effects or interactions (all $ps \geq 0.099$), indicating that none of the remaining factors influenced line bisection judgments before LPA.

We also re-analyzed the change in PSE (post LPA minus pre LPA) using a factorial ANOVA with the following between-subject variables: Stimulated Hemisphere (LH-TMS group, RH-TMS group), Initial Bias (Pseudoneglect, No-Pseudoneglect) and Sequence (A, B). This analysis revealed a significant main effect of Initial Bias [$F(1,19)= 13.585$ $p= 0.002$] and a Stimulated Hemisphere * Initial Bias interaction [$F(1,19)=6.8501$ $p= 0.017$] (Figure 3). LSD post-hoc tests revealed that the direction of the PSE change differed between the Pseudoneglect and No-Pseudoneglect sub-groups in the LH-TMS group ($p<0.001$), whereas no difference was found between these sub-populations in the RH-TMS group ($p= 0.579$). Furthermore, within the Pseudoneglect sub-population there was a significant difference in the PSE change between the RH-TMS (-1.021 mm) and LH-TMS (1.855 mm) groups ($p= 0.004$). Thus, the PSE shifted when PPC-M1 connectivity was measured in the LH, but not in the RH and within the LH-TMS group, the direction of

the PSE shift was opposite for the Pseudoneglect (rightward) and No-Pseudoneglect sub-populations (leftward).

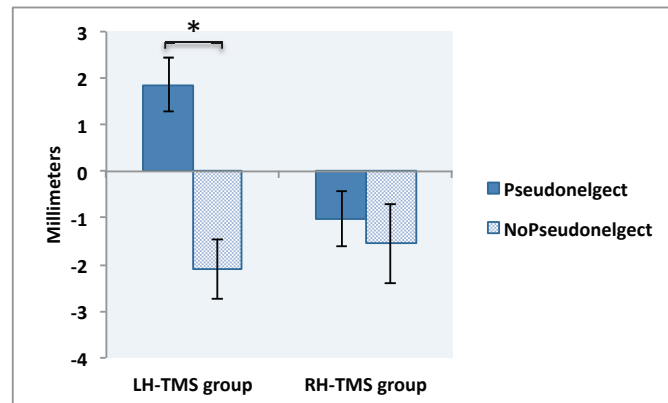


Figure 3. Average change in PSE (PostPA minus PrePA) after adaptation to LPA (n=27). The graph represents Rightward (positive values) or leftward (negative values) shifts in PSE induced by LPA. A rightward shift was observed only in those participants from the LH-TMS group who exhibited pseudoneglect at baseline. In the other three cases there was a leftward shift, which was significant only in those participants in the LH-TMS group who did not exhibit pseudoneglect at baseline. The change in PSE (y-axis) is represented in millimeters and error bars represent standard error of the mean (SEM).

To test whether the PSE shift induced by LPA was significantly different from zero in any of the four sub-groups we did a series of 2-tailed t-tests which revealed that in the LH-TMS group both the Pseudoneglect and No-Pseudoneglect sub-populations had significant shifts [respectively $t(7) = 3.25$ $p = 0.014$; $t(4) -3.26 = p = 0.031$], whereas in the RH-TMS group, neither sub-population showed any significant PSE shifts [respectively $t(7) = -1.75$ $p = 0.124$; $t(5) = -1.83$ $p = 0.127$]. Thus, only Pseudoneglect and No-Pseudoneglect participants in the LH-TMS group showed significant, but opposite, shifts in line bisection (rightward and leftward respectively).

Paired-pulse TMS

To assess whether the abovementioned factors influenced the strength of PPC-M1 connectivity measured at baseline (before LPA), we submitted the normalized CS-TS MEP amplitudes at baseline to a repeated measures ANOVA with ISI (2, 4, 6, 8 ms) as a within-subjects variable and Stimulated Hemisphere (LH-TMS group, RH-TMS

group) and Initial Bias (Pseudoneglect, No-Pseudoneglect) as between-subject variables. This analysis revealed a tendency for a Stimulated Hemisphere * Initial Bias interaction $p = 0.057$ (Figure 4) and no other main effects ($ps > 0.182$) or interactions ($ps > 0.237$).

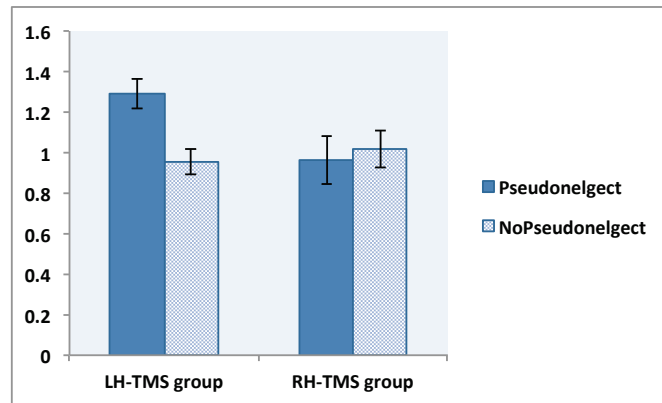


Figure 4. Normalized MEP amplitude (averaged across the 4 ISIs) at baseline (before adaptation to LPA) ($n=27$). MEP amplitude (y-axis) represents a proportion of TS-only MEP amplitude. Error bars represent standard error of the mean (SEM).

We then ran a repeated-measures ANOVA to analyze the change in PPC-M1 connectivity values (PostPA - PrePA) with ISI (2, 4, 6, 8 ms) as a within-subjects variable and TMS-Hemisphere (LH-TMS group, RH-TMS group) and Initial Bias (Pseudoneglect, No-Pseudoneglect) as between-subject variables. This revealed a significant TMS-Hemisphere * Initial Bias interaction $p = 0.043$ (Figure 5), and no other main effects ($ps > 0.197$) or interactions ($ps > 0.211$). LSD post-hoc tests revealed that in the LH-TMS group the change in PPC-M1 functional connectivity was different between Pseudoneglect and No-Pseudoneglect populations ($p = 0.026$) but that in the RH-TMS group these two populations did not differ ($p = 0.550$).

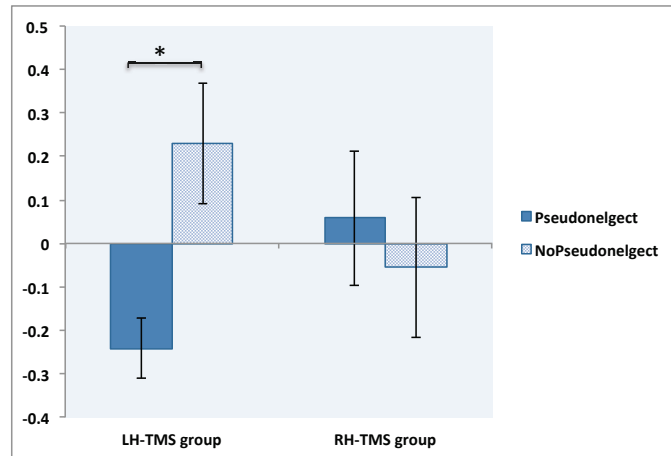


Figure 5. Average change in normalized MEP amplitude (PostPA minus PrePA) after adaptation to LPA (n=27). Negative values indicate a decrease and positive values an increase in the strength of PPC-M1 interactions after LPA. Error bars represent standard error of the mean (SEM).

Finally, to assess whether the amount of change in the strength of PPC-M1 functional connectivity was significant we compared the average (collapsed across the 4 ISIs) change for each sub-population (Pseudoneglect, No-Pseudoneglect) in the two groups (LH-TMS group, RH-TMS group) to zero. This series of 2-tailed t-tests against zero revealed that the only significant change was the decrease observed in the Pseudoneglect sub-population in the LH-TMS group [$t(7) = -3.53$ $p = 0.009$], the others comparison did not reach significance (all $ps \geq 0.173$).

Corticospinal excitability

To examine whether corticospinal excitability (CSE) was altered by LPA we conducted an ANOVA on the change in MEP amplitude for M1-only trials (TS) with TMS-Hemisphere (LH-TMS group, RH-TMS group) and Initial Bias (Pseudoneglect, No-Pseudoneglect) as between-subject variables. The only significant effect observed with this analysis was the TMS- Hemisphere * Initial Bias interaction [$F(91, 23) = 4.90$ $p = 0.037$] (Figure 6) (all other $ps \geq 0.358$). LSD post-hoc tests revealed that in the LH-TMS group there was a significant difference between the change in MEP amplitude in the Pseudoneglect, but not in the No-Pseudoneglect population ($p =$

0.040). A marginally significant trend was also found for a difference between the Pseudoneglect sub-population in the two TMS-Hemisphere groups ($p = 0.054$).

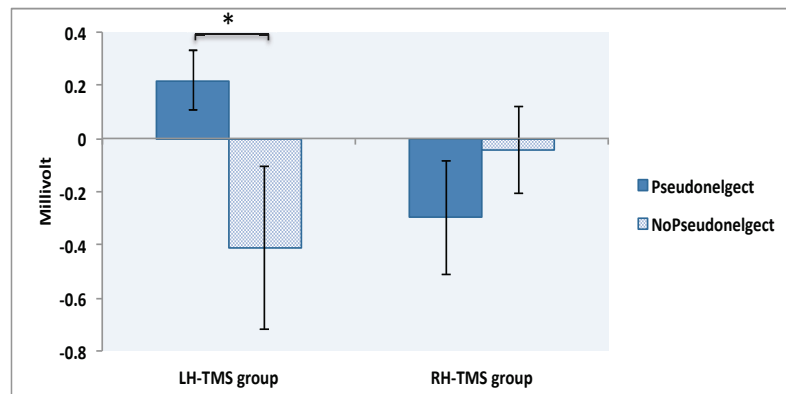


Figure 6. Average change in TS-only MEP amplitude (PostPA minus PrePA) after adaptation to LPA ($n=27$). Negative values indicate a decrease and positive values an increase of TS-only MEP amplitude after LPA. Change in MEP amplitude (y-axis) is represented in mV and error bars represent standard error of the mean (SEM).

Next we assessed whether the amount of change in TS-only MEP amplitude was significantly different by comparing the change in MEP amplitude for each sub-population (Pseudoneglect, No-Pseudoneglect) in the two groups (LH-TMS group, RH-TMS group) to zero. This series of 2-tailed t-tests against zero revealed that the change in TS-only MEP amplitude was never significantly different from zero (all p s ≥ 0.099).

Finally, we tested whether MEP amplitudes on TS-only and paired-pulse (CS-TS) trials were significantly different from each other before LPA. To do this we ran two separate repeated measures ANOVAs (one for each hemisphere group) on the raw MEP amplitudes with ISI (0 (TS), 2, 4, 6, 8 ms) as a within-subjects variable and Initial Bias as a between-subjects variable. For the LH-TMS group this analysis revealed no main effects but an almost significant ISI * Initial Bias interaction [$F(4,44) = 2.5473$ $p = 0.053$]. Exploratory LSD post-hoc tests suggested that in the Pseudoneglect sub-population MEP amplitudes were significantly larger in the 2ms ISI condition than in the TS-only condition ($p = 0.047$) (0.86 to 1.11 mV) (Figure 7a) and in the No-Pseudoneglect sub-population MEP amplitudes were significantly

smaller in the 4ms ISI condition than in the TS-only condition ($p = 0.014$) (1.23 to 0.83 mV). For the RH-TMS group this analysis revealed no significant main effects or interactions (all $p_s \geq 0.500$) (Figure 7b).

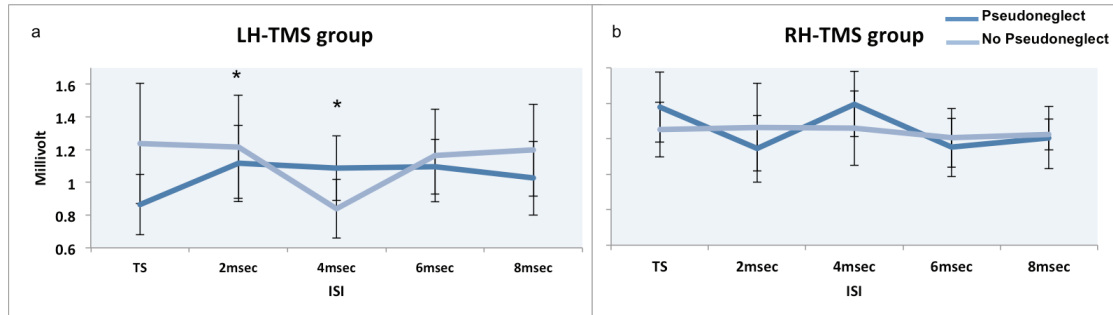


Figure 7 Average raw MEP amplitude before adaptation to LPA ($n=27$). A conditioning TMS stimulus (CS) was applied in the left hemisphere (Figure 7a) or right hemisphere (Figure 7b) at 4 different inter-stimulus intervals relative to the test stimulus (TS). MEP amplitude (y-axis) is represented in mV and error bars standard error of the mean (SEM).

Discussion

The aim of the present study was to investigate the physiological counterpart of the rightward shift in line bisection judgments induced by LPA in healthy individuals. We hypothesized that the LPA-induced neglect-like behavior in line bisection would decrease the strength of PPC-M1 connectivity in the RH, and increase it in the LH as a consequence of the release of interhemispheric inhibition.

Since LPA in normal participants induces a rightward shift on tasks that measure visuospatial cognition it is often described as inducing a neglect-like bias and is frequently used as a “model” of neglect. While there are similarities in the direction of the visuospatial shift observed in neglect and after LPA, to date there is no evidence for similar physiological changes in the two conditions. Since it was recently shown that PPC-M1 connections in the left hemisphere of neglect patients are hyperexcitable (Koch et al., 2008b) we tested whether the neglect-like behavioral bias induced by LPA in healthy participants is accompanied by changes in the excitability of right and/or left hemisphere PPC-M1 interactions.

When considered as a whole, since both groups underwent the same LPA procedure, the behavioral results from 27 participants revealed no shift in midline judgments after LPA. Quite astonishingly, this result fails to replicate the well-known, consistently replicated finding of a right visuospatial shift after LPA (Colent et al., 2000; Schintu et al., 2014). We considered the possibility that initial bias, that is the presence vs. absence of pseudoneglect, might have been influenced by factors like the sequence of administration of the tasks, or the hemisphere stimulated. This did not appear to be the case, however, since statistical analyses on the first PSE measure (before LPA) did not reveal any interactions between initial bias and stimulated hemisphere or experimental sequence. The presence of individual variability in line bisection performance is known (Jewell and McCourt, 2000), and it is possible that these two different observer types reflect two genuine observer type (Benwell et al., 2013) possibly driven by anatomical differences such as the asymmetries in the microstructure of fronto-parietal pathways that correlated with the amount of pseudoneglect as measured by manual line bisection task (Thiebaut de Schotten et al., 2011). Further analyses revealed that the LPA-induced visuospatial modulation interacted with both the initial bias shown by participants (presence or absence of pseudoneglect) and the hemisphere in which PPC-M1 functional connectivity was measured. While the no-pseudoneglect group shifted or tended to shift their PSE judgments leftward independently of the stimulated hemisphere, the pseudoneglect group had a tendency to shift leftward when the RH was stimulated and significantly shifted rightward when the LH was stimulated. In other words, none of the participants in the RH-TMS group modulated their line bisection judgments after LPA and those in the LH-TMS group who had an initial bias to the right of the line's midline (no pseudoneglect) significantly shifted leftward. We replicated the LPA-induced rightward shift solely in the pseudoneglect sub-population of the LH-TMS group. It is noteworthy that the presence or absence of pseudoneglect and its opposite directional shift following LPA interacted with the stimulated hemisphere as this rules out the possibility that the behavioral change we observed was solely determined by a 'regression to the mean' phenomenon (Newman et al., 2014). We suggest rather that

the opposite shifts in line bisection judgments induced by LPA in these two sub-populations might reflect the possibility that the direction of LPA-induced shifts depends upon the initial state of the system.

The pattern of changes observed in the functional connectivity data closely resembled that observed in the behavioral results. Namely, parieto-motor connectivity in the RH was not modulated by LPA whereas, in the LH the pseudoneglect and no-pseudoneglect sub-populations showed opposite changes: the strength of parieto-motor connectivity decreased in the pseudoneglect sub-population and seemed to increase in the no pseudoneglect population.

On the basis of previous work from our and other laboratories, we hypothesized that LPA would have induced a rightward shift on perceptual line bisection (neglect-like behavior). We further hypothesized that this effect would have been associated with an increase in the strength of the left posterior parietal cortex activity, possibly due to a release from the hypo-activated right PPC. Coherent with this expectation the no-pseudoneglect group, showed a non-significant tendency towards stronger PPC-M1 interactions - our proxy for the level of activity of the PPC. Their line bisection judgments, however, shifted leftward instead of rightward as would have been expected after LPA. In contrast to our expectations the pseudoneglect sub-population showed the predicted rightward line bisection shift but the strength of their PPC-M1 interactions decreased. These findings represent the opposite pattern of what we expected from the findings previously reported using a similar PPC-M1 protocol in neglect patients.

These findings provide the first evidence that LPA can modulate the strength of the parieto-frontal connectivity in healthy individuals. Since the change in TS-only MEP amplitudes (after – before LPA) was not significantly different from zero we ruled out the possibility that the change in the PPC-M1 connectivity was due to a change in M1 excitability. We can thus relate the change induced by LPA over left PPC-M1 connectivity to the influence of PPC over the ipsilateral M1.

Thus, on the basis of these preliminary results we suggest that LPA does not induce neglect-like behavior by increasing the strength of PPC-M1 connectivity in the LH. Further testing will be carried out to increase the size of the sample, but before collecting these data it is interesting to speculate that healthy individuals and neglect patients – who *prima facie* appear to be two sides of the same coin (i.e., pseudoneglect and neglect) may actually reflect activity of fundamentally different systems in the intact versus damaged brain. What is also extremely interesting is that neither the line bisection judgments nor the parieto-motor connectivity showed any significant change after LPA when our ppTMS protocol was applied over the RH. Instead, both line bisection judgments and PPC-M1 connectivity were significantly modulated solely when PPC-M1 was measured via TMS on the LH. Delivering TMS on the right parietal lobe, which is known to be involved in line bisection judgments (Fierro et al., 2000; Fink et al., 2000), might have prevented the emergence of the LPA-induced visuospatial shift. How a paired-pulse TMS protocol might have done this is not straightforward. It is, however, possible that stimulating PPC-M1 with such a protocol could have induced some cortico-cortical associative plasticity, similar to that recently shown between the posterior parietal and motor cortices (Chao et al., 2013). While the results of Chao and collaborators (2013) offer some clues towards an explanation of the results from our RH group, the duration of their paired associative stimulation was much longer than our PPC-M1 protocol and the delay between the PPC and M1 stimuli was always 8msec whereas we had four delays (between 2 and 8 ms). It is too early to know why our RH group did not behave as expected on the line bisection task, although some interference from the TMS protocol seems a very likely candidate and should be considered in future work.

In summary, in the LH group LPA induced opposite behavioral and physiological changes in the pseudoneglect and no-pseudoneglect sub-populations. The fact that the opposite shifts induced by LPA were not restricted to the behavioral performance, but also affected the physiological measure (PPC-M1 connectivity), reinforces the idea that the baseline measure of line bisection might reflect a state of the system. Which characteristic of the system determines this initial state is not clear

from our data. One possibility is that the physiological differences between the two populations lie in the relative excitability of their PPC-M1 connectivity in the two hemispheres, but since the LH and RH TMS groups were composed of distinct individuals we do not have the data to address this possibility. We do, however, have data from the LH of the two groups which suggest that the pseudoneglect and no pseudoneglect subgroups might differ in the average excitability of PPC-M1 connections within the left hemisphere, as pseudoneglect participants had slightly higher normalized MEP amplitudes than the no pseudoneglect participants, but further work is needed to test this possibility.

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5. GENERAL DISCUSSION

Prism adaptation (PA) is a visuomotor adaptation (Helmholtz, 1867) that can modulate visuospatial cognition, ameliorating neglect symptoms (Rossetti et al., 1998) as well as inducing *neglect-like* behavior in healthy individuals (Colent et al., 2000). Not only is PA a promising rehabilitation technique (Luauté et al., 2006a; Barrett et al., 2012) but it is also a research tool that can be used to investigate visuospatial cognition, and thus offers the possibility to draw parallels between the pathological and normal brain functioning. However, despite years of investigation the mechanisms underlying PA's effects on visuospatial cognition are poorly understood. Understanding PA's cognitive after-effects would substantially contribute to the understanding of intact and pathological visuospatial cognition.

The aim of my thesis was to investigate how prismatic adaptation can modulate intact visuospatial cognition in healthy subjects at both behavioral and neural levels.

In the first study we showed for the first time that the temporal dynamic of a visuospatial after-effect is not the same as that of the sensorimotor after-effect. More precisely, we found that LPA induced a significant rightward shift of the perceived center of visually presented pre-bisected lines (i.e. the point of subjective equality - PSE) that needed *some* time (~5 minutes) to become statistically significant, lasted at least 35 minutes after removal of the goggles, and fluctuated across time. In contrast, RPA induced a comparable sensorimotor after-effect (in terms of amplitude and dynamic), which was maximal immediately after exposure and progressively diminished with time, but failed to induce any significant effect on visuospatial cognition within the tested post-adaptation time window (40 minutes). In the second study we showed that both LPA and RPA significantly modulated visuospatial cognition, and that they did it with different temporal dynamics. We confirmed that LPA induced a significant rightward shift between 5 and 10 minutes after adaptation and established that the fluctuating effect protracted well beyond the timescale of 1 hour, since the rightward shift was again significant 4 and 8 hours after adaptation. In contrast, the leftward effect of RPA emerged slowly and gradually and became significant only 6 hours after adaptation. Importantly, in contrast to the cognitive effect, the sensorimotor after-effect had comparable temporal dynamics across both

PA directions. With the third study we investigated the possible physiological mechanism associated with the LPA-induced modulation of visuospatial cognition by measuring the functional connectivity between PPC-M1 in either the left or right hemisphere both before and after adaptation. In the whole group of subjects we failed to replicate our own result of a significant rightward shift on line bisection judgments after LPA. After looking more closely at these behavioral results we observed that the expected rightward shift was present only in the group of subjects stimulated on the left hemisphere whose initial bias was left of the true center (i.e. who showed pseudoneglect). When stimulated on the RH with the paired-pulse PPC-M1 protocol neither the group showing pseudoneglect nor the one without pseudoneglect exhibited any significant modulation in line bisection performance. This fact suggested to us that stimulation on the right hemisphere interacted with the development of the cognitive effect normally induced by LPA. The pattern of changes observed in the functional connectivity data closely resembled that observed in the behavioral results. Namely, parieto-motor connectivity in the RH was not modulated by LPA whereas, in the LH, the pseudoneglect and no-pseudoneglect sub-populations showed opposite changes: the strength of parieto-motor connectivity decreased in the pseudoneglect sub-population and increased in the no pseudoneglect population. These preliminary findings provide the first evidence that LPA can modulate the strength of parieto-frontal connectivity.

I will discuss the different aspects of the presence of a previously unreported temporal dimension in the visuospatial effects of PA in light of the two behavioral studies, the possible physiology of LPA-induced visuospatial modulation in light of the third study, and finally the general implications of these results.

5.1 A TEMPORAL DYNAMIC

Time is a dimension that has so far been neglected in PA research in healthy individuals. Whereas the duration of the PA-induced amelioration of USN symptoms has been investigated, mostly due to its clinical relevance (e.g. Farnè et al., 2002; Frassinetti et al., 2002; McIntosh et al., 2002; Pisella et al., 2002), the duration of the visuospatial modulation induced by PA in healthy individuals has never been explicitly questioned and previous studies only reported the duration of the

sensorimotor after-effect (Taub and Goldberg, 1973; Lackner and Lobovits, 1977; Fernández-Ruiz et al., 2004).

The observation that a visuospatial modulation in healthy subjects can last at least 35 minutes after a single session of PA was thus a new finding, and it was crucial for designing the third study, which aimed to investigate the physiology of PA-induced after-effects. Another novel observation was in contrast to the sensorimotor after-effect, which was immediately present after adaptation (i.e. within the first minute): our participants did not show a significant cognitive after-effect immediately after LPA, but instead needed some time for this effect to develop (~5 minutes). Interestingly, we also found that within the tested time window the LPA-induced shift in line bisection judgment fluctuated between being significantly and not significantly present. This was an unexpected result and was in sharp contrast with the sensorimotor aftereffect's dynamics, which progressively diminished but was always significantly different from the pre-adaptation measure of openloop pointing. It was already known that the two after-effects were uncorrelated in magnitude, (i.e. the amount of sensorimotor after effect does not predict the amount of visuospatial modulation or its magnitude), and this finding is reminiscent of the lack of correlation between straight-ahead pointing and line bisection in neglect patients after PA (Pisella et al, 2002) consistently with the different temporal profiles described here. However this is the first time that individual temporal dynamics for each after-effect have been shown.

One possibility is that this fluctuation of the PSE shift was due to differences between RPA and LPA in the variability in PSE modulation they each induced. There was, however, no significant difference in the amount of variability between the two groups. As such, variability differences cannot account for the presence of a significant shift in one group and the absence of a shift in the other. Rather, another possibility is that LPA itself induced the fluctuations. LPA is hypothesized to hypo-activate the right PPC and possibly release the left PPC from interhemispheric inhibition (Pisella et al., 2006). Given this, there are several possible explanations for the fluctuating effect we observed. It could be the expression of either inter-hemispheric interactions (e.g. Koch et al., 2011) or a local modulation of activity within the right inferior parietal lobule (IPL) which is involved in midline judgments in healthy participants (e.g. Fierro et al., 2000; Fink et al., 2000a). Another possibility

is that PSE fluctuations after LPA represent perceptual fluctuations (VanRullen et al., 2014). Since our study was not designed to examine the source of these fluctuations (which were in fact an unexpected result) we cannot distinguish between these different hypotheses and conclude that this fluctuating aspect of LPA-induced cognitive modulation deserves further investigation.

The observation that RPA and LPA had a different impact on intact visuospatial cognition was not a completely unexpected result (i.e. RPA did not induce any significant PSE shift in the time window tested in experiment one). Indeed it has been largely shown that PA has an asymmetric action on visuospatial cognition in both patients and healthy individuals. The same studies showing that LPA affects visuospatial perception in healthy participants have so far report no effect of RPA (Colent et al., 2000; Berberovic and Mattingley, 2003; Michel et al., 2003; Loftus et al., 2009; Bultitude et al., 2013; Reed and Dassonville, 2014) even though the sensorimotor aftereffects (the hallmark of PA) induced by both LPA and RPA have comparable magnitudes and opposite directions. One exception is the modulation of estimated time duration, which has been shown to be directionally and immediately modulated by both PA directions (Magnani et al., 2012). This negative evidence in the literature concerning RPA and the absence of an effect on intact visuospatial cognition contrasts with the prediction of the anatomo-functional model proposed by Pisella and colleagues (2006). This model posits that PA acts by hypo-activating PPC contralateral to the direction of the prismatic deviation and in turn may modify the hemispheric balance. With a single mechanism it explains both the therapeutic effects in neglect patients and the induction of neglect-like perceptual biases in healthy subjects. This model assumes that both LPA and RPA modulate the contralateral PPC, and therefore that both PA directions should modulate visuospatial cognition in healthy individuals. If this model is accurate, why then do LPA and RPA not induce equal-but-opposite visuospatial biases given that they do induce opposite and equal sensorimotor after effects?

The novelty of the temporal dynamic we observed in LPA-induced cognitive after-effects made us wonder whether a different temporal dynamic could have been responsible for the so far missing reports of significant visuospatial modulation induced by RPA. We thus hypothesized that RPA may need more time than LPA (i.e. more than 35 minutes at least since in this time window we were not able to see any

significant PSE change after RPA) to induce a behavioral modulation. We tested this hypothesis in the second study and we showed: i) that both LPA and RPA significantly and directionally modulated visuospatial cognition, confirming the prediction generated by the model (Pisella et al., 2006); ii) that they did it with two different temporal dynamics.

5.1.1 IN SUPPORT OF THE PISELLA ET AL., 2006 MODEL

The explanation previously offered for the absence of an effect of RPA on perceptual line bisection judgments in healthy subjects was that RPA acts on the contralateral (left) parietal cortex whereas line bisection relies on the right parietal cortex (Fierro et al., 2000; Fink et al., 2000a). However, the beneficial effect of RPA on the pathological line-bisection bias in neglect patients has been suggested to follow a reduction of the hyper-activation of the left hemisphere, which suggests that line-bisection performance, despite being uniquely solved within the right PPC, is influenced by interhemispheric competition. Furthermore, in healthy individuals line bisection performance appears to result from the interaction between the right-hemispheric specificity for the task (Fierro et al., 2000; Fink et al., 2000a) and the leftward bias in spatial attention generally exhibited by healthy individuals (Bowers and Heilman, 1980), which does not reflect a specific function of the right hemisphere, but is rather the result of the contribution of the two hemispheres (Kinsbourne, 1970; Charras et al., 2012; Szczepanski and Kastner, 2013). By showing that both LPA and RPA modulate line bisection performance our results support the idea that PA can modulate visuospatial cognition either directly by acting on the right hemisphere network specialized for line bisection or via spatial attention which results from the activity of a network involving (at least) both parietal cortices and their interhemispheric connections. There is experimental evidence of 1) the contribution of SPL in explicit length comparisons (Fink et al., 2002) as well as in contralateral attentional orienting (Szczepanski and Kastner, 2013), 2) bilateral hemispheric activation of SPLs following PA in patients (Luauté et al., 2006b; Saj et al., 2011), 3) lack of visuospatial effects when SPLs are damaged (Striemer et al., 2008) and 4) contrary to the SPLs, right IPL is usually damaged in USN, and there is a rebalancing between the two SPLs during spontaneous recovery of USN (Corbetta et al., 2005).

Therefore, PA might modulate the interhemispheric (im)balance via the SPLs instead of or in addition to acting on the IPL, and thereby modify line bisection performance.

5.1.2 DIFFERENT DYNAMICS BETWEEN LPA AND RPA AND POSSIBLE REASONS

The difference between right and left PA dynamics in modulating visuospatial cognition became clearer when we extended the post adaptation period beyond 40 minutes. RPA's cognitive after effect emerged slowly and gradually increased whereas LPA's effect was faster and fluctuated.

The different time-courses of the effects of LPA and RPA we observed cannot be attributed to differences in the strength of the sensorimotor adaptation, as the results from the sensorimotor measure we used as a proxy for PA aftereffects clearly showed that left and right PA-induced shifts that were opposite in direction but comparable in size, and appeared to have comparable decrease rates. Similarly, we can rule out a possible role of fatigue because the RPA-induced PSE shift increased steadily until reaching a maximum 6 hours after PA and then underwent a gradual reduction. Instead, if the spatial biases created by PA are triggered by reduced activity in the parietal cortex contralateral to the prismatic deviation, which in turn alters activity in interhemispheric connections (Pisella et al., 2006), then a tentative explanation for the different time courses of the visuospatial shifts can be proposed by referring to the results of recent work by Koch and colleagues (2011). It is possible that these different dynamics represent the behavioral correlate of asymmetries in parietal-to-parietal interactions (Koch et al., 2011). As already discussed in section 1.5.1, using a triple pulse TMS protocol Koch and collaborators (2011) showed that a conditioning pulse over the right PPC induces a stronger inhibitory interhemispheric (parietal-to-parietal) interaction, as measured by a resulting change in the strength of PPC-M1 connectivity in the left hemisphere, than when the conditioning pulse is delivered over the left PPC and the PPC-M1 connectivity is measured in the right hemisphere. That is, there appears to be stronger right-to-left than left-to-right interhemispheric inhibition. Since our second study shows that RPA induces a slower change in behavior than LPA, it is possible that the neural changes in the interhemispheric balance induced by RPA take more time than those induced by LPA.

The fact that the significant behavioral modulation appeared at such a late time (6 hours) after RPA does not exclude the possibility that PA induces direct neural changes as quickly as LPA, but indirect neural changes (via inter-hemispheric interactions) with behavioral expression at a later time might need more time to produce a significant PSE shift after RPA than LPA. A recent fMRI study supports this possibility as the results show an immediate neural change after RPA in healthy participants, but no significant behavioral changes in visual detection, visuospatial short-term memory, or verbal short-term memory tasks (Crottaz-Herbette et al., 2014). There was, however, a significant increase in BOLD activity in the left IPL and a decrease in the right IPL, contrary to what would be predicted by the model introduced by Pisella and colleagues (2006). Finally, the late onset of the RPA-induced cognitive effect calls to mind the cognitive behavior of the USN patients in Rossetti and collaborators' (1998) original study in which the RPA-induced effect was even stronger two hours after adaptation than immediately after adaptation. If RPA acts on the left PPC and inhibits the right PPC via interhemispheric communication (Pisella et al., 2006) it may require more time in healthy individuals than in patients because the right-to-left inter-hemispheric inhibition is intact in the healthy individuals and altered by the lesion in patients.

5.2 THE POSSIBLE PHYSIOLOGY OF LPA

The directions of the visuospatial modulation induced by LPA in healthy participants (e.g. Schintu et al., 2014b) and RPA in USN patients (e.g. Rossetti et al., 1998) match with the behavioral effects induced by inhibitory rTMS applied to the right PPC in healthy individuals (e.g., Fierro et al., 2000) or on the left PPC in patients (e.g. Koch et al., 2008). Both techniques induce neglect-like behavior in healthy individuals (i.e. right shift) and reduce neglect symptoms (i.e. left shift) in patients. TMS has been also employed to investigate functional interactions between two or more connected brain areas, and Koch and collaborators (2008) used a dual-site paired-pulse protocol to document one physiological expression of the LH's release from interhemispheric inhibition following RH damage (Kinsbourne, 1977; Corbetta et al., 2005). One expression of the LH's release from inhibition is hyper-excitability of PPC-M1 functional connectivity in the spared LH of neglect patients (Koch et al., 2008). Indeed, when this hyper-excitability is reduced by inhibitory rTMS on the LH the

severity of neglect symptoms decreases (Koch et al., 2008). Based on the results of our second study, which support an interhemispheric action of PA, and on the assumption that the action of PA is similar to rTMS both behaviorally and physiologically, we predicted that LPA would induce a neglect-like bias in the line bisection task by modulating the strength of PPC-M1 connections. Namely, we predicted that LPA would induce neglect-like behavior by decreasing the strength of the PPC-M1 connectivity in the RH, and increasing it in the LH. The main results of this third study, even if preliminary, do not appear to support our predictions as they show that i) the group of subjects who had a significant rightward shift on the line bisection task (neglect-like behavior) after LPA had a significant decrease in PPC-M1 connectivity in the left hemisphere; ii) the direction of both visuospatial (line bisection judgment) and physiological (PPC-M1 connectivity) modulations induced by a single session of LPA interacted with the presence or absence of pseudoneglect measured before LPA.

5.2.1 IS LPA A POSSIBLE MODEL OF USN?

Our finding that those participants who shifted their line bisection judgments rightward after LPA had a significant decrease in PPC-M1 connectivity is opposite to what we expected from the literature of PPC-M1 functional connectivity in USN. USN patients, who have a pathological right-sided bias, have hyper-excitable PPC-M1 connectivity in the LH. Thus, we were surprised to observe that a right shift was associated with a decrease in PPC-M1 connectivity within the LH, and on this basis conclude that the induction of neglect-like perceptual biases obtained by LPA does not appear to be a straightforward physiological model of neglect.

The interpretation of this counterintuitive result may lie in recent published evidence. Charras and collaborators (2012) investigated line bisection performance in both pathological and healthy populations, and with a novel methodological approach were able to dissociate the relative roles of a *left underestimation* and *right overestimation* in the left-right imbalance characteristic of neglect. These two components, which depend respectively on right *damaged* hemisphere and left *“preserved”* hemisphere, are both present in USN patients and both contribute to the final pathological performance in line bisection (Charras et al., 2012). Given that the

misperception of the right side of the line (overestimated in patients) depends on the activity of the LH, which has a hyper-excitable PPC-M1 connectivity (Koch et al., 2008), it is possible that the state of activation of the PPC-M1 functional connectivity determines the perception of the right side of line. Our preliminary results are coherent with this interpretation, as we observed a decrease of the left PPC-M1 connectivity that was associated with a rightward shift in line bisection, and a leftward shift in line bisection that was instead associated with a tendency for the left PPC-M1 to increase. From these preliminary findings we conclude that LPA modulates PPC-M1 connectivity (at least) in the left hemisphere, and is therefore likely to modulate the perception of the right side of the line – making it perceive it shorter when left PPC-M1 connectivity increases and longer when it decreases.

Previous studies have demonstrated that TMS over right PPC in healthy individuals produces a rightward bias when subjects perform the landmark task (Fierro et al., 2000; Pourtois et al., 2001; Brighina et al., 2002). All of these studies either did not examine the left PPC or did not report significant results after left PPC stimulation. The absence of effects after LH stimulation could suggest a dominant role of the RH in visuospatial attention (Heilman and Van Den Abell, 1980; Mesulam, 1981). However, studies supporting the interhemispheric competition account of visual attentional control show substantial, largely bilateral impairments in processing capacity in neglect patients, implying a major *non lateralized* aspect to this syndrome (Duncan et al., 1999). Each fronto-parietal area generates a spatial bias, or “attentional weight” toward the contralateral hemifield, and the sum of the weights within a given hemisphere determines the overall spatial bias that can be exerted over contralateral visual space (Szczepanski et al., 2010). It has been previously reported that the dorsal fronto-parietal attention network can be subdivided into at least 16 different areas² based on their topographic organization (Kastner et al., 2007; Konen and Kastner, 2008). Szczepanski and collaborators (2010) provided neural evidence in support of the interhemispheric competition theory by showing that each topographically organized fronto-parietal area generates a spatial bias or “attentional weight” toward

² These topographic areas include for each hemisphere six topographic region of interests (ROIs) in PPC (IPS1–IPS5 and SPL1) and two ROIs in frontal cortex [frontal eye field (FEF), precentral cortex/inferior frontal sulcus (PreCC/IFS)] and were defined in each hemisphere using a memory-guided saccade task.

the contralateral hemifield and that the sum of these weights constitutes the overall bias that is exerted across visual space.

In a more recent study Szczepanski and Kastner (2013) used a multimodal approach, consisting of fMRI of spatial attention signals, behavioral measures of spatial bias (perceptual line bisection task), and fMRI-guided single-pulse TMS to causally test the theory of interhemispheric competition. By interfering with attentional processing within specific topographic fronto-parietal areas the authors showed that the individuals' attentional weights, and thus their spatial attention behavior on the landmark task, could be predictably shifted toward one visual field or the other depending on the stimulated site. These results emphasize neural and behavioral individual differences, and have been suggested to provide compelling evidence that spatial attention is controlled through competitive interactions between hemispheres rather than a dominant right hemisphere in the intact human brain. Even more interestingly, with this multimodal and individual-subject-based approach the authors did not find any evidence for RH dominance of spatial attention control, but rather show that online single pulse TMS over left posterior parts of IPS shifts perceptual line bisection judgments leftward which is more consistent with an interhemispheric competition theory of attention (Capotosto et al., 2012). Interestingly, their group of subjects did not show pseudoneglect at the group level, reflecting the existence of substantial individual differences in landmark task performance (Bowers and Heilman, 1980; Manning et al., 1990a; McCourt and Olafson, 1997). Consistently the authors observed several asymmetries within this network across their subjects, but importantly, these right and left asymmetries were approximately balanced out across the entire network, supporting the idea that all areas of the fronto-parietal network contribute to the control of spatial attention rather than a few particular areas (Szczepanski et al., 2010). The authors calculated a lateralization index³ (LI; Szczepanski et al., 2010) to quantify *how much an area contributes to the control of spatial attention across the visual field by generating a spatial bias* (attention weight) towards the contralateral visual field, and the sum of

³ For each of the left and right ROIs to assess the degree to which the fMRI attention signals in each subject showed a preference for contralateral or ipsilateral presentations [LI= (Rcontra - Ripsi)/(Rcontra + Ripsi), in which R is response as mean signal change, contra is attention to contralateral presentations, and ipsi is attention to ipsilateral presentations]. Positive values indicate stronger responses to contralateral than ipsilateral presentations; negative values indicate the opposite (Szczepanski et al., 2010).

the weights contributed by each area within one hemisphere constitutes the overall spatial bias that is exerted over the contralateral space. The relationship between the strength of the spatial biasing signals across fronto-parietal topographic areas (LI) and the resulting behavioral spatial bias was shown to have a strong negative relationship: those subjects with stronger LI values on average in the LH tended to show a bias toward the RVF (absence of pseudoneglect) while performing the landmark task, and those with stronger LI values on average in the RH tended to show a bias toward the LVF (pseudoneglect). Our preliminary results concerning the LH are coherent with the recent and novel data published by Szczepanski and Kastner (2013), as in our sample the pseudoneglect and no pseudoneglect subgroups may indeed differ in terms of baseline measurements of the excitability of the left PPC-M1 connectivity, with pseudoneglect participants having slightly higher MEP amplitudes (greater connectivity) than the no pseudoneglect participants. In contrast, however, our preliminary results suggest that such a difference might not exist at baseline for RH PPC-M1 connectivity between the pseudoneglect and no pseudoneglect populations.

Furthermore, we cannot ascertain whether the LPA-induced modulation of the left PPC-M1 depended on the action of the RH as there was no detectable change at either the physiological or behavioral level when PPC-M1 connectivity was measured in the RH, which makes us think that we might have blocked the visuospatial modulation typically induced by LPA. How we possibly blocked the visuospatial modulation induced by LPA is not clear yet, but the fact that it appears to be the case raises the possibility that the RH is crucial for LPA, and clearly deserves further investigation.

Considering that both the right and left hemispheres (Charras et al., 2012; Szczepanski and Kastner, 2013) contribute to the attentional weight and thus to the perception of each side of the line, we can conclude that LPA may well have induced neglect-like behavior in healthy subjects by decreasing the strength of the PPC-M1 connectivity in the LH. Given that the results of the second study support an interhemispheric action of PA and that the PPC-M1 protocol might have blocked PA's cognitive effect when delivered on the RH, it is very tempting to speculate that LPA could induce neglect-like behavior in healthy individuals by acting on the right PPC and then (via interhemispheric inhibition) modulating left PPC-M1 connectivity.

5.2.2 PRE-ADAPTATION BIAS AND ITS INTERACTION WITH LPA

The other main result of the third study of this thesis was that the pseudoneglect and no pseudoneglect groups showed an opposite direction of the visuospatial modulation after LPA. In the group for whom PPC-M1 interactions were measured on the LH, LPA induced a significant rightward shift of the perceived midline for those participants who showed pseudoneglect at baseline, and a significant leftward shift for those who did not.

In a recent study of the time-on-task effect Benwell and collaborators (2013) showed that healthy participants had differential shifts based on the bias they exhibited at baseline. Participants who showed pseudoneglect at baseline shifted rightward, whereas those who did not show pseudoneglect at baseline shifted leftward. The authors concluded that this modulation based on the initial bias might arise from genuine observer subtypes, possibly driven by variations in anatomical and/or functional asymmetries (Benwell et al., 2013), which would lead to different behavioral patterns for time-on-task effects or for visuospatial modulation in general. Namely, the difference between those two kinds of observer subtype may depend on the degree of lateralization of the fronto-parietal fasciculus that as showed by Thiebaut de Schotten and collaborators (2011), which correlated with the amount of pseudoneglect showed by participants when manually bisecting lines. Using different spatial attention tasks Newman and collaborators (2014) confirmed the results of the Benwell and colleagues' study (2013), but after refined statistical analysis concluded that the data patterns were most likely driven by the phenomenon of 'regression towards the mean', rather than being indicative of true participant subtypes. Newman and collaborators' (2014) results could cast some doubts on the behavioral results of our third study, as similarly to (Benwell et al., 2013) we categorized our population according to their initial bias. However, the way of categorizing we employed (i.e. none of the subjects were excluded), as compared to the Benwell et al (2013) that used of 95% Intervals of Confidence, creates less extreme left and right initial bias groups which may be less prone to regression to the mean phenomenon as reported in Newman and collaborators (2014) and it is coherent with the idea that pseudoneglect occurs along a continuum of performance (Thiebaut de Schotten et al 2011). Moreover, the fact that the presence or absence of pseudoneglect interacted with the stimulated hemisphere rules out the possibility that the behavioral change we

observed was solely determined by a ‘regression to the mean’ phenomenon (Newman et al., 2014). Furthermore, the fact that the LPA-induced opposite modulation was not restricted to the behavioral performance, but it also affected directionally the physiological measure (PPC-M1 connectivity), reinforces the idea that the baseline measure might reflect a state of the system. Even if the presence of pseudoneglect has an anatomical counterpart (Thiebaut de Schotten et al., 2011), which characteristic of the system determines this initial state is not clear from our data. One possibility is that the physiological differences between the two populations lie in the relative excitability of their PPC-M1 connectivity in the two hemispheres, but since the LH and RH TMS groups were composed of distinct individuals we do not have the data to address this possibility. We do, however, have data from the LH of the two groups which suggest that the pseudoneglect and no pseudoneglect subgroups might differ in the average excitability of PPC-M1 connections within the left hemisphere, as pseudoneglect participants had slightly stronger PPC-M1 connectivity than the no pseudoneglect participants, but further work is needed to test this possibility, due to the small number of participants assigned to each subgroup. Another difference at baseline between the two populations that may be worth acknowledging, even if as I stressed earlier in the section these results might change once a larger sample size is reached, are the different profiles of the PPC-M1 connectivity at rest. In the pseudoneglect group in our experiment, solely for the LH, a conditioning pulse delivered on the left PPC facilitated the test pulse delivered on the contralateral M1 at the 2msec inter stimulus interval, whereas in the No pseudoneglect group an inhibition was found at 4 msec. We could conclude, in light of these preliminary but extremely interesting results, that that presence or absence of pseudoneglect could be related to the state of the PPC-M1 connectivity at baseline, with the limitation that how the state of the PPC-M1 connectivity is determined cannot be ascertained from the present data.

Inter-individual variability is present in line bisection performance, i.e. presence or absence of pseudoneglect in healthy population (Jewell and McCourt, 2000). A study investigating visuospatial modulation after both left and right PA showed that both prism directions can affect visuospatial cognition but that it depends on the bias shown at baseline by participants; LPA induced a rightward modulation in subjects with pseudoneglect, whereas RPA induced a leftward modulation in subjects

without pseudoneglect (i.e. rightward bias) (Goedert et al., 2010). The authors concluded that efficacy of PA depends on the bias shown by participants at baseline (Goedert et al., 2010). However, in contrast with Goedert and colleagues, our sample was adapted only to LPA, and still showed opposite and significant visuospatial shifts on the basis of their bias at baseline. Further studies need to be done in order to investigate whether the action of PA may be state dependent. It might be possible that the direction of the visuospatial bias present at baseline (pseudoneglect presence or absence) interacts with the direction of the displacement (RPA or LPA). It might also be possible that PA directionally modulates visuospatial cognition when bias at baseline and PA displacement are congruent (i.e. pseudoneglect participants and LPA or no pseudoneglect or USN and RPA). If our prediction is correct then no pseudoneglect individuals should show a leftward shift after RPA which is indeed what Goedert and collaborators (2010) found. However, a safe way to test this hypothesis, avoiding the influence of regression to mean would be to induce a pseudoneglect and no pseudoneglect *state* in healthy individuals, for example by manipulating line length, and then test the effect of PA on line bisection judgments.

5.3 FURTHER IMPLICATION OF OUR RESULTS

One question that logically follows from the discovery of a temporal dynamic of PA-induced visuospatial modulation is whether PA also has a particular dynamics for alleviating USN symptoms. Even if several studies have repeatedly assessed RPA after-effect hours and days after adaptation, to my knowledge there are no studies in which these after-effects been repeatedly measured at short regularly-spaced intervals. If there is a particular temporal dynamic in the RPA-induced amelioration of patient symptoms, an individual time-tailored intervention could be designed. To date, clinical studies investigating PA as a rehabilitation tool have not taken into account any individual variability, which means that the training is administered at fixed times, for example every morning at the same time for a certain number of days. If a temporal dynamic in the emergence of the symptom amelioration were also found in patients, it might provide an indication as to the moment at which the PA could be re-administered with the idea of reinforcing and strengthening its beneficial effect. Indeed, if the after-effect is still in the *ascending* phase, it may not be worth re-administering the training, whereas re-adapting the patient to RPA in the *descending*

phase could reinforce or consolidate it. As we have already seen, repeated sessions of PA in USN can induce long-lasting recovery, and this recovery could be even more efficient if tailored to the patient's own temporal profile. Although further studies are necessary to both clarify their origin and make a strict comparison between the time courses of aftereffects in the two populations, the fluctuations we observed in healthy participants may be relevant within the framework of both neglect pathology and its recovery.

Finally, throughout this thesis I have asserted that RPA does not affect visuospatial cognition and mentioned the body of evidence showing that time perception is modulated by both LPA and RPA, with RPA modulating time representation toward an underestimation and LPA toward an overestimation (Frassinetti et al., 2009; Magnani et al., 2012). By showing that RPA and LPA modulate visuospatial cognition with different temporal dynamics, which are probably attributable to the asymmetric interhemispheric inhibition exerted by the two parietal cortices in healthy subjects (stronger right-to-left parieto-parietal inhibition), our results question the ATOM (Walsh, 2003a). A dissociation between physical and mental number lines has already been shown in right brain damaged patients (Doricchi et al., 2005) and supported by other studies (Rossetti et al., 2004b, 2011; van Dijck et al., 2012). More recently it has been discovered that in right brain damaged patients the right hemisphere supports the representation of small numerical magnitudes independently of their mapping on the left or the right side of a spatial-mental layout (Aiello et al., 2012). These findings raise the question of whether this might be also the case for perception of time. However, since the *representational aspect of* visuospatial cognition was not the object of this thesis, I have chosen not to go into detail regarding this final possible implication of our results, but instead I want to simply suggest that the existence for a particular temporal dynamics in PA adaptation provides important evidence that needs to be taken into consideration for future interpretation of PA-induced cognitive modulations, such as for time perception.

6. CONCLUSION

Attentional resources are directed by two distinct and interacting fronto-parietal networks, the ventral system directs the attentional set by detecting relevant salient stimuli that are localized by the two dorsal systems (Corbetta and Shulman, 2002). The right and left dorsal fronto-parietal networks compete in allocating attention to each contralateral side of space (Kinsbourne, 1977). The attentional weight of each fronto-parietal areas contributes to the perception of respective contralateral side of a line (Szczepanski et al., 2010; Szczepanski and Kastner, 2013), and the parieto-to-parietal interhemispheric communication is asymmetric, in favor of a right inhibitory influence (greater right-to-left inhibition compared to the left-to-right inhibition) (Koch et al., 2011). Because of the inhibitory influence of the right PPC over the left, a lesion to the right hemisphere not only compromises contralesional perception, but also induces a hyper-activation of the left PPC (Kinsbourne, 1977), which is expressed in the hyperactivity of PPC-M1 functional connectivity (Koch et al., 2011). In visuospatial terms, the RH lesion that causes neglect induces a constant underestimation of the left side of the line, whereas the release of the LH induces an overestimation of the left side of line, and both impairments contribute to performance on line bisection tasks (Charras et al., 2012).

Prismatic adaptation modulates line bisection performance in both healthy individuals and patients and we suggest that LPA likely modulates the left PPC-M1 functional connectivity and thus the perception of the right side of space (of the line). By demonstrating different temporal dynamics for left and right PA in healthy subjects we support the interhemispheric action of PA (Pisella et al., 2006). We propose that PA might modulate the right IPL, which is the neural correlate of line bisection (Fink et al., 2000a), and that both right and left SPL might provide the interhemispheric transfer. Indeed, the left SPL is crucially involved in explicit length comparisons (Fink et al., 2002), and the right SPL is a crucial parietal structure within the right dorso-parietal network (Szczepanski and Kastner, 2013) and it is usually preserved in neglect patients.

Our results can contribute to the development of tailored treatment options for USN, and to improving our understanding of this syndrome. By suggesting that the individual differences observed among healthy individuals are functionally

meaningful we provide a possible explanation for the incongruences in performance and high variability that have characterized line bisection tasks in both populations. Finally, our results support the recent evidence highlighting the important contribution of the LH in the genesis of visuospatial biases.

Our data suggest that what might *prima facie* seem to be two sides of the same coin (i.e., pseudoneglect and neglect) may actually reflect activity of fundamentally different systems; the intact versus damaged brain. Because of their right hemisphere lesion USN patients appear to be in the constant presence of the distortion of the left side of the line, whereas the perception of the right side the line (i.e. left hemisphere) is relatively preserved, as it is not lesioned but rather hyper-activated. Therefore the LH may be comparable across the two populations and it appears to be similarly modulated by rTMS in patients and LPA in healthy individuals.

Neglect and pseudoneglect may be two *half* sides of the same coin.

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