Université de Montréal

Développement et fonctionnement des mécanismes de résonance motrice chez l'humain

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Thèse présentée à la Faculté des études supérieures
en vue de l'obtention du grade de Philosophiae Doctor (Ph.D.)
en psychologie, option neuropsychologie recherche-intervention

Juin 2010

Université de Montréal
Faculté des études supérieures

Cette thèse intitulée :

Développement et fonctionnement des mécanismes de résonance motrice chez l'humain

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Résumé

La découverte dans le cerveau du singe macaque de cellules visuo-motrices qui répondent de façon identique à la production et la perception d'actes moteurs soutient l'idée que ces cellules, connues sous le nom de *neurones-miroirs*, encoderaient la *représentation* d'actes moteurs. Ces neurones, et le système qu'ils forment, constitueraient un système de compréhension moteur; par delà la simple représentation motrice, il est également possible que ce système participe à des processus de haut niveau en lien avec la cognition sociale.

Chez l'humain adulte, des études d'imagerie récentes montrent d'importants chevauchements entre les patrons d'activité liés à l'exécution d'actes moteurs et ceux associés à la perception d'actions. Cependant, malgré le nombre important d'études sur ce système de résonance motrice, étonnamment peu se sont penchées sur les aspects développementaux de ce mécanisme, de même que sa relation avec certaines habiletés sociales dans la population neurotypique. De plus, malgré l'utilisation répandue de certaines techniques neurophysiologiques pour quantifier l'activité de ce système, notamment l'électroencéphalographie et la stimulation magnétique transcrânienne, on ignore en grande partie la spécificité et la convergence de ces mesures dans l'étude des processus de résonance motrice.

Les études rassemblées ici visent à combler ces lacunes, c'est-à-dire (1) définir l'existence et les propriétés fonctionnelles du système de résonance motrice chez l'enfant humain, (2) établir le lien entre ce système et certaines habiletés sociales spécifiques et (3) déterminer la validité des outils d'investigation couramment utilisés

pour mesurer son activité.

Dans l'article 1, l'électroencéphalographie quantitative est utilisée afin de mesurer l'activité des régions sensorimotrices chez un groupe d'enfants d'âge scolaire durant la perception d'actions de la main. On y démontre une modulation de l'activité du rythme mu aux sites centraux non seulement lors de l'exécution de tâches motrices, mais également lors de l'observation passive d'actions. Ces résultats soutiennent l'hypothèse de l'existence d'un système de résonance motrice sensible aux représentations visuelles d'actes moteurs dans le cerveau immature.

L'article 2 constitue une étude de cas réalisée chez une jeune fille de 12 ans opérée pour épilepsie réfractaire aux médicaments. L'électroencéphalographie intracrânienne est utilisée afin d'évaluer le recrutement du cortex moteur lors de la perception de sons d'actions. On y montre une modulation de l'activité du cortex moteur, visible dans deux périodes distinctes, qui se reflètent par une diminution de la puissance spectrale des fréquences beta et alpha. Ces résultats soutiennent l'hypothèse de l'existence d'un système de résonance motrice sensible aux représentations auditives d'actions chez l'enfant.

L'article 3 constitue une recension des écrits portant sur les données comportementales et neurophysiologiques qui suggèrent la présence d'un système de compréhension d'action fonctionnel dès la naissance. On y propose un modèle théorique où les comportements d'imitation néonataux sont vus comme la résultante de mécanismes d'appariement moteurs non inhibés.

Afin de mesurer adéquatement la présence de traits empathiques et autistique dans le but de les mettre en relation avec l'activité du système de résonance motrice, l'article 4 consiste en une validation de versions françaises des échelles *Empathy Quotient* (Baron-Cohen & Wheelwright, 2004) et *Autism Spectrum Quotient* (Baron-Cohen *et al.,* 2001) qui seront utilisées dans l'article 5. Les versions traduites de ces échelles ont été administrées à 100 individus sains et 23 personnes avec un trouble du spectre autistique. Les résultats répliquent fidèlement ceux obtenus avec les questionnaires en version anglaise, ce qui suggère la validité des versions françaises.

Dans l'article 5, on utilise la stimulation magnétique transcrânienne afin d'investiguer le décours temporel de l'activité du cortex moteur durant la perception d'action et le lien de cette activité avec la présence de traits autistiques et empathiques chez des individus normaux. On y montre que le cortex moteur est rapidement activé suivant la perception d'un mouvement moteur, et que cette activité est corrélée avec les mesures sociocognitives utilisées. Ces résultats suggèrent l'existence d'un système d'appariement moteur rapide dans le cerveau humain dont l'activité est associée aux aptitudes sociales.

L'article 6 porte sur la spécificité des outils d'investigation neurophysiologique utilisés dans les études précédentes : la stimulation magnétique transcrânienne et l'électroencéphalographie quantitative. En utilisant ces deux techniques simultanément lors d'observation, d'imagination et d'exécution d'actions, on montre qu'elles évaluent possiblement des processus distincts au sein du système de résonance motrice.

En résumé, cette thèse vise à documenter l'existence d'un système de résonance motrice chez l'enfant, d'établir le lien entre son fonctionnement et certaines aptitudes sociales et d'évaluer la validité et la spécificité des outils utilisés pour mesurer l'activité

au sein de ce système. Bien que des recherches subséquentes s'avèrent nécessaires afin de compléter le travail entamé ici, les études présentées constituent une avancée significative dans la compréhension du développement et du fonctionnement du système de résonance motrice, et pourraient éventuellement contribuer à l'élaboration d'outils diagnostiques et/ou de thérapeutiques chez des populations où des anomalies de ce système ont été répertoriées.

Mots-clés : électroencéphalographie, développement, rythme mu, stimulation magnétique transcrânienne, compréhension d'action, neurones miroirs, autisme

Abstract

The discovery of cells in the macaque brain that respond both to action production and perception brings support to the hypothesis that these *mirror-neurons* (MN) code for the *representation* of action. These cells, and the system they form (the so-called mirror neuron system; MNS), appear to underlie action understanding by simulating the perceived action into the observer's brain. Beyond simple action understanding, it has been suggested that this system contributes to higher-order processes related to social cognition.

In human adults, recent imaging studies have shown important ovelaps in the activity patterns during both action production and execution, supporting the existence of a system similar to that shown in monkeys. However, surprisingly few studies have investigated the presence and the development of the MNS in the human child, and its relationship with socio-cognitive abilities in healthy individuals. Moreover, we still ignore the specificity of measures widely used to assess this system.

The studies that follow aim at clarifying these issues. More specifically, the main objectives of this work are to : (1) establish the existence and the properties of motor resonance mechanisms in children; (2) clarify the relationship between activity of the MNS and social abilities in healthy individuals; and (3) determine the specificity of neurophysiological tools widely used to measure MNS activity in humans.

In the first article, quantitative electroencephalography is used to assess the activity of sensorimotor regions in a group of school-age children during the observation

of simple hand movements. We show a modulation of mu rhtyhm activity at central sites not only during motor production, but also during passive action observation. These results support the existence of an action-execution pairing system sensitive to visual actions in the immature brain.

In the second article, we present an experiment conducted in a 12 year-old child undergoing presurgical monitoring for intractable epilepsy. Intracranial electroencephalography is used to assess motor cortex involvement in the perception of action-related sounds. We show a modulation of motor cortex activity at two distinct time-periods in the alpha and beta bands. These results suggest the presence of a motor matching system sensitive to auditory stimuli in the child's brain.

In the third article, we present an overview of behavioral and neurophysiological data supporting the idea that an action-understanding system is present from birth in humans. We propose a theoretical model whereby neonatal imitation is the result on an uninhibited motor resonance system.

In order to adequatly measure the presence of empathic and autistic traits in healhy individuals to assess their link with motor resonance, article 4 consists of a french validation of questionnaires used in the fifth article, the *Empathy Quotient* (Baron-Cohen & Wheelwright, 2004) and the *Autism Spectrum Quotient* (Baron-Cohen *et al.,* 2001). Translated versions of these scales were administered to 100 healthy adults and 23 individuals with autistic spectrum disorders. Our results replicate faithfully those obtained with the original version of the scales.

In the fifth article, transcranial magnetic stimulation is used to assess the timecourse of motor cortex activity during action observation, as well as its relationship with empthic and autistic traits in healthy individuals. We show that the motor cortex is rapidly modulated following movement onset, and that its activity correlates with specific socio-cognitives measures. These results suggest the presence of a rapid mechanism taking place in the motor resonance system that is related to social ability.

The sixth acticle aims at clarifying the specificity of the neurophysiological tools used in the preceeding studies to quantify MNS, namely transcranial magnetic stimulation and quantitative electroencephalography. Using both techniques simultaneously during action observation, imagination and execution, we show that these measures capture different aspects of motor resonance.

In summary, this thesis aims at documenting the existence of a motor resonance mechanism in children, establishing the relationship between MNS activity and socio-cognitive traits and assessing the specificity of the measures used to quantify activity within this system. Although further studies are needed to complete the task begun here, these studies contribute significantly to our understanding of the development and function of motor resonance mechanism is humans. In the long run, they could contribute to the elaboration of diagnostic markers, and ultimately therapeutic targets, in clinical populations where abnormalities of this system have been documented.

Keywords : electoencephalography, development, mu rhythm, transcranial magnetic stimulation, action understanding, mirror neurons, autism

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Liste des sigles et abréviations

BA : Aire de Broadman

EEG : Électroencéphalographie

EMG : Électromyographie

F1 : Cortex moteur primaire du singe

F4 : Cortex prémoteur latéral du singe

F5 : Cortex prémoteur ventral du singe

GFI : Gyrus frontal inférieur

IRM : Imagerie par résonance magnétique

IRMf : Imagerie par résonance magnétique fonctionnelle

LPI : Lobule pariétal inférieur

MEG : Magnétoencéphalographie

MMN : Composante négative de discordance

M1 : Cortex moteur primaire

NM : Neurones-miroirs

PÉÉ : Potentiel évoqué électroencéphalographique

PÉM : Potentiel évoqué moteur

SNM : Système neurones miroirs

SNMh : Système neurones miroirs humain

SMT : Stimulation magnétique transcrânienne

SMTr : Stimulation magnétique transcrânienne répétitive

STS : Sulcus temporal supérieur

7b : Portion rostrale du lobule pariétal inférieur du singe

« I do not like it, and I am sorry I ever had
anything to do with it. »
Erwin Schrödinger (1887-1961)
Physicien autrichien, Prix Nobel 1933
À propos de la mécanique quantique

Remerciements

J'aimerais tout d'abord remercier mon directeur de recherche, Hugo Théoret, qui, à sa manière personnelle, s'est avéré un mentor exceptionnel à plusieurs égards. À travers son humour et son intelligence, il m'a montré qu'il est possible de rester soi-même quoique l'on fasse.

Je tiens aussi à souligner la contribution des professeurs et des professionnels qui m'ont influencé au cours des nombreuses discussions formelles et informelles. Parmi ceux-ci, j'aimerais particulièrement remercier Elaine de Guise, Maryse Lassonde, Jean-Paul Guillemot, Dave Saint-Amour, François Champoux et Michelle Mckerral. Je tiens à remercier spécialement Franco Lepore pour m'avoir donné l'opportunité de travailler dans l'environnement de recherche unique qu'est le CERNEC.

Mes études doctorales auraient été mornes sans l'esprit de camaraderie qui règne au sein du CERNEC et à la faune bigarrée qui le peuple. À cet effet, je tiens à mentionner mes collègues étudiants avec qui j'ai partagé ces dernières années, ainsi que de nombreuses frustrations et plusieurs joies : Étienne, Louis, Martin, Pierre, Luke, Madeleine, Maude, Julie, les gens de ma cohorte ainsi que plusieurs autres, trop nombreux pour être mentionnés ici. Je veux aussi remercier MCD et Sara pour leur bonne humeur contagieuse et leurs apports précieux à mes projets de recherches.

Les travaux qui constituent cette thèse n'auraient pu être effectués sans l'appui financier du Centre de Recherche de l'Hôpital Sainte-Justine ainsi que des Instituts de Recherche en Santé du Canada (IRSC). Je me dois aussi de souligner la contribution

importante de Maria Sanchez et de Stéphane Denis à mes travaux et mon parcours académique, deux personnes essentielles au bon déroulement de mes études doctorales et à celles de nombreux autres étudiants.

Finalement, je veux aussi remercier ma famille, mon père Jean-Yves, de même que mes sœurs Nathalie et Caroline pour leur soutien tranquille et constant. Je tiens spécialement à remercier Mélissa pour son amour, sa présence et son soutien indéfectible, ainsi qu'à Malik, pour me montrer ce qui est réellement important dans la vie.

Chapitre 1

Introduction

1.1. Introduction générale

Dans son œuvre maitresse, « Principes de la Psychologie », William James (1890) proposait que le cerveau humain recrute ses propres réseaux neuronaux afin de simuler une expérience qui est vécue par un autre individu. De cette manière, l'observateur serait capable de se mettre à la place de l'autre et de comprendre ses sensations, émotions et pensées. Cette hypothèse, connue sous le nom de théorie de la simulation (Gallese, 2003), a reçu considérablement d'appuis des recherches expérimentales conduites au cours des dernières décennies. À ce jour, de nombreuses études montrent de façon éloquente l'existence d'un important chevauchement dans les réseaux neuronaux sollicités lors d'expériences directes d'événements sensoriels (Schaefer, Xu, Flor, et Cohen, 2009), nociceptifs (Jackson, Rainville, et Decety, 2006), moteurs (Gazzola et Keysers, 2009) ou émotionnels (Pfeifer, Iacoboni, Mazziotta, et Dapretto, 2008), et ceux recrutés lorsqu'un individu observe passivement un congénère vivre ces expériences. On réfère souvent à ce phénomène où les mêmes patrons d'activité cérébrale sont sollicités durant la perception passive et l'expérience directe sous le terme de *résonance*.

La découverte des *neurones miroirs* (NM) au début des années 1990 par un groupe de chercheurs italiens (Di Pellegrino, Fadiga, Fogassi, Gallese, et Rizzolatti, 1992; Gallese, Fadiga, Fogassi, et Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, et Fogassi, 1996) est sans contredit à la base de l'imposante littérature actuelle qui traite des mécanismes de résonance. Ces chercheurs notèrent que certains neurones de la région F5 qui répondaient lorsque le singe effectuait des gestes de préhension, déchargeaient également lorsque le singe observait passivement l'expérimentateur prendre un objet. Ainsi, pour la première fois, on démontrait l'existence d'un substrat neuronal incarnant l'appariement direct entre une représentation sensorielle et son équivalent moteur.

Présumément, ces cellules permettraient de traduire un mouvement perçu, un stimulus visuel dénué de signification, en un patron moteur compréhensible à l'observateur. Dans son ensemble, ce mécanisme d'appariement moteur sous-tendu par les NM constituerait un système de compréhension d'action.

Cependant, par delà la « simple » compréhension motrice, le système neurones miroirs (SNM), en incarnant un espace commun et partagé entre soi et l'autre, pourrait également contribuer significativement à des processus de haut niveau, tels l'acquisition du langage (Arbib, 2005), l'imitation (Iacoboni et al., 1999) et l'empathie (Gallese, 2007). En effet, les réponses neuronales motrices des NM, qu'on pourrait qualifier de vicariantes, nous amènent à considérer l'hypothèse que l'empathie résulte d'une mécanique similaire; on partage et comprend les émotions et les états d'esprit de l'autre parce que les observer chez quelqu'un déclencherait leurs représentations correspondantes dans notre cerveau (Gazzola et Keysers, 2009).

L'apport potentiel des NM aux processus sociaux comme l'empathie a largement contribué à l'intérêt marqué des chercheurs envers les NM (plus de 1000 articles ont « mirror neuron» comme mot-clé dans la base de données de PubMed). Cependant, malgré cet intérêt, étonnamment peu d'études s'étaient penchées sur les aspects développementaux de ce système jusqu'à tout récemment. Ceci est d'autant plus surprenant que peu après leur découverte, on proposait déjà que les NM pourraient jouer un rôle clef dans la manifestation de certains des symptômes typiquement retrouvés au sein de troubles neurodéveloppementaux et psychiatriques (Williams, Whiten, Suddendorf, et Perrett, 2001).

Plusieurs ont en effet proposé que les déficits sociaux retrouvés au sein de certaines pathologies, dont les troubles du spectre autistique (TSA), résultent en partie d'une dysfonction du SNM humain (SNMh) (Nishitani, Avikainen, et Hari, 2004;

Williams et al., 2001). Cette hypothèse a reçu des appuis empiriques au cours des dernières années, alors qu'on a documenté chez les personnes avec un TSA des anomalies morphologiques (Hadjikhani, Joseph, Snyder, et Tager-Flusberg, 2006) et fonctionnelles (Bernier, Dawson, Webb, et Murias, 2007; Cattaneo et al., 2007; Dapretto et al., 2006 ; Martineau, Cochin, Magne, et Barthelemy, 2008; Oberman et al., 2005 ; Oberman, Ramachandran et Pineda, 2008; Théoret et al., 2005; Williams et al., 2006) du SNMh (voir aussi pour résultats négatifs : Avikainen, Kulomäki, et Hari, 1999; Raymaekers, Wiersema, et Roeyers, 2009). De plus, chez cette population, on a montré que les déficits sociaux étaient inversement corrélés avec l'activité de certaines régions du SNMh (Dapretto et al., 2006). Pour l'instant, le diagnostic des troubles du spectre autistique repose essentiellement sur les manifestations comportementales atypiques reliées à cette condition. Une meilleure documentation du développement normal du SNM pourrait potentiellement contribuer à l'élaboration de nouveaux outils diagnostiques ainsi qu'à la mise en place de traitements plus adaptés pour des pathologies impliquant une dysfonction du SNMh (Fecteau, Lepage, et Théoret, 2006).

Les objectifs principaux de cette thèse sont : 1) d'établir la présence et le fonctionnement du système de résonance motrice chez l'enfant sain; 2) de déterminer le décours temporel de l'activité de ce système et d'investiguer le lien entre les processus de résonance motrice et les traits sociocognitifs chez l'individus sain; 3) d'évaluer la spécificité de l'électroencéphalographie (EEG) quantitative et de la stimulation magnétique transcrânienne (SMT) dans la quantification de l'activité du SNMh. Ces objectifs permettront d'approfondir les connaissances relatives au fonctionnement du SNM chez l'humain en développement, de définir le lien entre l'activité du SNMh et les aptitudes sociales et de répondre à des questions méthodologiques cruciales dans l'étude du SNMh.

En guise d'introduction aux études composant cette thèse, la littérature documentant les caractéristiques des neurones miroirs et du système qu'ils constituent chez le singe sera résumée. Par la suite, les études comportementales et neurophysiologiques réalisées chez l'être humain suggérant l'existence d'un système comparable seront examinées. Ce faisant, les différents systèmes de résonance observés chez l'humain, dont le système de résonance motrice, ainsi que leurs liens avec les aptitudes sociales, seront abordés. L'aspect du décours temporel de l'activité du système de résonance motrice, notamment au niveau du cortex moteur primaire (M1), ainsi que la distinction entre la résonance hâtive et tardive, seront aussi discutés. Finalement, les techniques d'investigation utilisées dans le cadre des recherches présentées seront aussi abordées, de même que les substrats neurophysiologiques auxquels ils réfèrent. Il sera notamment question de la SMT et des rythmes cérébraux enregistrés en EEG dans la mesure de l'activité du cortex moteur durant la perception d'action.

1.2. Le système neurones-miroirs chez le singe macaque

1.2.1. Les neurones-miroirs : découvertes et propriétés

Les NM furent initialement découverts dans la région F5 du cerveau du singe macaque (*Macaca nemestrina*) (Di Pelligrino et al., 1992). Les premières recherches portant sur les propriétés visuomotrices des cellules de cette région montrent qu'environ 25% des neurones enregistrés présentent des propriétés dites « miroirs », c'est-à-dire qu'ils répondent de façon similaire lorsque le singe exécute un acte moteur et quand il perçoit un mouvement semblable être exécuté (Gallese et al., 1996; Rizzolatti et al., 1996). Ces mêmes recherches mettent en évidence un spectre de sensibilité nuancé quant à la congruence nécessaire entre les actions exécutées et celles observées afin d'engendrer une réponse neuronale. Approximativement un tiers des NM de la région F5

montrent un degré de sélectivité élevé en terme de réponse lors de l'observation; c'est-à-dire que l'action exécutée (ex. préhension d'un objet) doit être la même lors des deux conditions. La majorité des NM de cette région présente une sélectivité moindre quant à la congruence entre les actions exécutées et celles perçues, de sorte que des gestes plus ou moins similaires suffisent pour induire une réponse dans cette population neuronale (Rizzolatti et al., 1996; Rizzolatti et Craighero, 2004).

Par delà la représentation visuelle d'action à laquelle les NM sont sensibles, il a été montré qu'ils répondaient également aux représentations d'actions sous d'autres modalités. En effet, au sein de la région F5, certains neurones qui répondaient sélectivement lors de l'exécution et l'observation d'actions spécifiques (ex. craquer une arachide), étaient également sensibles au son de cette même action (le son d'une arachide qui craque) (Köhler et al., 2002). Ainsi, considérant la pluralité des sources capables d'engendrer une réponse neuronale spécifique (exécution d'un acte moteur, représentation visuelle et auditive), il est vraisemblable que ces cellules visuo-auditivo-motrices codent réellement pour la *représentation* d'actes moteurs.

Les premières études portant sur les NM se concentraient sur la portion antérieure de la région F5, où des neurones sensibles aux actions manuelles ont été identifiés. Les études subséquentes ont montré qu'une certaine somatotopie existait au sein de cette région frontale. Alors que la portion ventrale (F5) est peuplée de neurones répondant aux actions manuelles, la portion latérale (F4) contient des neurones répondant aux mouvements buccaux. Parmi ceux-ci, certains répondent spécifiquement aux gestes communicatifs, d'autres uniquement lors de l'ingestion et la mastication d'aliments (Rizzolatti et Craighero, 2004). Les réponses discriminatives de ces neurones suggèrent que par-delà la simple représentation kinesthésique prenant place au sein du

système, la population neuronale se montre également sensible au but accompli pour le mouvement produit.

Cette sensibilité au but relié à l'action a été montrée de façon éloquente par le groupe de Rizzolatti (Umiltà et al., 2001), suggérant fortement un rôle de ces cellules dans la compréhension d'action. Selon leur raisonnement, si les NM codent pour la représentation d'action, il ne serait pas essentiel de percevoir l'acte moteur complet afin d'évoquer une réponse neuronale; il suffirait d'engendrer la *représentation* de cette action chez l'observateur. Avec cette hypothèse à l'esprit, ils présentèrent des mouvements de préhension dont le geste final était invisible au singe. Dans une condition, un objet préhensible avait précédemment été disposé derrière une cloison à la connaissance du singe; dans une autre condition, aucun objet n'avait été mis en place avant que la cloison ne soit installée. Les résultats démontrèrent que les neurones qui déchargeaient lors de l'observation du mouvement complet répondaient également lorsque le mouvement était dirigé vers un objet préhensible invisible au singe (Umiltà et al., 2001). Il paraît donc vraisemblable que ces neurones de la région F5 ne codent pas seulement la représentation visuelle des actes moteurs, mais également la représentation mentale d'actions.

1.2.2. Organisation fonctionnelle du système neurones-miroirs chez le singe macaque

Suite aux études portant sur les régions F5 et F4, d'autres recherches conduites chez le singe ont permis d'établir une cartographie plus ou moins précise des régions dotées de NM et des liens fonctionnels qu'elles entretiennent entre elles. Fogassi et collaborateurs (2005) mirent en évidence des neurones aux propriétés semblables au NM

dans la région 7b du cerveau du singe, qui constitue la portion rostrale du lobule pariétal inférieur (LPI). Fait intéressant, cette région entretient d'importantes connexions avec F5 (Cavada and Goldman-Rakic, 1989 ; Matelli, Camarda, Glickstein, et Rizzolatti, 1986; Petrides et Pandya, 1984; Rozzi et al., 2006). Cependant, les propriétés des neurones de cette région diffèrent légèrement de celles des neurones trouvés en F5, ceux-ci étant majoritairement sensibles aux stimuli sensoriels (90%). Cependant, près d'un neurone sur deux de la région 7b répond également aux actes moteurs, et satisfait ainsi le critère essentiel pour être qualifié de NM (Fogassi et al. 2005; Rozzi, Ferrari, Bonini, Rizzolatti, et Fogassi, 2008). Notons que cette région est fortement innervée par le sulcus temporal supérieur (STS), une région connue pour être impliquée dans le traitement du mouvement biologique (Puce et Perret, 2003). Cependant, contrairement à F5 et 7b, et bien qu'elle soit dotée de neurones sensibles à l'observation d'actions, les cellules du STS ne sont pas impliquées dans la production d'actions motrices et ne constituent donc pas des NM selon la définition classique du terme.

Bien que centrale à la production motrice, M1 n'était pas considérée comme faisant partie du système de résonance motrice en soi, étant donné que les études antérieures ne recensaient aucun NM dans la région motrice primaire (Di Pellegrino et al. 1992, Gallese et al., 1996, Rizzolatti et al., 1996). Plusieurs études utilisant l'EEG, la SMT et la magnétoencéphalographie (MEG) rapportent néanmoins une activité cérébrale quantifiable dans M1 dans différents contextes d'observation d'actions chez l'humain (Cochin, Barthelemy, Lejeune, Roux, et Martineau, 1998 ; Fadiga, Fogassi, Pavesi, et Rizzolatti, 1995; Hari et al., 1998). Cette modulation de l'activité de M1 suite à la perception d'action était conçue comme étant le résultat de l'activité des régions corticales en amont, notamment F5, une région riche en NM qui est fortement connectée à l'aire motrice primaire. Cependant, de récentes études (Tkach, Reimer, et Hatsopoulos, 2007; Dushanova et Donoghue, 2010) montrent la présence de neurones sensibles à la représentation visuelle d'actes moteurs au sein même du cortex moteur primaire du

singe (F1). En effet, près de la moitié (46%) des neurones de F1 sollicités durant la production motrice le sont également lors de l'observation passive d'un geste de préhension effectué par un humain (Dushanova et Donoghue, 2010). Parmi cette population, une minorité (38%) présente une grande concordance quant à leur direction préférentielle et au rythme de réponse neuronale durant les deux tâches (exécution/observation), alors qu'une majorité (62%), répond tout de même, mais en variant quant à la direction préférentielle et au rythme de réponse. Dans l'ensemble, le patron d'activité neuronale durant l'observation d'actions était tel qu'il permettait de prévoir la direction et la trajectoire du mouvement observé. Ces récents résultats suggèrent que l'activité du cortex moteur lors de l'observation d'actions ne découle pas uniquement de l'activité des régions en amont, mais que F1 participe activement au processus de transformation de l'information visuelle en son équivalent moteur.

Bien que le circuit pariéto-fronto-central du singe soit relativement bien défini, il existe peu d'information quant aux rôles respectifs des différentes régions composant ce système dans la compréhension et l'organisation d'actions. Certaines études suggèrent néanmoins une spécialisation au sein de ces régions. Au niveau de la production motrice, 7b et F5 jouent des rôles différents dans l'organisation et la planification motrice (Bonini et al. 2010; Matelli et al., 1986), 7b étant fortement impliquée dans l'organisation de la séquence et F5 dans la mise en branle de cette séquence. Suivant cette logique, il a été proposé que 7b ait un rôle prépondérant dans l'organisation temporelle de la séquence motrice perçue, alors que F5 serait voué à une représentation plus abstraite de l'action effectuée, davantage en fonction du but que du schéma moteur (Rizzolatti, Fabbri-Destro, Cattaneo, 2009). Étant donné la découverte récente de NM dans F1 (Dushanova et Donoghue, 2010), peu d'hypothèses ont été avancées quant à sa fonction dans le système. Considérant sa position tardive dans la chaine structurelle du système de compréhension d'action, une possibilité envisageable serait que F1 participe à la représentation dynamique du membre utilisé pour effectuer l'action. Ainsi, 7b serait

responsable de l'organisation complexe et temporelle de la séquence motrice, F5 coderait pour le but de l'action et ne serait que peu sélectif quant au moyen choisi pour l'accomplir, et F1 participerait à l'appariement du schéma moteur observé sur la représentation corporelle.

En résumé, les enregistrements unicellulaires réalisés chez le singe macaque montrent l'existence de neurones multimodaux sensibles à la représentation d'actes moteurs, que ceux-ci soient visuels, auditifs ou même sous la forme de représentations mentales. Ces NM se retrouvent majoritairement au sein de trois régions (F5, 7B et F1), ont des rôles différents, et sont organisés en réseau. Bien que plusieurs hypothèses circulent quant aux rôles exacts de ce système, il paraît vraisemblable qu'il contribue principalement à la compréhension d'actes moteurs.

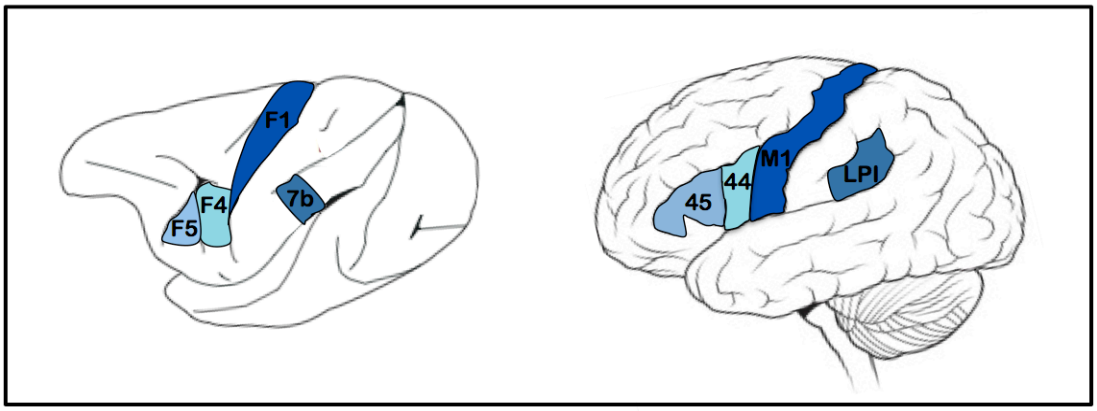
1.3. Le système de neurones-miroirs chez l'humain

1.3.1. Correspondance anatomique et cellulaire: du singe à l'humain

Au niveau cytoarchitectonique, les études d'anatomie comparée entre le singe et l'humain suggèrent que la région F5 du singe, zone riche en NM, correspondrait à l'aire 44 de Broadman (BA44), qui constitue l'essentiel du gyrus frontal inférieur (GFI) (Petrides et Pandya, 2002). De même, le lobule pariétal inférieur (LPI) serait l'homologue de la région 7b (Petrides et Pandya, 1984), autre région où l'on a répertorié la présence de cellules visuomotrices. Une correspondance similaire est établie quant aux régions motrices primaires du singe (F1) et de l'humain (BA4; M1) (Petrides et Pandya, 1984). Cette correspondance anatomique entre le singe et l'humain semble aussi trouver son équivalent au plan fonctionnel, alors que des études en IRMf suggèrent d'importantes similitudes quant au rôle de ces régions dans la production motrice des

deux espèces. Par exemple, chez l'humain, des tâches de manipulation manuelle sollicitent le GFI, de même que le LPI et les régions somatosentorielles et motrices (Matelli et Lupino, 1997). Ce réseau cortical est identique à celui du singe lors de tâches similaires, où l'on retrouve des activités au niveau de F5, 7b et de la région motrice primaire (F1) (Rizzolatti et Craighero, 2004). La figure 1 montre les régions dotées de NM chez le singe et leurs équivalents anatomiques chez l'humain.

Figure 1. Le système neurones-miroirs chez le singe et l'humain



Au niveau cellulaire, Mukamel et collaborateurs (sous presse) ont montré, grâce à des enregistrements unicellulaires chez des patients épileptiques, la présence dans le cerveau humain de cellules aux propriétés similaires aux NM répertoriés chez le singe. En effet, parmi les 1177 cellules enregistrées, une portion significative des neurones de l'aire supplémentaire motrice (17 neurones; 14%), de l'hippocampe (19 neurones; 11%) et de la région para-hippocampique (18 neurones; 12%) répondait à la fois lors de l'exécution et l'observation de mouvements du visage ou des mains. Un sous-groupe de ceux-ci démontrait une excitation lors de l'exécution d'action et une inhibition durant l'observation. D'après les auteurs, ce patron de réponse inversé pourrait contribuer à inhiber l'imitation spontanée à laquelle on pourrait s'attendre. Ce patron est d'ailleurs

identique à celui des neurones pyramidaux de la région F5 du singe, dont la majorité présente une diminution de la fréquence des potentiels d'action durant l'observation d'actions (Kraskov, Dancause, Quallo, Shepherd, et Lemon, 2009). Il est important de noter que ces enregistrements unicellulaires sont effectués dans un cadre clinique auprès de patients épileptiques. En raison de ces considérations cliniques, les chercheurs n'ont pu investiguer la présence de NM dans les aires corticales correspondant aux régions miroirs du singe. Nonobstant, le fait qu'ils aient montré l'existence de neurones aux propriétés visuomotrices dans le cerveau humain renforce l'idée qu'un système similaire à celui du singe puisse y être présent.

Cette découverte apporte un soutien considérable aux études utilisant l'imagerie par résonance magnétique fonctionnelle (IRMf), la tomographie par émission de positons (TEP), la MEG, la SMT et l'EEG. Celles-ci convergent et démontrent d'importantes similarités entre les circuits neuronaux impliqués dans l'observation passive et l'expérience directe d'événements sensoriels (Schaefer et al., 2009), émotionnels (Pfeifer et al., 2008), douloureux (Jackson et al., 2006) ou moteurs (Gazzola et Keysers, 2009). Dans les sections suivantes, les données expérimentales supportant l'existence de résonance *motrice et émotionnelle chez l'humain,* centrales à la présente thèse, seront abordées.

1.3.4. Le système de résonance motrice chez l'humain

Chez l'adulte en santé, l'observation d'un acte moteur n'induit pas automatiquement une activité motrice notable chez l'observateur. Ceci est par contre le cas chez certains individus cérébrolésés, chez qui la simple observation d'un mouvement est suffisante pour induire un comportement d'imitation spontanée (Bien, Roebroeck, Goebel, et Sack, 2009). Même si les études sont relativement inconstantes quant aux

substrats cérébraux exacts associés à ce phénomène d'imitation automatique (Bien et al., 2009), elles suggèrent néanmoins l'existence d'un lien privilégié entre la perception d'action et son exécution dans le cerveau humain. Cette idée est également soutenue par des observations effectuées chez l'adulte, puisque plusieurs études réalisées chez les personnes saines montrent la présence d'une activité musculaire subtile, néanmoins mesurable par électromyographie, lorsqu'elles observent des mouvements faciaux (Magnée, Stekelenburg, Kemner, et De Gelder, 2007). Qui plus est, cette activité accrue se manifeste seulement dans les muscles impliqués dans l'émotion faciale observée (Achaibou, Pourtois, Schwartz, Vuilleumier, 2008).

Au niveau cérébral, une multitude d'études en IRMf montrent de façon robuste que le GFI et LPI sont impliqués à la fois dans les processus d'exécution et de perception d'actes moteurs (Chong, Cunnington, Williams, Kanwisher, et Mattingley, 2008 ; Decety et Grezes, 1999 ; Dinstein, Hasson, Rubin, et Heeger, 2007; Gazzola et Keysers, 2009; Iacoboni et al., 1999;). Il a aussi été montré à l'aide de paradigmes d'habituation que ce sont les mêmes populations neuronales qui sont impliquées dans les deux processus, notamment au sein du GFI (Kilner, Neal, Weiskopf, Friston, et Frith, 2009) et du LPI (Chong et al., 2009). Bien que les études d'imagerie soient inconstantes quant à l'implication de M1 durant l'observation d'action, des données obtenues par SMT (Fadiga et al., 1995) et EEG (Muthukumaraswamy et Johnson, 2004a , 2004b), soutiennent l'idée que M1 soit partie intégrante du système de compréhension d'actions chez l'humain.

On découvre à peine les différentes fonctions des principales régions constituant le SNMh. Si l'on considère l'existence de caractéristiques fonctionnelles distinctes au sein des différentes régions dotées de NM chez le singe, nous sommes en mesure de nous attendre à une spécialisation similaire chez l'humain. Notamment, le GFI,

l'homologue de la région F5 du singe, pourrait coder pour le but de l'action, alors que le LPI, correspondant à la région 7b, serait impliqué dans la représentation kinématique du mouvement (Rozzi et al., 2008). Cette transposition du singe à l'humain semble valable dans une certaine mesure.

En utilisant différents membres du corps (pied, main et bouche) ainsi que différentes actions (trainer, échapper, prendre et pousser), il a été montré que le GFI et le LPI sont respectivement influencés par des facteurs particuliers lors de l'observation d'actions (Jastorff, Begliomini, Fabbri-Destro, Rizzolatti, et Orban, 2010). En effet, l'activité du GFI est principalement modulée en fonction du membre utilisé dans l'action, alors que celle du LPI réagit en fonction du type de mouvement observé. Au sein de cette même zone, les patrons d'activité diffèrent dépendamment de la relation spatiale entre l'acteur et l'objet : les mouvements effectués pour amener l'objet vers l'acteur (prendre et trainer) activent un site ventral et les mouvements pour l'éloigner (échapper et pousser) induisent une activité plus dorsale (Jastorff et al., 2010). Qui plus est, les auteurs suggèrent que les représentations des actions faites avec la main servent de canevas pour représenter ces mêmes actions réalisées avec d'autres membres corporels. Ces données suggèrent l'existence d'une ségrégation fonctionnelle entre le GFI et le LPI, et où la signification comportementale des mouvements perçus induit des activités différentielles au sein du SNMh.

Bien que plusieurs hypothèses circulent quant au rôle exact du système de résonance motrice (Gallese, 2003), l'un des rôles principaux de ce système serait de permettre la compréhension d'action et d'ainsi contribuer à l'imitation motrice (Iacoboni et al., 1999). Des données convergentes soutiennent le rôle du SNMh dans l'imitation. Premièrement, comme l'illustrent les études précédemment mentionnées, le LPI et le GFI sont activés à la fois lors de l'exécution et l'observation d'action, suggérant une

participation commune de ces régions aux deux processus (Buccino et al., 2001). Deuxièmement, au sein de ces régions, le niveau d'activité est accru lorsque le sujet observe une action avec le but de l'imiter comparativement à la simple observation du mouvement (Iacoboni et al., 1999). Bien que corrélationnelles, ces deux démonstrations montrent que le réseau fronto-pariétal du SNMh semble participer aux tâches d'imitation. Ces démonstrations corrélationnelles ont été complémentées par une étude utilisant la SMT répétitive (SMTr) pour établir un lien de causalité entre l'activité du SNMh et les capacités d'imitation. Celle-ci montre que la perturbation de l'activité du GFI à l'aide de la SMTr induit une baisse significative des performances imitatives (Heiser, Iacoboni, Maeda, Marcus, et Mazziotta, 2003). Ainsi, l'ensemble de ces résultats expérimentaux supporte fortement l'hypothèse selon laquelle le SNMh, possiblement en permettant la compréhension d'actions, joue un rôle fonctionnel dans les processus imitatifs.

1.3.4.1. Décours temporel de l'activité au sein du système de résonance motrice

Bien qu'il soit maintenant bien établi que la perception d'actes moteurs induise une activité accrue au sein d'un réseau neuronal précis, le décours temporel de cette activité demeure en grande partie à déterminer. Par delà les « régions miroirs » dont le GFI (Di Pellegrino et al., 1992), le LPI (Rozzi et al., 2008) et M1 (Tkach et al. 2007; Dushanova et Donoghue, 2010), le SNMh reçoit des contributions du sulcus temporal supérieur (STS) (Rizzolatti et Craighero, 2004), une région connue pour être impliquée dans le traitement du mouvement biologique (Puce et Perret, 2003). Toutefois, les données des enregistrements unicellulaires effectués chez le singe actuellement disponibles ne permettent pas de définir précisément le moment où chaque région de ce système est sollicitée.

Les premières études sur le décours temporel de l'activité du SNMh ont été effectuées par Nishitani et collaborateurs (2000, 2002, 2004), qui étudièrent la séquence d'activité corticale durant l'observation d'actions à l'aide de la MEG. Leurs résultats suggèrent une activité séquentielle et ordonnée au sein du SNMh; alors que les régions visuelles sont activées en premier (≈118ms), suivi du STS (≈193ms), du LPI (≈224ms), du GFI (≈255ms) et finalement de M1 (≈345ms). Ces données chronométriques suggèrent que l'appariement moteur prenant place dans M1 se situe à la fin d'un processus relativement long, où les différentes régions du SNMh sont activées de façon sérielle.

Toutefois, des données récentes obtenues par MEG et TMS suggèrent la présence d'un mécanisme d'appariement d'action beaucoup plus rapide que celui documenté par Nishitani et collaborateurs (2000, 2002, 2004). Notamment, une étude MEG utilisant des champs neuromagnétiques latéralisés préparatoires (*neuromagnetic lateralized readiness fields*) montre la présence d'un effet de résonance dans M1 à 83ms après le début du mouvement observé (van Schie et al., 2008). Argumentant également en faveur d'un système de résonance rapide, il a été montré à l'aide de la SMT que l'excitabilité corticospinale de la représentation motrice des muscles de la langue était augmentée 100ms après la présentation de pseudo-mots qui contenaient des sons requérants des mouvements de langue (Roy, Craighero, Fabbri-Destro, et Fadiga, 2008).

Ainsi, les études font état de données divergentes quant au moment où M1 est sollicité durant la perception d'action. D'une part, certains soutiennent que l'activité dans le SNMh suit une route séquentielle où M1 serait la dernière station (Nishitani et Hari, 2000, 2002), alors que d'autres suggèrent une voie rapide entre la perception et le processus de résonance prenant place au sein de M1 (Roy et al, 2008; van Schie et al., 2008). Déterminer le moment auquel les différentes régions du SNMh sont actives

pourrait nous renseigner non seulement sur leurs rôles respectifs dans la résonance motrice, mais aussi sur leur niveau d'automaticité. Cela contribuerait également à clarifier l'importance que revêtent les anomalies répertoriées dans ce flot d'activité chez certaines populations cliniques (Nishitani et al., 2004).

1.3.5. Le système de résonance émotionnelle chez l'humain

Les régions corticales associées aux émotions paraissent également être activées de façon vicariante lorsqu'un individu perçoit les états émotionnels d'autrui. En effet, percevoir le dégout (Jabbi, Swart et Keyser, 2007), la joie (Hennenlotter et al., 2005) ou une combinaison d'émotions (Carr, Iacoboni, Dubeau, Mazziotta, et Lenzi, 2003) active les régions de l'insula antérieure et de l'operculum frontal, à l'image de ce qui est observé lorsque l'individu expérimente directement ces émotions. De plus, des études de cas documentent l'incapacité concomitante à vivre et à reconnaître des émotions à la suite de lésions à ces régions (Adolphs, Damasio, Tranel, Cooper, et Damasio, 2000; Adolphs, Tranel et Damasio, 2003).

La démonstration expérimentale la plus frappante de l'existence d'un mécanisme de résonance émotionnel est probablement celle effectuée par Singer et collaborateurs (2004). Utilisant l'IRMf, ils ont quantifié l'activité cérébrale d'individus dans deux conditions : (1) lorsqu'ils étaient soumis à un stimulus nociceptif et (2) lorsqu'ils savaient qu'un être aimé vivait cette même expérience. Tel qu'attendu, ils observèrent un chevauchement important dans les patrons d'activité dans les deux conditions, notamment une augmentation de l'activité bilatérale de l'insula antérieure et du cortex cingulaire antérieur. Fait intéressant, le niveau d'activité de ces deux régions était corrélé avec les résultats individuels à des échelles d'empathie (Singer et al., 2004). Il

semble donc que percevoir, ou même induire la présence d'états émotionnels particuliers chez quelqu'un d'autre est suffisant pour engendrer une activité dans les régions associées à leurs expériences directes.

Le fonctionnement du système de résonance émotionnel semble intimement lié à celui des systèmes de résonance motrice, sensoriel et nociceptif (Keyser et Gazzola, 2009). En effet, bien qu'il soit facile de percevoir les actions et les stimuli sensoriels vécus par autrui, l'accès direct à leurs états émotionnels est la plupart du temps impossible. Les divers systèmes de résonance moteur, sensoriel et nociceptif permettraient cependant d'inférer les pensées et émotions que les autres ressentent et vivent.

Anatomiquement, l'insula et l'operculum frontal reçoivent des afférences du cortex préfrontal, du système moteur et de l'ensemble des modalités sensorielles. Les études d'IRMf récentes soutiennent d'ailleurs l'hypothèse selon laquelle la résonance émotionnelle dépend, du moins en partie, du fonctionnement des autres systèmes de simulation. Par exemple, des études de connectivité fonctionnelle montrent que l'activité accrue du GFI durant la perception d'émotions faciales, une région cruciale à la résonance motrice, est corrélée à l'activité des régions émotionnelles (Carr et al., 2003); de même, l'activité du système de résonance nociceptif semble liée à la résonance émotionnelle lors de la perception de douleur (Zaki, Ochsner, Hanelin, Wager, et Mackey, 2007). Prises dans leur ensemble, ces données suggèrent que l'insula et l'operculum fontal peuvent interagir avec un large éventail de régions corticales, incluant celles associées à la résonance motrice afin d'induire la représentation neuronale des émotions que nous percevons chez nos semblables.

1.3.6. Liens entre les mécanismes de résonance et les aptitudes sociocognitives chez l'humain

Par-delà le « simple » appariement moteur qui prend place au sein des mécanismes de résonance, le SNMh a reçu une attention considérable en raison de sa contribution potentielle aux habiletés reliées à la sphère sociale. En effet, peu de temps après leur découverte, Gallese et Goldman (1998) proposaient que les NM soient au centre de la compréhension sociale. Selon cette « théorie motrice de l'empathie » (Gallese et Goldman, 1998), le système d'appariement moteur incarné par les NM permettrait d'inférer les états d'esprit d'autrui et serait crucial à la mise en place de processus de haut niveau comme l'empathie.

Même si cette hypothèse a été largement discutée, relativement peu d'études ont montré l'existence d'un tel lien dans la population normale. Les données les plus probantes quant à l'existence de ce lien proviennent d'une série d'études IRMf où l'activité du SNMh se trouva corrélée avec des attributs sociaux (Gazzola, Aziz-Zadeh, et Keysers, 2006; Kaplan et Iacoboni, 2006; Pfeifer et al., 2008). Plus précisément, chez des individus sains, le niveau d'activité du GFI durant l'observation d'actions corrèle positivement avec différentes sous-échelles (*Perspective Taking* (Gazzola et al., 2006), *Empathic Concern* (Kaplan & Iacoboni, 2006; Pfeifer et al., 2008)*, Fantasy* (Pfeifer et al., 2008), *Personal Distress* (Pfeifer et al., 2008)) de l'index de réactivité interpersonnelle (IRI; Davis, 1980), une mesure largement utilisée d'empathie. De plus, des indices provenant de populations cliniques où les déficits sociaux sont bien documentés, tels que les troubles du spectre autistiques (TSA), suggèrent un lien entre l'empathie et le SNMh (Bernier et al., 2007; Dapretto et al., 2006; Oberman et al., 2005; Théoret et al., 2005; Williams et al., 2006). À cet égard, une étude IRMf effectuée avec des enfants TSA montre que l'activité du GFI, une région centrale du SNMh, est

négativement corrélée avec la sévérité de certains symptômes sociaux (Dapretto et al., 2006).

Même si aucune de ces études ne rapporte d'activité dans M1, elles suggèrent néanmoins que l'activité de certaines régions du SNMh est reliée à l'empathie. Notons aussi que des états émotionnels et des traits des personnalités on été mis en relation avec l'activité de M1 durant la perception d'actions. Notamment, le niveau d'anxiété (Wassermann, Greenberg, Nguyen, et Murphy, 2001) ainsi que les traits psychopathiques (Fecteau et al., 2008) chez des individus normaux ont été associés à des altérations de l'excitabilité corticale de M1, ce qui suggère que l'activité du SNMh mesuré à M1 pourrait servir de marqueur des processus du SNMh que l'on croit liés aux compétences sociales.

1.3.7. Résumé des mécanismes de résonance chez l'humain

L'ensemble des études présentées converge et montre des similarités importantes entre les systèmes neuronaux durant l'expérience directe et l'observation de stimuli émotionnels, nociceptifs, sensoriels ou moteurs. Bien plus que simplement corrélationnelles, certaines des études présentées montrent un lien causal entre l'activité de ces régions d'activité commune, notamment le GFI, et le bon fonctionnement des mécanismes de résonance.

Par delà le « simple » appariement entre soi et autrui qui prend place à travers ces différents systèmes, ceux-ci paraissent être associés à des aptitudes sociocognitives, notamment l'empathie. En effet, dans l'ensemble, les résultats montrent la présence

d'activité accrue dans les régions du SNMh pour les individus empathiques et ceux avec de meilleures habiletés sociales.

1.4. Le système neurones-miroirs chez l'enfant

1.4.1. Le système neurones-miroirs chez l'enfant et son importance clinique potentielle

Malgré l'abondance de données suggérant la présence d'un SNMh chez adulte, étonnamment peu d'études se sont penchées sur son développement. Pourtant, celle-ci revêt une importance théorique et clinique certaine. La documentation du fonctionnement de ce mécanisme chez l'enfant contribuerait à plusieurs théories; parmi d'autres, celle de l'acquisition du langage (Rizzolatti et Arbib, 1998) et du développement de la théorie de l'esprit (Trevarthen et Aitken, 2001), qui accordent toutes deux une place importante au SNMh.

Au point de vue clinique, plusieurs ont suggéré qu'une dysfonction du SNMh pourrait sous-tendre la manifestation de déficits sociaux rencontrés au sein de diverses psychopathologies (Gallese, 2003; Williams et al., 2001). De récentes études EEG (Oberman et al., 2005; 2008) et TMS (Théoret et al., 2005) ont en effet documenté des anomalies du SNMh chez des personnes atteintes d'un trouble du spectre autistique. De plus, dans cette population, on a montré que l'ampleur des déficits sociaux observés était inversement corrélée avec l'activité de certaines régions du SNMh (Dapretto et al., 2006). Pour l'instant, le diagnostic des troubles du spectre autistique repose essentiellement sur les manifestations comportementales atypiques. Une meilleure documentation du développement normal du SNMh pourrait potentiellement contribuer

à l'élaboration de nouveaux outils diagnostiques ainsi qu'à la mise en place de traitements plus adaptés pour des pathologies impliquant une dysfonction du SNM (Fecteau et al., 2006).

1.4.2. Indices neurophysiologiques de l'existence du système neurones-miroirs chez l'enfant sain

Jusqu'à récemment, très peu d'études s'étaient penchées sur le du développement du SNMh. Bien que plusieurs études comportementales suggèrent la présence d'un système d'appariement d'action chez l'enfant, notamment en raison des capacités d'imitation néonatales, il n'existait presque aucune donnée neurophysiologique quant à l'activité du système pariéto-frontal de compréhension d'action chez l'enfant. En fait, la majorité des études portant sur la perception d'action chez l'enfant se sont penchées sur la capacité de reconnaissance du mouvement biologique (Hirai et Hiraki, 2005; Pavlova, Krageloh-Mann, Sokolov, et Birbaumer, 2001).

Avant la parution des travaux qui forment cette thèse, une seule étude avait investigué la perception d'actions en relation avec le fonctionnement du SNMh chez l'enfant (Fecteau et al., 2004). Dans cette étude de cas, Fecteau et collaborateurs utilisèrent l'EEG intracrânien afin de démontrer l'existence d'un mécanisme de résonance motrice chez un enfant de 36 mois. Comparativement à la condition de repos, ils observèrent une diminution de la puissance spectrale de la bande alpha (8.5-12.5 Hz) pour deux électrodes situées sur la région sensorimotrice de la main droite, à la fois lors de l'exécution et de l'observation de mouvements de la main. Le fait que les mêmes régions corticales répondent à l'exécution et à l'observation chez l'enfant supporte la présence d'un SNMh. Ces résultats font écho à ceux obtenus chez l'adulte avec la même méthode (Tremblay et al., 2004). Cependant, comparativement à l'adulte, l'étendue spatiale du SNMh chez l'enfant telle que rapportée par Fecteau et collaborateurs (2004)

semble plutôt limitée. Pour expliquer ce fait, les auteurs avancent l'hypothèse que la différence de distribution du SNMh reflète la modification que subirait le système au cours du développement. Dans ce processus, l'expérience jouerait vraisemblablement un rôle et, à travers un raffinement progressif de cette « cartographie miroir », mènerait ultimement à l'établissement d'un mécanisme précis et sélectif.

1.4.3. Indices comportementaux de l'existence du système neurones-miroirs chez l'enfant sain

1.4.3.1. L'imitation néonatale

Malgré l'absence relative de données quant à l'existence du SNMh chez l'enfant, les quelques auteurs ayant abordé tangentiellement la question du développement du SNMh proposent de manière implicite son caractère inné (Rizzolatti, Fadiga, Matelli, Fogassi, et Gallese, 2002 ; Meltzoff et Decety, 2003). Cette position est principalement motivée par les études comportementales sur l'imitation néonatale.

Bien qu'indirectement, les capacités d'imitation motrice fournissent une importante indication quant à la présence de mécanismes de compréhension d'action et d'appariement moteur, puisqu'elles nécessitent la mise à contribution de circuits neuronaux similaires à ceux recrutés par l'acte perçu. Il semblerait en effet que les processus d'imitation reposent en grande partie sur le fonctionnement du SNMh (Iacoboni et al., 1999; Wohlschlager & Bekkering, 2002). Cette hypothèse est supportée par le fait que, d'une part, on retrouve des dysfonctions du SNMh au sein de pathologies présentant des déficits d'imitation (Dapretto et al., 2006; Oberman et al., 2005; Théoret et al., 2005), et, d'autre part, certaines personnes présentant une lésion dans la région de Broca, une région centrale au SNMh, manifestent des déficits d'imitation (Saygin, Wilson, Dronkers, et Bates, 2004). La présence de capacités d'imitation chez le

nourrisson constituerait donc un indice important quant à la présence d'un SNMh fonctionnel.

La littérature portant sur les capacités d'imitation chez les nouveaux nés est abondante. Piaget, pionnier de la psychologie du développement, lui accordait un rôle central dans le développement cognitif de l'enfant. Celui-ci croyait que les capacités d'imitation se développaient autour de l'âge d'un an et de manière concomitante à la capacité d'agir intentionnellement. L'imitation résulterait donc en grande partie de l'exploration tactile de son propre corps et de celui d'autrui (Piaget, 1962). Toutefois, Meltzoff et Moore (1977) établirent la présence de capacités d'imitation de manière étonnamment précoce chez l'humain. Ils démontrèrent que des nouveaux nés âgés de 42 minutes imitaient spontanément les gestes orofaciaux qui leur étaient présentés (Meltzoff et Moore, 1983). Cette démonstration mit à mal les théories piagétiennes du développement qui stipulaient une dissociation entre les espaces visuels et moteurs (Piaget, 1962); il semblerait plutôt que le lien entre la vision et la motricité soit inné.

Lorsqu'on lui présente une mimique faciale, la première réaction d'un nourrisson est d'activer la partie homologue de son propre visage (Meltzoff et Moore, 1997). Par exemple, lorsqu'il observe un mouvement de lèvres, le nouveau-né mettra ses lèvres en mouvement, alors que devant un mouvement de langue, il activera cette dernière. Dans l'éventualité où l'acte observé ne soit pas proprement imité, la partie corporelle correspondante à celle observée sera néanmoins mise en mouvement. Cette activation s'accompagne souvent d'une diminution de l'activité d'autres parties sans rapport à l'action (Meltzoff, 1997). Donc, même si le nouveau-né n'a pas la capacité de mettre en branle un programme moteur identique à celui qui lui est présenté, la partie corporelle mise en cause dans l'acte observé est tout de même identifiée et associée de manière spécifique à la représentation de son propre corps.

Au-delà de la correspondance physique, le nouveau-né est capable de répondre de manière concordante à différentes actions impliquant la même partie du visage. Il ouvre la bouche à l'observation d'une telle action, alors qu'il la ferme ou bouge les lèvres si le modèle le fait. De plus, si le modèle sort la langue du côté gauche, le bébé sortira sa langue à la médiane pour ensuite l'orienter graduellement du même côté que le modèle (Meltzoff et Moore, 1997). Les jeunes enfants sont aussi capables d'imiter le geste observé de manière temporelle, alors qu'ils gardent la bouche ouverte plus longtemps si le modèle fait de même (Meltzoff, 1997). Ces résultats suggèrent que non seulement la correspondance physique semble établie à la naissance, mais la correspondance motrice elle-même, tout comme la perception des relations spatiales et temporelles, ne semble pas nécessiter d'apprentissage. Le tarissement d'activités non reliées avant l'activation de la région d'intérêt dans l'action pourrait refléter le fait que les nourrissons vont isoler quelle partie du corps bouge avant de déterminer comment la bouger (Meltzoff et Decety, 2003). On ignore si ces processus d'inhibition et d'activation concomitantes résultent de mécanismes neuronaux automatiques ou s'ils sont le reflet de la mobilisation de l'intérêt de la part du nourrisson.

Le fait que la partie corporelle que le nourrisson doit bouger est hors de sa vue constitue l'un des aspects importants de l'imitation faciale. Bien que les mouvements qui peuvent être exécutés avec la bouche soient relativement simples et limités, l'imitation faciale indique que le pairage moteur et physique effectué ne nécessite pas la contribution de la modalité visuelle dans l'établissement de la correspondance entre le geste de l'enfant et celui observé. Dans cette situation, seules les informations proprioceptives peuvent fournir une rétroaction sur les mouvements exécutés, ce qui constitue un argument en faveur de la présence (et de la connaissance) d'un schéma corporel inné. Un tel schéma est le fondement à partir duquel les actions, les nôtres et celles d'autrui, pourraient être représentées et appariées.

La majorité des études portant sur l'imitation chez le nourrisson ont utilisé des stimuli simples lors de leur démonstration, limités aux mouvements de langue et à la gestuelle orofaciale (Heimann, Nelson, et Schaller, 1989; Meltzoff et Moore, 1983; Meltzoff et Moore, 1977). Bien que ce genre de stimuli revête un intérêt certain, ceux-ci comportent des limitations majeures. D'une part, la fréquence des mouvements faciaux spontanés (comme sortir la langue et ouvrir la bouche) est très élevée chez le nouveau-né, de sorte qu'il est difficile de différencier un véritable comportement d'imitation d'un acte spontané. Ceci pourrait expliquer les difficultés à reproduire les résultats de Meltzoff (Heimann et al., 1989). Aussi, ces actions sont peu complexes et faciles à exécuter, et n'écartent pas totalement l'hypothèse du mécanisme de relâchement inné.

1.4.3.2. Transfert intermodal : Entendre l'action

Bien qu'elles s'avèrent informatives, les études d'imitation chez le nouveau-né reposent essentiellement sur la modalité visuelle. Or, l'une des caractéristiques principales du SNMh est la capacité de répondre à des stimuli tant visuels qu'auditifs qui sont associés à un acte moteur. Pour cette raison, l'étude du SNMh en relation avec la perception du langage est d'un intérêt certain. De manière attendue, voir et entendre simultanément un congénère parler augmente l'activité du cortex moteur chez l'adulte (Sundara, Namasivayam, et Chen, 2001). À un moindre degré, la simple audition de vocalisations (Fadiga, Craighero, Buccino, et Rizzolatti, 2002) module également l'activité du cortex moteur. Comme la théorie de l'appariement directe le suppose, dans les deux cas, cette activité est restreinte aux muscles recrutés dans l'action perçue.

Meltzoff et Kuhl furent les pionniers dans l'investigation de la perception des attributs de la parole chez le jeune enfant (Kuhl et Meltzoff, 1982). Dans une de leurs nombreuses expérimentations sur le sujet, ils investiguèrent l'imitation de production vocale chez le nourrisson. Lors de l'observation de vidéos sonores montrant un adulte

prononcer une voyelle donnée (/a/, /i/ ou /u/), ils démontrèrent que des enfants âgés d'aussi peu que 12 semaines produisaient des vocalisations apparentées à celles observées (Kuhl & Meltzoff, 1996). Dans une expérience préalable, ils avaient étudié la perception bimodale de la parole chez des enfants âgés de 18 à 20 semaines (Kuhl, 1982). Pour ce faire, ils présentèrent simultanément deux films montrant les gestuelles faciales de la production d'un /i/ et d'un /a/, accompagnés d'un seul son concordant à l'un ou l'autre des vidéos (/i/ ou /a/). Les enfants soumis à l'expérimentation passèrent significativement plus de temps à observer le film concordant avec le son (73.6%) que le film alternatif, manifestant une reconnaissance de la correspondance entre le son et la motricité qui y est associée. Subséquemment, ils présentèrent les mêmes vidéos, mais les sons de vocalisations (/a/ et /i/) furent substitués par des tonalités pures correspondant aux sons initiaux. Ces nouveaux sons étaient similaires aux premières vocalisations en temps et en tonalité. Cependant, dans cette condition, le pattern d'observation des vidéos était aléatoire, les sujets n'accordant pas plus d'attention au vidéo concordant qu'à l'autre. Ils observèrent également que l'exposition à la vocalisation humaine dans la première expérimentation élicitait davantage de productions sonores chez l'enfant, comparativement à celle avec les tonalités pures. Outre l'imitation vocale, ces études démontrent que le nourrisson est capable d'identifier correctement quelle est l'action motrice associée à la production d'un son précis. La présence hâtive de cet appariement entre les modalités auditives et motrices au niveau perceptuel est intrigante. La dernière étude suggère quant à elle que le caractère biologique (et donc moteur) de la production sonore est important à cette discrimination. Il est intéressant de noter que le SNMh répond sélectivement aux sons d'actions biologiques; il est donc plausible qu'il contribue d'une quelque manière à cette discrimination.

Une étude récente portant sur la perception des vocalisations chez le nouveau-né a apporté un éclairage nouveau aux capacités de transfert intermodal chez cette population. Lors des études précédentes, les informations visuelles et auditives étaient

présentées de manière concomitante, de sorte qu'il était impossible de déterminer la contribution relative de chaque modalité. Afin de déterminer le rôle de la modalité auditive dans les comportements d'imitation orofaciale, Chen et collaborateurs étudièrent la motricité orofaciale en relation avec l'audition exclusivement (Chen, Striano, et Rakoczy, 2004). Ils étudièrent les performances orofaciales de 25 nouveaux nés âgés de moins d'une semaine lors de l'audition de vocalisation (/a/ ou de /m/) où aucun indice visuel relié à la production sonore n'était disponible. Ils démontrèrent que les nourrissons exécutaient des mouvements buccaux qui correspondaient à la prononciation correcte des sons entendus. Lors de la présentation du son /m/, les nourrissons exécutaient un plus grand nombre d'occlusions de bouche que d'ouvertures, et vice-versa lors de l'audition de la voyelle /a/.

Cette expérimentation va au-delà de la simple imitation, et démontre que la gestuelle orofaciale associée à la production de vocalisation peut être élicitée lors de la simple audition. Conséquemment, elle suggère la mise à contribution du schéma moteur spécifique à la production vocale entendue et laisse supposer que des informations autres que visuelles peuvent engendrer une reproduction de la motricité associée à la production vocale perçue. On peut établir un lien entre ces résultats comportementaux et les données neurophysiologiques obtenues chez l'adulte, où la perception de vocalisations engendre l'activation de circuits moteurs également mis à contribution dans la production (Fadiga et al., 2002). Il est tentant de conclure que le nourrisson « saurait » de manière innée comment prononcer les sons qu'il entend.

En bref, le nourrisson est apte à 1) identifier la partie corporelle observée facilitant le mouvement de la partie homologue de son propre corps ; 2) reproduire le mouvement qu'il observe chez autrui ; 3) reconnaître les incongruités entre les sons et le mouvement observé ; et 4) exécuter les mouvements associés à la production de sons biologiques qu'il a entendus. L'ensemble de ces résultats comportementaux soutient

l'idée de la présence d'un mécanisme de résonance motrice chez le nouveau-né. Toutefois, ces données sont indirectes, et bien que les comportements d'imitation néonatale sollicitent des schémas moteurs similaires, il n'existe pas d'études documentant l'appariement direct au moment de l'observation d'action. Il est donc envisageable que d'autres mécanismes entrent en jeu dans plusieurs des phénomènes rapportés précédemment. Il est possible que l'imitation relève de mécanismes alternatifs, qui reposent sur des aspects plus cognitifs que purement moteurs. Similairement, il se peut que la discrimination de la correspondance entre les sons et les gestes orofaciaux soit davantage due à des indices d'ordre temporel et à des processus d'intégration de bas niveau. Il est cependant plus ardu d'expliquer comment le nourrisson s'y prendrait pour activer un schéma moteur qui concorde avec la prononciation de la vocalisation qu'il n'a qu'entendue sans l'apport d'un système appariant le son et sa représentation motrice. Quoi qu'il en soit, l'hypothèse de la présence du SNMh de manière innée amène invariablement à se questionner sur les fondements d'un tel mécanisme dans le cerveau humain.

Cependant, ces démonstrations comportementales se heurtent à une absence quasi complète de données neurophysiologiques sur les mécanismes qui les sous-tendent. En effet, la totalité des enregistrements démontrant le fonctionnement des neurones miroirs ont été effectués chez des singes à la fois âgés et expérimentés au plan visuomoteur. Aucun enregistrement n'a cependant été effectué chez des singes en bas âge ou inexpérimentés. De plus, il n'existe pour le moment aucune démonstration, même indirecte, de la présence d'un tel système chez un nouveau-né, singe ou humain. Dans cette optique, certains ont soulevé l'hypothèse que l'activité du SNMh et son aspect multimodal pourraient être le résultat d'apprentissages visuomoteurs (Heyes, 2010 ; Hurford, 2002). Il serait en effet surprenant que l'appariement entre l'action de craquer une arachide et le son spécifique que produit une noix qui craque soit inné; un nombre quasi infini de tels pairages devrait être présent à la naissance. Aussi, le SNM paraît

malléable, alors que plusieurs études démontrent les effets de la pratique et de l'exposition à des actes moteurs sur son fonctionnement chez l'adulte (Calvo-Merino, Glaser, Grezes, Passingham, et Haggard, 2005; Ferrari, Rozzi, et Fogassi, 2005; Haslinger et al., 2005). Il est donc possible que les systèmes de résonance motrice s'établissent subséquemment à la perception d'actions produites par autrui et par soi.

1.5. La stimulation magnétique transcrânienne dans l'investigation du système neurones miroirs

1.5.1. Introduction et principes de fonctionnement

Les outils d'investigation neurophysiologiques procurent des informations variant sur un spectre de précision quant au moment et au lieu de l'activité cérébrale associée à une tâche donnée. Bien que des designs expérimentaux rigoureux nous ont permis d'établir avec une certitude relative la contribution de certaines aires cérébrales aux processus cognitifs, la plupart des techniques d'imagerie traditionnelles ne permettent pas d'établir un lien de *causalité* entre l'activité d'une aire cérébrale et le déroulement d'un processus cognitif. Cependant, il est possible d'établir la présence d'un tel lien grâce à l'utilisation de la SMT. La SMT, en utilisant la variation de champ magnétique afin d'induire un courant électrique dans le cerveau, perturbe le fonctionnement normal d'une région cérébrale et permet ainsi d'établir sa contribution à un comportement ou un processus cognitif donné. Ces perturbations transitoires induites par la stimulation répétée d'une région sont connues dans le domaine des neurosciences cognitives sous le nom de « lésions virtuelles ». Cependant, par delà les lésions virtuelles, la SMT s'avère un outil particulièrement sensible dans la *mesure* de l'activité corticale et corticospinale. De plus, son excellente résolution temporelle et spatiale permet la mesure du décours temporel de l'activité dans un circuit neuronal. Par

l'utilisation de différents protocoles, la SMT permet aussi d'étudier une multitude de caractéristiques du système moteur, tant au niveau de la physiologie que des mécanismes neurochimiques.

La force électromagnétique se manifeste à la fois dans les champs magnétiques et électriques. En fait, tous deux constituent les facettes indissociables d'une même pièce : l'apparition d'un courant électrique génère un champ magnétique; et une variation de champ magnétique induit un courant électrique dans un matériau situé à proximité. Ainsi, lorsqu'une charge électrique passe à travers un conducteur, cela produit un bref champ magnétique, qui peut à son tour générer une activité électrique dans un autre matériau conducteur. C'est sur ce principe d'induction électromagnétique, découvert en 1831 par Michael Faraday, que repose le fonctionnement de la SMT. Le taux de changement du champ magnétique et sa capacité à induire par la suite une activité électrique dépendent directement du taux de changement du courant électrique initial. Ainsi, plus la variation de courant à la hausse sera importante, plus la variation de champ magnétique, et par conséquent son effet, sera puissante.

Dans la SMT (Figure 2.A.), une charge électrique est générée dans une unité de production de pulsations contenant plusieurs condensateurs. La charge produite est relâchée dans une bobine de cuivre recouverte d'une gaine isolante (le stimulateur), ce qui génère une stimulation magnétique. Lorsque le stimulateur est placé sur la tête d'un participant, le champ magnétique ainsi généré passe au travers du crâne sans aucune atténuation. Grâce à la conductivité du tissu cérébral, le champ électrique produit un courant ionique dans le cortex et, subséquemment, une dépolarisation de la population neuronale qui se trouve sous cet effet.

Il existe plusieurs types de stimulateurs dont la forme vient influencer la force et la précision des stimulations magnétiques. Nous retiendrons parmi eux deux types de stimulateurs les plus couramment utilisés, tous deux capables d'engendrer des champs magnétiques d'une puissance allant de 1.5 à 2.5 Teslas à leur surface. Le premier, le stimulateur circulaire, en forme de loupe, permet d'activer un large réseau de neurones se retrouvant sous le centre du stimulateur. Le second, le stimulateur en forme de huit est constitué de deux filaments de cuivre circulaires adjacents. La force du champ magnétique produit par celui-ci est maximale au centre de la zone de chevauchement des deux cercles, endroit où il y a sommation des champs électriques. Ce type de stimulateur a l'avantage d'être plus focal et précis, ce qui permet de stimuler un volume de cortex relativement restreint d'environ 1 cm^3 (Figure 2.B. et 2.C.). En raison de sa précision, ce type de stimulateur et habituellement privilégié dans les études sur la cognition.

1.5.2. La stimulation magnétique transcrânienne dans l'étude de la cognition et de la neurophysiologie humaine

1.5.2.1. La stimulation magnétique transcrânienne comme outil de perturbation de l'activité cérébrale

Trois différents types de paradigmes sont couramment utilisés lorsqu'il s'agit de perturber l'activité corticale d'une région afin d'en déduire la fonction dans un processus cognitif. Tout d'abord, la SMT à pulsation unique consiste à administrer une seule pulsation sur une région du cortex durant une tâche donnée. Cette technique permet d'interférer avec l'activité cérébrale normale de façon transitoire par l'introduction d'une activité neuronale aléatoire dans la région stimulée. Si la région stimulée est nécessaire à l'exécution d'une tâche donnée, la performance à celle-ci devrait en être altérée. Ceci permet d'établir un lien de causalité entre la fonction précise et la fonction de la région cérébrale. L'interférence provoquée par la SMT est d'une durée de quelques

millisecondes, cette résolution temporelle nous informe sur le moment où la région cérébrale contribue de façon significative au processus relié à la tâche (Robertson, Theoret et Pascual-Leone, 2003).

La SMT peut aussi être utilisée pour perturber l'activité d'une région cérébrale pour une plus longue période que celle associée à une pulsion unique. Ceci permet d'observer les effets comportementaux causés par la mise hors service d'une région corticale, et d'ainsi inférer sa fonction dans un processus cognitif. On réfère à cette technique par le terme de « lésion virtuelle », car à l'instar d'une lésion, la partie du cerveau stimulée devient inopérante. Une lésion virtuelle peut être faite par l'entremise de deux différentes méthodes, soit la SMTr utilisée durant la tâche (online SMTr) ou précédant la tâche (offline SMTr). Ces deux méthodes offrent la possibilité de couvrir une fenêtre temporelle plus large que la pulsation unique et permettent d'explorer plus facilement quelles sont les régions qui contribuent de façon significative à une tâche.

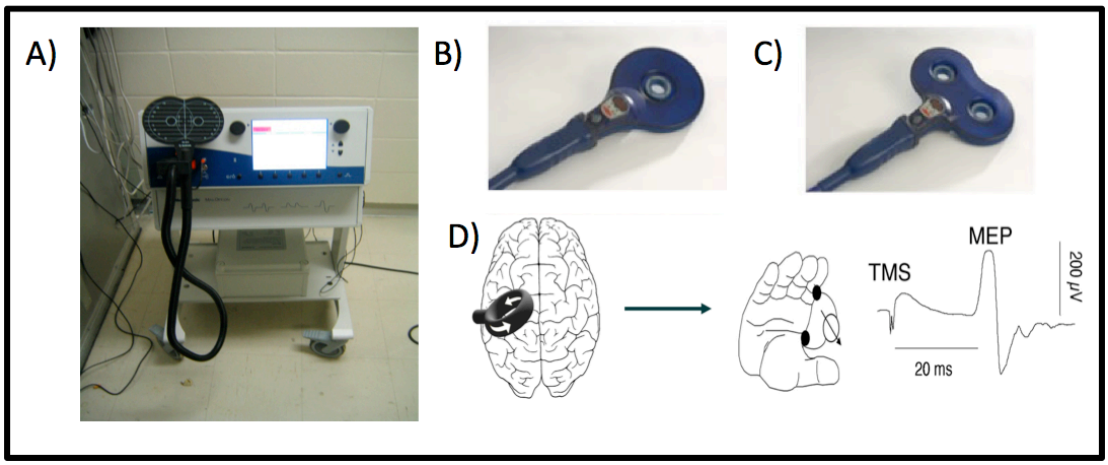
1.5.2.2. La stimulation magnétique transcrânienne dans la mesure de l'activité corticale et corticospinale

Les premières utilisations de la SMT furent surtout faites dans le contexte d'études investiguant différentes propriétés du système moteur (Cracco, 1987; Levy, 1987). Ceci est facilement compréhensible, considérant que les effets de la SMT sur le cortex moteur sont facilement observables et quantifiables. En effet, puisque le cortex moteur (M1) comporte des projections directes vers la moelle épinière, sa stimulation avec la SMT active automatiquement la voie corticospinale et provoque une contraction involontaire du muscle correspondant à la région stimulée. Cette contraction musculaire, qui peut être mesurée grâce à l'électromyographie, est connue sous le nom de potentiel évoqué moteur (PÉM). Les PÉM résultent de la dépolarisation des neurones pyramidaux

au niveau du cortex moteur, et plus l'intensité de stimulation est forte, plus l'amplitude du PÉM sera grande (Figure 2.D.).

Dans certains contextes, les PÉM induits par la SMT peuvent être utilisés comme mesure de l'activité corticale de M1. En effet, lorsque l'intensité de la stimulation appliquée au niveau de M1 est constante, les variations d'amplitudes des PÉM reflètent le niveau d'activité intrinsèque des neurones pyramidaux de M1 (Jahanshahi et Rothwell, 2000). Il est ainsi possible d'inférer le niveau de l'activité corticospinale de façon indirecte en fonction d'un niveau de base : une augmentation de l'activité se traduit par une facilitation motrice (une augmentation de la taille des PÉM), alors qu'une réduction de celle-ci indique une diminution de l'activité corticospinale. Afin de maximiser la variabilité des PÉM, l'intensité de la SMT est généralement réglée individuellement afin d'évoquer un PÉM d'environ 1 mV au repos. Si une intensité trop élevée était utilisée, la forte amplitude des PÉM masquerait la contribution de l'activité corticale au signal, alors qu'une intensité trop faible ne permettrait pas de mettre en lumière une diminution d'activité et serait incapable d'induire des PÉM dans de nombreux cas.

Figure 2. La stimulation magnétique transcrânienne



1.5.3. La stimulation magnétique transcrânienne à pulsation unique dans l'étude du système de résonance motrice humain

Ainsi, de par sa résolution spatiale et temporelle, de même qu'en raison de sa capacité à mesurer divers aspects de la neurophysiologie du cortex moteur, la SMT s'avère être un outil de choix dans l'étude des mécanismes de résonance motrice. C'est d'ailleurs en utilisant la SMT que Fadiga et collaborateurs (1995) démontrèrent pour la première fois l'existence d'un mécanisme d'appariement d'action chez l'humain.

Comme nous l'avons vu précédemment, la SMT, lorsqu'appliquée au niveau du cortex moteur, induit une volée corticospinale qui engendre une contraction du muscle correspondant à la région stimulée. La mesure des PÉM résultants peut servir d'indicateur du degré d'activité dans M1. C'est en utilisant cette technique que Fadiga et collaborateurs (1995) ont montré une augmentation des PÉM des muscles de la main induite par des stimulations uniques lorsque les sujets observaient passivement des mouvements de la main. Cette augmentation des PÉM, relativement à un niveau de base,

reflète l'état d'activité accrue du système moteur de l'observateur durant la perception de mouvements. Cette technique est maintenant couramment utilisée dans l'étude du SNMh.

Suite à l'étude de Fadiga (1995), plusieurs études en SMT se sont avérées fructueuses et ont mis en lumière des caractéristiques subtiles du SNMh. Notamment, il a été montré que cette facilitation motrice était spécifique et limitée aux muscles recrutés par l'action observée (Maeda, Kleiner-Fisma et Pascual-Leone, 2002), ce qui illustre bien la finesse de l'appariement moteur qui prend place au sein du SNMh. En utilisant une approche chronométrique telle que précédemment décrite, il a été montré que l'activité de M1 suivait le décours temporel du mouvement observé (Gangitano, Mottaghy, et Pascual-Leone, 2001). De plus, diverses études ont montré l'influence des caractéristiques perceptuelles et physiques des stimuli présentés sur la modulation de l'activité corticospinale, comme la latéralité de la main observée (Aziz-Zadeh, Maeda, Zaidel, Mazziotta, & Iacoboni, 2002), son orientation (Théoret et al., 2005) et l'intensité de la force manifestée (Alaerts, Swinnen, et Wenderoth, 2010).

1.6. L'électroencéphalographie dans l'étude du système neurones miroirs

1.6.1. Introduction et principes de fonctionnement

L'électroencéphalographie (EEG) est probablement le plus ancien outil d'investigation neurophysiologique utilisé aujourd'hui. Au XIXe siècle déjà, on savait que le cerveau produisait une activité électrique quantifiable (Swartz et Goldensohn, 1998). Cependant, c'est avec la découverte des potentiels évoqués (PÉ) (Pravdich-Neminsky, 1912), qui consistent à isoler l'activité électrique du cerveau associé à un

stimulus donné, que l'EEG prit vraiment son envol. Chez l'humain, c'est à Hans Berger (1873-1941) que revient le crédit d'avoir conduit les premières études EEG (Swartz, 1998). Depuis, l'utilisation de l'EEG a connu un essor considérable, tant dans un cadre clinique qu'expérimental.

Toutes les cellules des tissus animaux sont polarisées électriquement; c'est-à-dire qu'elles maintiennent une différence de voltage entre l'intérieur et l'extérieur de la cellule grâce à la surface membranaire. Dans le neurone, cette polarité résulte du déséquilibre ionique induit par le fonctionnement complexe de pompes à ions situés dans la membrane synaptique. Lorsque la charge membranaire atteint un certain seuil (environ -55 mV), celle-ci ouvre ses canaux à ions, ce qui dépolarise la membrane et engendre la décharge d'un courant électrique : le potentiel d'action. Celui-ci voyage à travers l'axone et cause le relâchement de neurotransmetteurs dans la synapse, l'aire de contact entre deux neurones. Ce relâchement neurochimique engendre à son tour une cascade d'activités électriques dans les neurones suivants. La sommation de l'activité électrique de millions de neurones corticaux, conduit à travers les tissus du crâne et le liquide céphalorachidien, constitue le signal électrique capté par l'EEG grâce à des électrodes situées au cuir chevelu, et dans de rares occasions, directement sur le tissu cérébral.

1.6.2. L'utilisation des potentiels évoqués électroencéphalographiques (PÉÉ) dans l'étude de la cognition

À l'exception de certains phénomènes cérébraux particuliers, il est difficile de déduire par la simple observation du signal EEG non-traité si le cerveau est occupé à une tâche précise. En effet, le signal électrique du cerveau, lorsque présenté graphiquement

en continu, ressemble fortement à de l'activité électrique aléatoire de faible intensité. De plus, même si l'on sait à quelle tâche s'affaire un sujet, il est ardu d'inférer l'activité du cerveau qui s'y rapporte à partir d'enregistrements continus.

L'une des façons les plus anciennes et les plus répandues d'obtenir de l'information sur l'activité électrique du cerveau en lien avec une tâche donnée consiste à administrer une grande quantité de stimuli pour ensuite moyenner l'activité EEG reliée à sa présentation. Cette technique, connue sous le nom des potentiels évoqués électroencéphalographiques (PÉÉ), permet d'éliminer l'activité électrique aléatoire qui forme le bruit dans le signal pour ne conserver que l'activité électrique associée à la présentation du stimulus ou à la tâche effectuée. La disposition spatiale, l'amplitude, de même que le moment auquel survient cette activité électrique peuvent procurer des informations sur le lieu, l'efficacité et le niveau d'automatisation d'un processus cognitif (Luck, 2005).

La découverte de la composante négative de discordance (*mismatch negativity,* MMN) par Näätänen et collaborateurs (1978) est un excellent exemple du potentiel que confère l'utilisation des PÉÉ dans l'étude de la cognition. La MMN, qui peut survenir dans n'importe quelle modalité sensorielle, se produit lorsqu'un stimulus divergent rare est inséré parmi une série de stimuli similaires, dits *standards*. Par exemple, la composante MMN-auditive est une onde négative d'amplitude maximale au niveau fronto-central dont la source principale serait le cortex auditif primaire et secondaire. Bien qu'on la retrouve typiquement à une latence de 150-250ms après l'apparition du son déviant, sa latence peut être devancée par l'utilisation d'un stimulus qui diffère largement des sons standards. Le son déviant peut différer en terme de tonalité, de durée, d'intensité ou même de catégorie sonore. Ainsi, afin d'induire une MMN-auditive, un son déviant (d) est placé parmi une séquence de sons fréquents (s) (ex. s s s s s s s s s d s

s s s s s d s s s d s s s s...). Étant donné sa flexibilité, le protocole de MMN a été utilisé dans plusieurs contextes afin de mettre en évidence la détection automatique de stimuli divergents sur des propriétés de haut niveau. À titre d'exemple, il été utilisé pour démontrer le traitement pré-attentionnel préférentiel, traduit par une amplitude plus élevée de la MMN pour les voix familières comparativement aux voix inconnues (Beauchemin et al., 2006).

1.6.3. L'utilisation des analyses temps-fréquences dans l'étude de la cognition

La présentation visuelle de l'activité EEG est souvent produite sous la forme de lignes continues qui oscillent et où chaque ligne représente l'activité enregistrée par une électrode. Ces oscillations, qui reflètent l'activité synchronisée de populations neuronales, présentent différentes caractéristiques quant à leurs distributions spatiales ou leurs fréquences. Ces deux facteurs déterminent en grande partie la classification et l'appellation de ces fréquences, dont la nomenclature est la suivante : delta (0.1-4Hz), thêta (4-7Hz), alpha (8-12Hz), beta (12-30Hz), gamma (30Hz et plus). Plusieurs de ces fréquences présentent des patrons relativement spécifiques au plan spatial, et leurs origines neuronales de même que leurs corrélats cognitifs sont même connus dans certains cas (Buzsàki, 2006).

L'étude des fréquences EEG en lien avec la cognition est restée relativement restreinte avant les années soixante-dix. En effet, l'utilisation encore limitée de l'ordinateur rendait la quantification et la classification des différents rythmes cérébraux

extrêmement ardue. Ceci a toutefois changé avec le perfectionnement des algorithmes d'analyse des fréquences spectrales proposée par Cooley et Tukey (1965), la transformation rapide de Fourier (TRF). Simplement, la TRF est un algorithme qui décompose un signal continu sous la forme de la somme de sinusoïdes. Appliquée au signal EEG, elle permet de décomposer celui-ci en bandes de fréquences de puissances variables. Cette analyse rend la quantification de l'activité des fréquences simple, et permet ainsi d'étudier leurs modulations en lien avec des processus cognitifs ou perceptuels.

Bien qu'elle permette de quantifier facilement les différentes fréquences composant le signal, de par ses propriétés mathématiques, la TRF ne donne aucune information quant à l'évolution du signal dans le temps, puisqu'elle transpose uniquement l'information du signal analysé au domaine fréquentiel. Ceci constitue une limite importante de la TRF, puisque même si elle permet de conclure à une augmentation ou une diminution de la puissance d'une certaine fréquence dans une fenêtre temporelle définie, elle ne permet pas de déterminer *quand* survient la modulation dans le segment.

L'utilisation de l'analyse par ondelettes permet cependant de circonvenir à la limitation temporelle de la TRF, puisqu'à l'inverse de cette dernière, elle se situe à la fois dans les sphères *fréquentielle* et *temporelle*. Par définition, l'ondelette est une oscillation de moyenne nulle. L'analyse par ondelettes consiste en une fonction mathématique de carrés sommables sur l'espace euclidien qui permet la décomposition d'un signal par l'utilisation d'une famille d'ondes qui sont traduites sur le signal de façon à capter les changements en fonction du temps. Alors que la TRF ne repose que sur des fonctions sinusoïdales sans facteur de translation, l'analyse par ondelettes permet de mettre en évidence des changements transitoires et localisés dans l'espace spectral et

le temps. Il est donc possible de savoir dans quelles fréquences surviennent les changements de puissance, mais également à quel moment ceux-ci surviennent.

Récemment, les analyses temps-fréquences se sont avérées d'un apport précieux dans la compréhension des mécanismes physiologiques liés au recrutement cortical. Utilisant cette technique conjointement à l'IRMF, Ritter et collaborateurs (2009) ont montré que l'intensité du signal BOLD était inversement corrélée avec la puissance du rythme alpha au niveau du cortex somatosensoriel et avec la force de la bande beta émanant du cortex moteur. Ceci soutient l'idée de plus en plus répandue que l'analyse fréquentielle de l'EEG permet d'entrevoir de façon rapide, peu couteuse et non invasive, l'activité métabolique du cortex.

1.6.4. L'électroencéphalographie comme mesure de l'activité du système de résonance motrice

1.6.4.1. Les analyses temps-fréquences dans l'étude du système de résonance motrice

Il est connu depuis longtemps que l'activité motrice est associée à une désynchronisation de certains rythmes cérébraux. Dans les années 1950 déjà, on savait que des rythmes EEG de la région centrale étaient diminués durant la production d'actes moteurs (Chatrian, Petersen, et Lazarte, 1959). Typiquement, la bande de fréquence sensible à la production motrice se situe dans la bande alpha (8-12Hz) et son appellation diffère en fonction des époques et des domaines d'études. Alternativement connu sous le nom de rythme en arceau, central, wicket, sensorimoteur et plus récemment rythme mu, cette bande de fréquence est restée peu étudié jusque dans les années 1960.

En utilisant la TRF, Babiloni et collaborateurs (1999) ont confirmé l'existence d'un lien entre la production motrice et la bande alpha, à savoir que la production d'actes moteurs induisait une forte réduction de la puissance de cette bande de fréquence au niveau du cortex moteur controlatéral au membre activé (Babiloni et al., 1999). De plus, cette diminution de la puissance de la bande alpha est limitée à la région de l'homoncule moteur qui est activée. En effet, si un mouvement de main est effectué, on observe une diminution de la puissance de la bande alpha pour la région motrice de la main, mais une augmentation pour la région du pied. Alternativement, bouger le pied produit l'effet inverse (Pfurtscheller, Neuper, Andrew, et Edlinger, 1997). La diminution de la puissance spectrale de la bande alpha reflèterait l'état d'activité accru du cortex induit par des entrées thalomo-corticales (Buzsaki, 2006; Pineda, 2005).

Étant donné sa sensibilité apparente aux processus moteurs, il a été proposé que l'activité de cette bande de fréquence aux sites centraux pourrait agir d'indicateur du recrutement de M1 dans le contexte d'observation d'actions (Muthukumaraswamy et Jonhson, 2004a, 2004b). En effet, en absence de mouvements explicites, la modulation de la bande alpha au niveau moteur serait la conséquence de l'activité de populations de neurones au niveau du circuit fronto-parietal du SNMh (Pineda, 2005). En adoptant ce raisonnement comme hypothèse de travail, Muthukumaraswamy et collaborateurs (2004a) utilisèrent la TRF pour montrer une diminution de la puissance de la bande alpha durant la perception d'action malgré l'absence de production motrice. Plus spécifiquement, ils montrèrent un patron de modulation nuancé durant l'observation d'action : la performance motrice modulait fortement la bande alpha, suivie par l'observation d'un mouvement de préhension, alors que l'observation d'une main immobile n'influençait pas l'activité de cette bande de fréquences comparativement à la condition de repos. À quelques nuances près, ces résultats ont été confirmés par de

nombreuses études utilisant des protocoles similaires (Bernier et al., 2007; Calmels et al., 2006 ; Hadjidimitriou et al., sous presse; Oberman et al., 2005 ; Oberman et al., 2008), mais aussi dans des contextes d'imagerie mentale motrice (Pineda, Allison, et Vankov, 2000). Ainsi, longtemps considérée comme l'état de repos du cortex, cette fréquence apparaît maintenant, à la lumière des récentes recherches, être un indicateur des processus intégratifs transformant « la vision et/ou l'audition en action » (Pineda, 2005).

Subséquemment, Muthukumaraswamy et collaborateurs (2004b) ont mis à profit la résolution temporelle de l'analyse par ondelette afin d'investiguer l'activité du cortex moteur durant l'observation d'actions. En quantifiant l'activité du cortex moteur suivant la stimulation du nerf médian, ils montrèrent une atténuation du rebond dans les bandes de fréquences alpha et beta à la fois durant l'exécution de mouvements, mais également lors de l'observation passive de mouvements de la main. Cette atténuation du rebond était significative de 500-1000ms post-stimulus pour la bande alpha, et de 750-1300ms dans la bande beta. Ces résultats font écho à ceux obtenus par l'utilisation de la MEG dans des contextes identiques, alors que l'observation d'actions influence simultanément ces deux bandes de fréquences (Hari et al., 1998; Rossi et al., 2002). Il est donc plausible que ces bandes de fréquences reflètent le recrutement du cortex sensorimomoteur durant la perception d'action.

Des études récentes soutiennent cette hypothèse, alors qu'un nombre croissant de recherches montrent un lien entre l'activité du cortex tel que quantifiée par le signal BOLD et la puissance des bandes alpha et beta (Laufs et al., 2006 ; Michels et al., 2010; Ritter et al., 2009; Storti, Formaggio, Beltramello, Fiaschi, et Manganotti, 2010) En effet, en utilisant l'EEG et l'IRMf simultanément, il a été montré que le signal BOLD était négativement corrélé avec la puissance de la bande alpha au niveau du cortex

postcentral et avec la bande beta dans la région précentrale (Ritter et al., 2009). Ces observations soutiennent ainsi l'idée que la puissance de ces bandes de fréquences puisse agir d'indicateur du niveau d'activité de certaines régions corticales, notamment au niveau moteur et sensoriel.

1.6.4.2. Les potentiels évoqués électroencéphalographiques dans l'étude du système de résonance motrice

À ce jour, un nombre relativement restreint d'études ont utilisé les PÉÉ afin d'étudier l'activité du SNMh durant la perception d'actions (Nyström, 2008; Hauk Shtyrov, & Pulvermüller, 2006). Ces études ont adapté des protocoles existants afin de mettre en évidence une modulation différentielle d'ondes EEG connues en lien avec des stimuli associés à des actions motrices.

Un exemple d'une telle approche est l'utilisation élégante du paradigme de MMN dans l'investigation du SNMh (Hauk et al., 2006). Utilisant un protocole de type « oddball » pour induire une MMN durant la perception de sons associés à la production motrice (ex. claquement de doigts et de langue) et de sons contrôles appariés, les chercheurs montrèrent non seulement la présence d'une plus grande amplitude de la MMN lorsque les sons déviants étaient des sons d'actions, mais aussi qu'en comparaison avec les sons contrôles, une différence d'amplitude était perceptible à 100 ms post-stimulus. De plus, les analyses de localisation de sources effectuées suggéraient une contribution du cortex moteur à cet effet hâtif, ainsi qu'une organisation somatotopique du pairage prenant place au sein du cortex moteur. Par exemple, les sons de doigts élicitaient une activité latérale, alors que les sons de langue étaient associés à une zone d'activité ventrale, en accord avec la représentation de l'homuncule moteur.

1.6.4.3. Résumé de l'utilisation de l'électroencéphalographie dans l'étude du système de résonance motrice chez l'humain

En révélant les patrons d'activité électrique du cerveau durant la perception d'actes moteurs, l'EEG permet d'investiguer l'activité corticale associée aux processus de résonance motrice. Comme nous l'avons vu, les analyses temps fréquences, notamment la TRF et les analyses par ondelettes, illustrent le recrutement cortical des régions sensorimotrices par la quantification de la puissance de différentes bandes de fréquence. La bande alpha (rythme mu) semble particulièrement sensible au système moteur, que ce soit durant la production d'actes moteurs ou lors de leur seule observation. Les PÉÉ procurent également des informations quant à l'activité des mécanismes de résonance motrice. La résolution temporelle des PÉÉ permet de cibler les moments précis ou le système moteur est activé durant la perception d'actions, alors que la localisation de source donne une idée approximative du lieu où prend place l'appariement.

1.7. Objectifs expérimentaux

1.7.1. Le système neurones-miroirs chez l'enfant sain

La paucité des données neurophysiologiques sur l'état du SNMh chez l'enfant constitue la motivation principale des études au centre des articles 1, 2 et 3 qui forment cet ouvrage. L'objectif premier de cette thèse est de documenter l'existence et le fonctionnement du système de résonance motrice chez l'enfant normal dans les sphères visuelle et auditive. Ceci permettra de mieux comprendre le développement de ce

système chez l'humain et pourra servir de point de référence quant à son évolution atypique au sein de populations présentant des pathologies neurodéveloppementales.

1.7.1.1. Article 1 : Description et hypothèses

Dans l'article 1, l'EEG quantitatif est utilisé chez un groupe d'enfants d'âge scolaire afin d'investiguer l'activité du SNMh, telle que quantifiée par la désynchronisation du rythme mu, dans un paradigme d'observation d'actions. Considérant les études antérieures menées chez l'adulte, nous sommes en mesure de formuler les hypothèses suivantes :

1) le rythme mu peut être utilisé comme marqueur de l'activité du SNMh dans une population pédiatrique.

2) l'observation de mouvements de préhension induira une diminution significative du rythme mu comparativement à l'observation d'une main immobile et à la condition de repos.

1.7.1.2. Article 2 : Description et hypothèses

Dans l'article 2, l'EEG intracrânien est utilisé chez une jeune fille de 12 ans dans un contexte préchirurgical afin d'investiguer l'activité du cortex moteur lors de la perception de sons d'actions. En combinant la résolution spatiale de l'EEG intracrânien et la résolution temporelle des analyses par ondelettes, nous émettons les prédictions suivantes :

1) La perception de sons d'action induira une modulation dans les bandes de fréquences alpha et beta au niveau du cortex moteur.

2) À partir des données antérieures (Nishitani et Hari, 2002; van Schie et al., 2008), il est attendu que deux périodes de modulation, l'une précoce et l'autre tardive, seront observées.

1.7.1.3. Article 3 : Description et hypothèses

L'article 3 constitue une recension des indices comportementaux et neurophysiologiques concernant les mécanismes de résonance motrice chez l'enfant et le nouveau-né humain. À la lumière des faits qui y sont présentés et à l'intérieur d'un cadre théorique qui y est élaboré, nous émettons l'hypothèse suivante :

1) Le SNMh est présent et fonctionnel dès la naissance, et l'imitation néonatale constitue la démonstration des mécanismes d'appariement moteur non inhibés qui y prennent place.

1.7.2. Décours temporel, spécificité biologique et relation avec les traits sociocognitifs de l'activité du système de résonance motrice.

Considérant les résultats divergeants en ce qui concerne le décours temporel de l'activité au sein du SNMh chez l'humain, il demeure incertain à quel moment le cortex moteur est sollicité durant la perception d'actes moteurs. De plus, en raison de l'utilisation d'échelles sociocognitives dont la validité externe à été mis en doute, la relation qu'entretient le système de résonance motrice avec certaines capacités associées au fonctionnement social demeure incertaine. C'est avec ces problématiques en tête que les études des articles 4 et 5 ont été élaborées.

1.7.2.1. Article 4 : Description et hypothèses

Afin de circonvenir aux limites associées à l'utilisation d'échelles dont la validité externe à été questionnée, les mesures sociocognitives utilisées dans l'article 5, les versions françaises du *Quotient d'Empathie* et le *Quotient de Traits Autistiques*, ont fait l'objet d'une étude de validation. Dans l'article 4, les versions traduites en français du Empathy Quotient et du Autistic Spectrum Quotient ont été administrées à une centaine d'étudiants universitaires et 23 adultes présentant un diagnostic de trouble du spectre autistique afin d'établir la validité de ces mesures. Considérant les résultats obtenus auprès des populations anglophones (Baron-Cohen et al., 2004), nous sommes en mesure d'émettre l'hypothèses suivante :

1) Comparativement aux personnes neurotypiques, les individus avec un trouble du spectre autistique auront un score significativement plus élevé au Quotient Autistique et un résultat significativement moins élevé au Quotient d'Empathie

1.7.2.2. Article 5 : Description et hypothèses

Dans l'article 5, la SMT à pulsion unique est utilisée dans une approche chronométrique afin d'investiguer le moment où le cortex moteur est activé lors de la perception d'actions motrices. La spécificité de cette activité aux stimuli biologique, de même que sa relation avec des mesures de traits sociocognitifs tels que l'empathie et les traits autistiques est également abordée. Considérant les résultats expérimentaux présentés précédemment, nous sommes en mesure de proposer les hypothèses suivantes :

1) Dans un contexte d'observation d'action, l'excitabilité corticospinale de la région de la main, telle que quantifiée par PÉM, sera modulée rapidement à la hausse suite à la présentation du mouvement.

2) Cette augmentation de l'activité corticospinale sera spécifique aux mouvements biologiques.

3) Cette modulation de l'activité corticospinale sera spécifique au muscle observé.

4) Cette augmentation d'excitabilité corticospinale sera positivement corrélée avec une échelle d'empathie et négativement avec une mesure des traits autistiques.

1.7.3. Aspects méthodologiques : concordance des mesures électroencéphalographiques et de stimulation magnétique transcrânienne dans l'étude du système neurones-miroirs humain

Comme nous l'avons vu, la SMT à pulsion unique ainsi que les analyses par TRF du signal EEG sont couramment utilisées dans l'étude des mécanismes de résonance motrice chez l'humain. Cependant, la relation que ces deux mesures entretiennent entre elles est inconnue. En effet, on ignore si les processus reliés à la modulation des PÉM durant la perception d'action sont les mêmes qui influencent l'activité du rythme mu.

1.7.3.1. Article 6: Description et hypothèses

Dans l'article 6, la spécificité des mesures utilisées dans les études au cœur des articles 1, 2 et 5, est investiguée. Dans le but de déterminer si l'activité de M1 mesurée par ces deux techniques est reliée aux mêmes substrats neurophysiologiques, l'EEG quantitatif et la SMT à pulsation unique sont utilisées simultanément pour quantifier l'activité du cortex moteur durant l'observation, l'imagination et l'exécution d'actes

moteurs. Considérant les études présentées, nous sommes en mesure d'effectuer les prédictions suivantes :

1) Les résultats antérieurs concernant l'EEG et la SMT dans ces conditions expérimentales seront répliqués, à savoir une diminution de la puissance spectrale de la bande alpha dans toutes ces conditions ainsi qu'une augmentation de l'excitabilité corticospinale mesurée par l'amplitude des PÉM dans ces mêmes situations.

2) L'utilisation simultanée de la SMT et de l'EEG quantitatif dans la mesure du SNMh durant la perception, l'imagination et l'exécution d'actes moteurs mettra en évidence une convergence des mesures utilisées, qui se traduira par une corrélation négative entre la puissance du rythme mu et l'amplitude des PÉM.

Chapitre 2

Article 1

EEG evidence for the presence of an action observation-execution matching system in children

European Journal of Neuroscience, 2006, (9):2505-10

EEG evidence for the presence of an action observation-execution matching system in children

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Article publié dans *European Journal of Neuroscience*, 2006, (9):2505-10

2.1. Abstract

In the adult human brain, passive observation of actions performed by others activates some of the same cortical areas that are involved in the execution of actions, thereby contributing to action recognition. This mechanism appears to occur through activation of a population of action-coding cells known as mirror neurons (MN). In the adult motor cortex, performing actions and observing human movement reduces the magnitude of the mu (8-13 Hz) rhythm, possibly reflecting MN system activity. Despite the wealth of information available regarding the adult MN system, little is known about its existence in children. Here, we used EEG to probe mu rhythm modulation in 15 children during observation and execution of hand actions. Our data show that mu rhythm attenuation occurs in children under 11 years of age during observation of hand movements. Similarly to what has been reported in adults, observation of goal/object-oriented movement produces greater modulation of the mu rhythm than intransitive movement. These data confirm the existence of an observation/execution matching system in the immature human brain and may be of clinical value in the understanding of neurodevelopmental disorders associated with a faulty MN system such as autism spectrum disorder.

2.2. Introduction

It is now well documented that observing a conspecific performing a motor action activates patterns in the observer's brain similar to those involved in the execution of the same act. In human adults, the existence of such a mechanism, matching action-execution and action-observation, is well established (Rizzolatti & Craighero, 2004). This matching system is thought to rely primarily on the functioning of a specific category of cells known as "mirror neurons" (MN). First discovered in the monkey's premotor cortex, MN have been shown to respond both when an agent performs a motor act as well as to the observation of a similar action being performed by a peer (Gallese *et al.*, 1996; Rizzolatti *et al.*, 1996). In humans, a number of brain areas appear to possess mirror properties, namely the lower part of precentral gyrus, the posterior inferior frontal gyrus and the rostral part of the inferior parietal lobule (Rizzolatti & Craighero, 2004). These regions are part of a complex network receiving inputs from the visual cortex via the superior temporal sulcus (Nishitani *et al.*, 2004), a region involved in processing biological motion (Puce & Perrett, 2003).

The MN system has been extensively explored in humans these past few years using a variety of techniques (Cochin *et al.*, 1999; Fadiga *et al.*, 1995; Hari *et al.*, 1998; Iacoboni *et al.*, 1999; Tremblay *et al.*, 2004). This impressive quantity of literature has provided valuable information as to the subtle properties of this system. Among other characteristics, the activity of the MN system as been shown to strictly match the temporal course of the observed action (Gangitano *et al.*, 2001), to be specific to the muscles involved in the observed action (Maeda et al., 2002) as well as to be influenced by laterality (Aziz-Zadeh *et al.*, 2002) and orientation of the observed body part (Maeda *et al.*, 2002). However, there are surprisingly few studies detailing the presence of such a mechanism in children. Whereas many studies have investigated biological motion perception in children and newborns (Cochin *et al.*, 2001; Fox & McDaniel, 1982; Hirai & Hiraki, 2005; Pavlova *et al.*, 2001), few studies have directly dealt with the issue of

normal development within the system matching the observation and execution of actions in children. In a 36 month-old child undergoing intracranial recording for intractable epilepsy, Fecteau and collaborators (Fecteau *et al.*, 2004) looked at EEG modulation over the sensorimotor area corresponding to the representation of the hand. They showed a diminution of spectral power in the alpha (7.5-12.5 Hz) band during the execution of hand movements as well as during observation of similar movements compared to a resting condition. Interestingly, this frequency band encompass the mu rhythm, which is thought to reflect sensorimotor processing in the frontoparietal network (Pineda, 2005). Indeed, many have suggested a relationship between mu rhythm and MN system functionning (Cochin *et al.*, 1998; Cochin et al., 1999; Muthukumaraswamy & Johnson, 2004; Muthukumaraswamy *et al.*, 2004; Oberman *et al.*, 2005). The mu rhythm over sensorimotor areas is strongly inhibited during the performance of a motor act. In the absence of overt movement, as during the observation of actions, mu rhythm modulation is believed to reflect the desynchronisation of motor cortex neurons related to the MN system (Pineda, 2005). Using this rationale, we investigated mu rhythm modulation during passive observation of hand actions in children to determine the presence of a MN system in the immature brain.

2.3. Methods

Participants: 18 healthy children (8 males, 10 females) with no history of neurological or psychological problems aged between 52 and 133 months of age (mean = 99.3 months) were recruited via public announcement. All subjects were right handed according to parental report (Oldfield, 1971). Parental inform consent was obtained for each participant. The experimental paradigm was approved by Sainte-Justine Hospital's ethics board.

Apparatus : The experiment was conducted using an apparatus similar to the one used elsewhere in adults (Muthukumaraswamy & Johnson, 2004; Muthukumaraswamy

et al., 2004). It consists of an infrared light-emitting diode in which the emitter and receptor are respectively situated at the bottom and at the top of the device. When the beam is broken, it generates an electrical signal marking the time of the event on the EEG recording system (Figure 1).

Procedure: Participants were comfortably seated at a distance of half an arm's length from the apparatus located on a table. The height of the table was adjusted to minimize participants' movement during the procedure. The experiment consisted of four conditions: *rest*, *flat hand-observation (flat)*, *grip-observation (grip)* and *grip execution (execution)*. In the *rest* condition, participants remained immobile for four minutes watching the apparatus. For this condition only, event-markers were added manually post-recording. In the *flat* and *grip* conditions, the participants passively observed the experimenter either moving an extended hand into the apparatus or performing a precision grip. In the *execution* condition, the participants executed self-paced precision grips similar to those seen in the grip-observation condition. Conditions were pseudo-randomized and performed bimanually, one hand at a time, in blocks of a minimum of 40 trials with a six-second interval between individual trials. During right hand execution/observation, the experimenter was seated at the right of the participant, and at the left for the left hand.

EEG recording: EEG was acquired from a 128 channels Sensor Net (Electrical Geodesic Inc., Eugene, OH) and recorded using Net Station running on a MacIntosh G4 computer. EEG was sampled at 250 Hz, with a bandpass filter at 0.1-100Hz, electrodes impedance inferior to 50 kΩ and CZ used as reference. Recording took place in a Faraday room. Participants' movements were monitored by the experimenter and video recorded for off-line analysis; if the subject moved during an observation task, the trial was discarded.

EEG data analysis: Offline analyses were performed using BrainVision Analyzer. EEG was re-referenced to the common average and segmented in epochs of 1020 ms, starting 250 ms before the trigger. This time window was selected given that cortical activity during grip observation has been shown to be at its peak when the observed hand is at maximal aperture, which in this case was just before the event marker. EEG recordings were inspected visually to eliminate artefacts. A minimum of 30 segments for each condition of sufficient quality was required for further analysis. If this criterion was not met, the participant was discarded. Fast Fourier Transformation (FFT) was performed on kept segments (256 points Hanning window) and averaged for each condition. As performed in similar experiments conducted with adults (Muthukumaraswamy *et al.*, 2004) the frequency band corresponding to mu rhythm for each subject was defined by subtracting the *flat* condition from the *execute* condition. This was done to control for the difference of spectral power that could be due to the mere presentation of visual stimuli. In addition, the 2Hz bandwith best resembling mu desynchronization (Babiloni *et al.*, 1999) was selected as the individual's mu frequency band. This method of analysis was selected for two main reasons. Firstly, as the current experiment's primary goal was to test for the presence of a mirror neuron-like system in children and detect similarities with the adult MN system, we employed an analysis technique rigourously matching that of a previous study with adult subjects (Muthukumaraswamy *et al.*, 2004). Secondly, this method enabled the precise definition of the frequency band that is modulated by the execution of a hand action in each individual subject. Indeed, we also contrasted the *execute* from the *rest* condition to define the mu band. However, the resulting differences in spectral power were larger, but also more widespread in the alpha band, hence making it difficult to precisely define the mu band. Interestingly, similar results have been reported in adult subjects when contrasting execute with rest conditions (Muthukumaraswamy *et al.*, 2004). By definition, mirror motor areas should be sensitive to the execution and the observation of actions. In this case, it was thus imperative to determine the frequency band that

desynchronizes during a precision grip and then determine if the same band is also modulated by the mere observation of the same movement. Contrasting the *flat* and *excute* conditions, as reported in adults (Muthukumaraswamy *et al.*, 2004), allowed for a clearer definition of the mu rhythm in our group of subjects. Finally, in addition to the mu rhythm, two frequency bands, theta 1 (3.5-5.5Hz) and theta 2 (5.5-7.5Hz), were investigated as in young children, those bands might bear a relationship similar to the mu rhythm and alpha band in adults (Cochin *et al.*, 2001; Marshall *et al.*, 2002; Stroganova *et al.*, 1999). Two clusters of four electrodes, which were the closest to C3 and C4, were selected for analysis.

2.4. Results

Three subjects were rejected from analysis, two due to an insufficient number of clean segments to perform spectral analysis, and one because we were unable to define a mu band. Fifteen subjects were thus included in the analysis. The average mu frequency band was 9-11 Hz and subject age was not correlated with individual mu rhythm band. A repeated measures ANOVA with hemisphere (left, right) and condition (execute, grip, flat, rest) as factors revealed a main effect of condition ($F = 8.31$; $p < 0.01$) and no effect of hemisphere ($F = 0.05$; n.s.) for the mu rhythm band. The interaction was also non-significant ($F = 0.10$; n.s.). Post-hoc comparisons (Bonferroni) showed that in both hemispheres, observing a grasping hand induced significantly greater mu suppression than observing a flat hand ($p < 0.05$) or being at rest ($p < 0.05$) (Figure 2A). There was no significant difference between the rest and flat conditions. There was no correlation between age of the subjects and amount of mu rhythm modulation, expressed as the percent difference between the *grip* and *flat* ($r = 0.25$; n.s.; Figure 2B), *grip* and *rest* ($r = 0.33$; n.s.) or *flat* and *rest* ($r = 0.18$; n.s.) conditions. Repeated measures ANOVA revealed a main effect of condition for the theta 1 ($F = 5.66$; $p < 0.01$) and theta 2 bands ($F = 6.33$; $p < 0.01$) (Figure 3). Post-hoc analysis showed that neither theta bands displayed mirror properties, as the execution condition did not differ from the rest

condition (all $p > 0.05$) although observation of hand movement (both grip and flat conditions) resulted in decreased amplitude compared to rest (all $p < 0.05$) and the difference between the flat and grip conditions was not significant.

As transcranial magnetic stimulation studies have reported increased motor cortex excitability in both hemipsheres when observing hand movements from the contralateral hand compared to the ipsilateral hand (Aziz-Zadeh et al., 2002), EEG data were pooled across hemispheres with regards to hand observed. A repeated measures ANOVA with hand (ipsilateral, contralateral) and condition (execute, grip, flat, rest) as factors revealed a main effect of condition ($F = 8.31$; $p < 0.01$) whereas the hand ($F = 0.65$; n.s.) and interaction ($F = 0.512$; n.s.) factors were not significant.

2.5. Discussion

Stronger mu suppression during the observation of a grasping movement compared to both the observation of a flat-hand movement and a rest condition supports the existence of a mechanism matching observation and execution of motor actions in children. These results are in agreement with those recently obtained by Dapretto and collaborators (2006) using fMRI in a group of 9 male children (12.37 2.22 years), as well with a case study showing mirror activity in a 36 month-old child undergoing intracranial recordings (Fecteau *et al.*, 2004). To our knowledge, this study constitutes the demonstration of the earliest presence of a motor resonance mechanism in a group of children, and establishes the validity of the EEG technique in the investigation of the MN system in young populations.

Interestingly, the pattern of activity of the mu rhythm that we report in children is strikingly similar to that reported in adults (Muthukumaraswamy & Johnson, 2004; Muthukumaraswamy *et al.*, 2004). If taken as reflective of MN system activity, the apparent consistency of mu rhythm modulation during action observation from late

childhood to adulthood suggests that system maturation occurs relatively early in development. However, even if the degree of activation remains stable, it does not exclude the possibility that subtle qualitative and/or quantitative changes and refinement during this time period. Also, the brain goes through substantial changes in the first years of life, and it is plausible that the age sample used in this study did not allow the detection of earlier changes within the system.

Moreover in infants, unlike older children and adults, the alpha band is of weak power compared to lower frequency bands. Consequently, it has been proposed that theta activity (4-8Hz) over central sites in infants might be a precursor of alpha and sensorimotor rhythms (Lairy, 1975; Stroganova *et al.*, 1999). Also, some have pointed-out to an "alpha-like activity" at central sites in the theta band that could bear a functional relationship with the adult mu rhythm (Stroganova *et al*., 1999). This so called "central-alpha" appears at around 4 months between 4-7Hz and remains stable at 7Hz during the first year of life (Hagne, 1968, 1972). Its activity then gradually shifts towards higher frequencies, 8Hz at 18 months, 9Hz at around 4 years, and stabilizes at around 10Hz during adolescence. It has been suggested that these changes in EEG patterns during early brain development, notably the decrease of lower frequencies co-occurring with the increase of higher, alpha range frequencies, might reflect the growing motor and visuomotor processing abilities of children (Hagne *et al.*, 1973). For the moment, the precise nature of the relationship between this "central-alpha" and the mu rhythm remains elusive and it is still uncertain whether the theta band could reflect mirror processing in infants.

In older children however, it is unlikely that the theta band would possess properties similar to those of the mu rhythm corresponding to a motor resonance mechanism. Cochin and collaborators (Cochin *et al.*, 2001) suggested an equivalence between mu rhythm and the theta 1 band (3.5-5.5Hz) based on the fact that in their

sample of children aged between 2-8 years old (mean age of 5,2 years), 1) the theta band was preponderant in their sample, similarly to the alpha band in adults; and 2) the spectral power of the theta band (3.5-7.5) was decreased during observation of biological movement compared to non-biological movement. In the present study, decreased spectral power in theta 1 and theta 2 bands was also observed, supporting the idea that those bands are sensitive to the observation of biological movement. However, unlike the mu rhythm, the type of observed movement did not yield differences in activity. Moreover, as there was no decrease in spectral power in any of the theta bands during the *execute* condition, spectral power decreases in these frequencies during observation conditions cannot be said to reflect mirror mechanisms as usually defined (Rizzollati & Craighero, 2004).

Undeniably, the human brain undergoes fast and considerable maturation in the first years of life and experience plays an important role in shaping visuo-motor connections (Heyes *et al.*, 2005). Whether the MN system is present at birth remains to be investigated. If this is not the case, we can speculate that the MN system, being highly selective for biological action (Jarvelainen *et al.*, 2004; Tai *et al.*, 2004) and to schematic representation thereof (Press *et al.*, 2005) develops either subsequently or concurrently to biological motion perception. However, recent behavioral data suggest that the MN system of adults could also be responsive to robotic movements when they closely match movements of a human hand (Press *et al.*, 2005). It however remains to be seen if such movements would modulate motor cortex activity. Recent studies suggest that biological perception is mature as early as 8 months of age (Hirai & Hiraki, 2005). Whether a mirror mechanism is also present at this stage remains to be determined and constitutes an important challenge in the study of motor resonance mechanisms in the immature human brain.

In keeping with adult data, mirror activity in our group of children was stronger

during the observation of a transitive, goal-related action. This is particularly relevant in light of the fact that in children, imitation is guided by goals. In a study of pre-school children (Bekkering *et al.*, 2000) participants were asked to copy movements performed by an experimenter. It was found that reducing the number of possible goals decreased the numbers of errors made by the participants and that total absence of goals (targets) also decreased imitative performance. It was later reported that a similar mechanism operates in adults where the presence of a goal favorably modulated imitation in both error patterns and response time (Wohlschlager & Bekkering, 2002). As it is now well established that the mirror neuron system in humans is intimately linked to imitative behavior (e.g. Iacoboni et al., 1999), the importance of goals for imitation might underlie MN system preference for these types of movement. It must be noted that modulation of motor cortex activity by passive observation of intransitive movements has been reported in adults using transcranial magnetic stimulation (e.g. Maeda et al., 2001). This could mean that mu rhythm modulation specifically codes for object-directed movements. Alternatively, differences between observation of flat and grip movements may be age-related, where this aspect of the system matching execution and observation matures later on during development. Additional studies are needed to elucidate this question. Differences in brain activation during passive observation of *articulated* versus *non-articulated* movement may also explain the pattern of mu desynchronization reported here. Although the presence of articulatory movement in the observed hand may modulate motor cortex activity by itself (e.g. Maeda et al., 2002), we suggest that it is the presence of a goal that is the crucial cue driving this modulation. Using fMRI, it has been shown that the addition of a simple goal during imitation of finger movements significantly increases activity within the main MN system areas (Koski et al., 2002). Additionally, suppression of mu rhythm has been shown to be greater when observing a precision grip performed on an object compared to an empty grip (Muthukumaraswamy et al., 2004). Taken together, these data suggest that observing articulated movement may be sufficient in driving mu rhythm modulation although the presence of a goal taps

into a more fundamental role of the MN system. Finally, as individual mu frequencies were defined through the execution of a grasping movement, it may argued that the stronger suppression during grip observation reflects the fact that the tested frequency band was the one responding more strongly to the execution of a grasping movement. This, in turn, would suggest that specific frequecies within the mu band are tuned to specific movement configurations, although it appears unlikely that such a specificity would exist within the alpha band in response to the observation of simple hand movements.

The presence of a functional MN system in infancy also bears considerable clinical interest. It has recently been shown that individuals with autism spectrum disorder (ASD) display abnormal MN function (Nishitani *et al.*, 2004; Oberman *et al.*, 2005; Théoret *et al.*, 2005; Dapretto *et al*., 2006). Interestingly, Oberman and collaborators (2005) showed lack of mu suppression during hand movement observation in individuals with ASD.It has been suggested that a faulty MN system could lead to a myriad of impairments found in ASD (Williams *et al.*, 2001). As the link between social deficits and abnormal MN system activity has recently been supported in ASD (Dapretto *et al*., 2006), early detection of MN system dysfunction may complement available diagnostic tools and perhaps foster new therapeutic approaches.

2.6. Acknowledgements

This work was supported by grants from the National Sciences and Engineering Research Council of Canada (HT), the Canada Foundation for Innovation, the Fonds de Recherche en Santé du Québec, and the Canadian Institutes of Health Research to HT. We thank Marie-Christine Désy, Alexia Ptito, Manon Robert and Phetsamone Vannassing for skillful technical help.

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2.8. Figure legends

Figure 1: Hand positions and apparatus used in the experiment. **(A)** Flat hand. **(B)** Grip.

Figure 2: (A) Magnitude of the mu rhythm over electrodes C3 and C4 in 15 children while passively observing hand movements, during execution of hand movements, and during rest. **(B)** Graph showing the lack of correlation between mu rhythm modulation and age of the participants during passive observation of hand movements. EXEC: execution of a precision grip; GRASP: passive observation of a precision grip; FLAT: passive observation of a flat hand movement; REST: passive observation of the testing apparatus.

Figure 3: Modulation of EEG spectral power in (**A)** theta 1 and **(B)** theta 2 frequencies during the four experimental conditions. Although theses bands are sensitive to biological motion, they do not meet the criteria for possessing mirror properties as the execution condition does not elicit frequency modulation. EXEC: execution of a precision grip; GRASP: passive observation of a precision grip; FLAT: passive observation of a flat hand movement; REST: passive observation of the testing apparatus.

Figure 1.

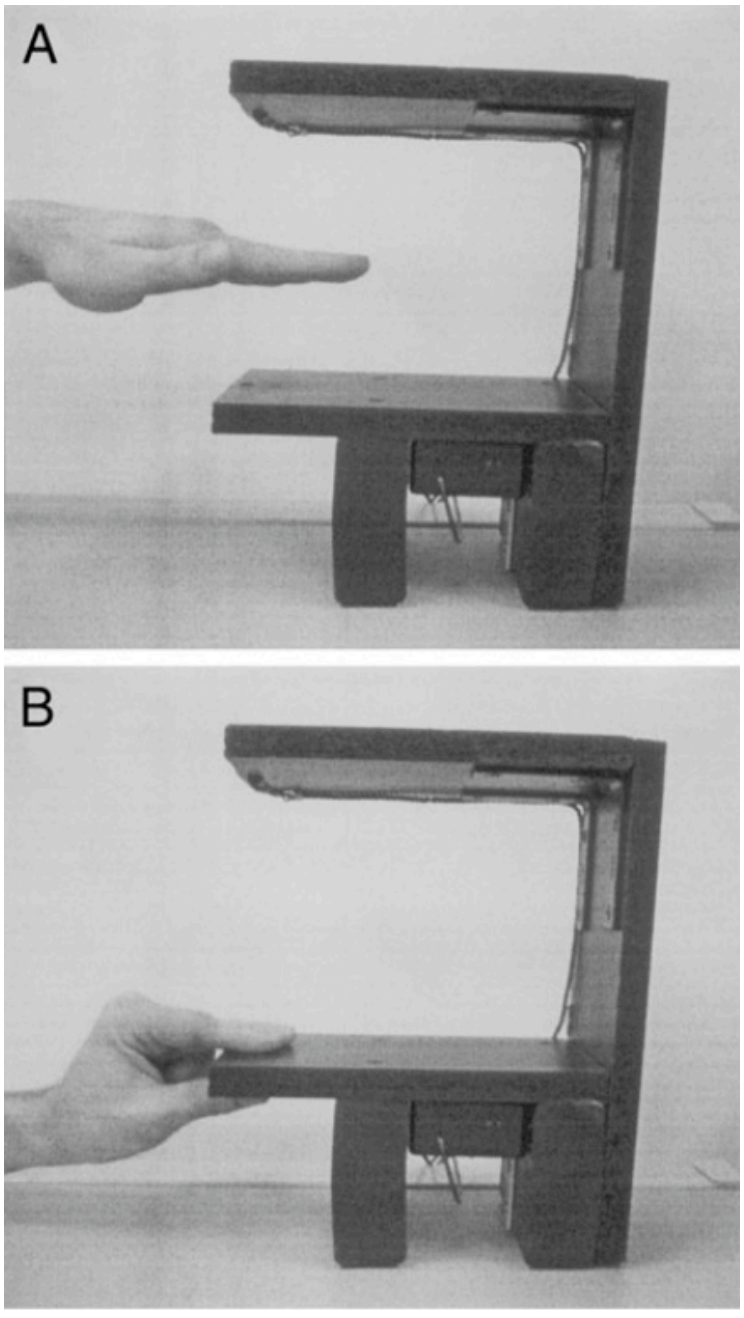


Figure 2.

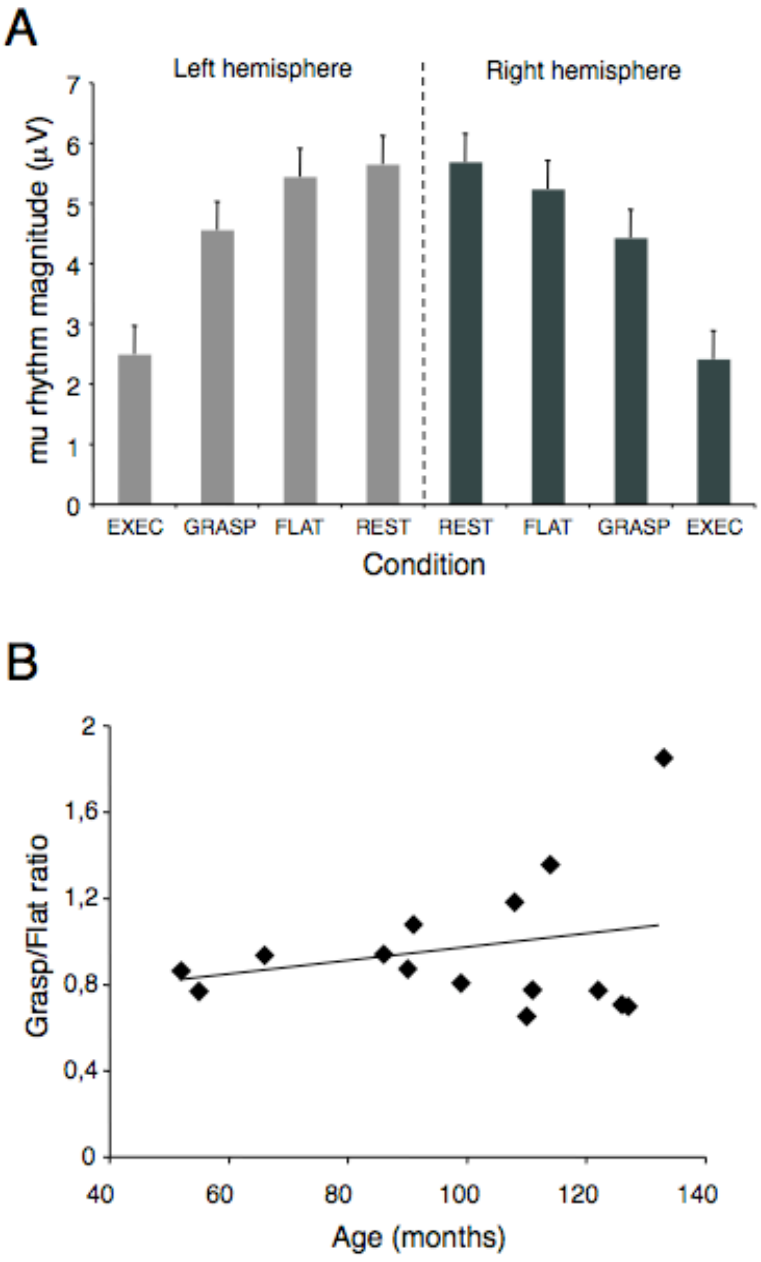
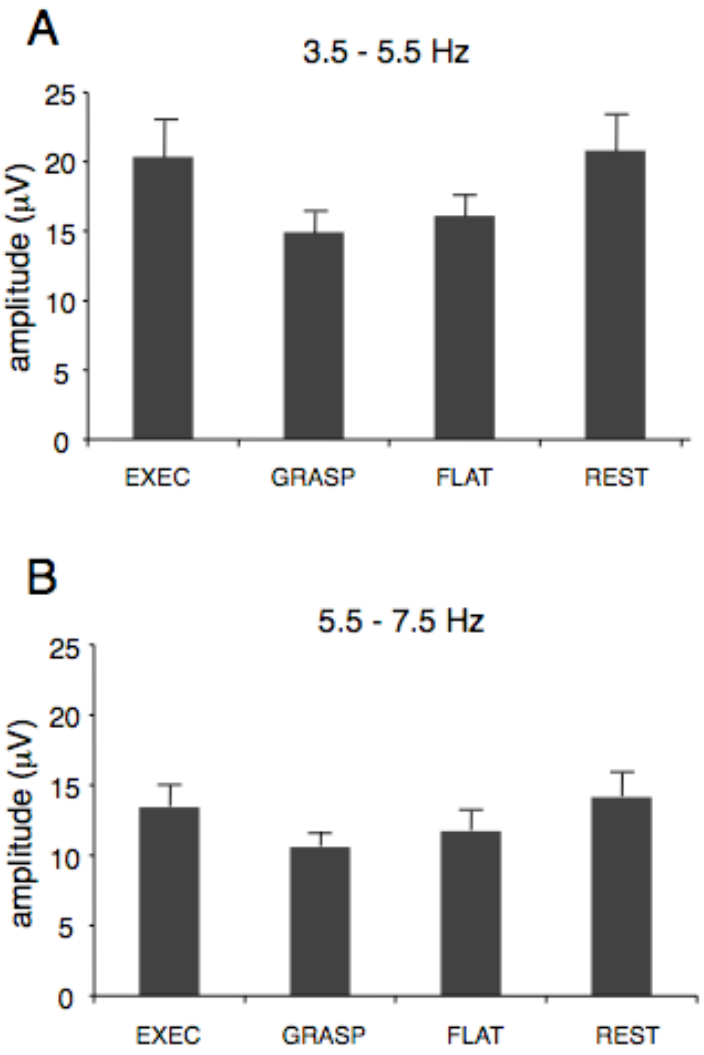

A
Left hemisphere
Right hemisphere
mu rhythm magnitude (μV)
0
1
2
3
4
5
6
7
EXEC
GRASP
FLAT
REST
REST
FLAT
GRASP
EXEC
Condition
B
Grasp/Flat ratio
0
0,4
0,8
1,2
1,6
2
40
60
80
100
120
140
Age (months)

Figure 3.


A
3.5 - 5.5 Hz
amplitude (μV)
25
20
15
10
5
0
EXEC
GRASP
FLAT
REST
B
5.5 - 7.5 Hz
amplitude (μV)
25
20
15
10
5
0
EXEC
GRASP
FLAT
REST

Chapitre 3

Article 2

Action related sounds induce early and late modulation of motor cortex activity

Neuroreport, 2009, **21(4):250-3**

Action related sounds induce early and late modulation of motor cortex activity

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Article publié dans *Neuroreport*, 2010, 21(4):250-3.

3.1. Abstract

It is now well established that the human brain is endowed with a mechanism that pairs action perception with its execution. This system has been extensively studied using visual stimuli and recent evidence suggests that it is also responsive to the sound of motor actions. Here, we presented action (finger and tongue clicks) and acoustically-matched sounds to investigate action-related sound processing in a 12 year-old child undergoing intracranial monitoring of epileptic seizures. EEG grids were located over a large portion of the right hemisphere, including motor cortex. Wavelet analysis carried out on electrodes overlying the functionally defined hand representation of the motor cortex revealed early (100ms) and late (250-450ms) decreases in mu rhythm power (12 and 20 Hz) selective for natural finger-clicks compared to control sounds. These data suggest the presence of a rapid, multimodal resonance mechanism presumably taking place in the motor cortex.

3.2. Introduction

The existence of a resonance mechanism by which the perception of actions activates cortical regions similar to those recruited during their execution is well documented in the human brain. The human mirror neuron system (hMNS), which is presumed to underlie motor resonance, has been extensively described in adults [1] and increasing efforts are devoted to track its development during childhood and adolescence [2,3]. An important characteristic of the hMNS is its selectivity to biological movement. While some behavioral data suggest the existence of motor resonance during the observation of non-biological actions that closely match those of a biological agent [4], neuroimaging studies support the biological selectivity of the hMNS [5]. This feature has been extensively studied in the visual domain and it has been shown that observation of biological movement, even in its simplest form as exemplified by Johansson's point-light-walker [6], recruits motor areas of the brain [7].

There is increasing evidence that the auditory representation of actions also activates the hMNS, in line with the existence of audiovisual mirror neurons in area F5 of the macaque monkey [8]. Recent studies have shown that hand action sounds increase primary motor cortex (M1) excitability [9] and that premotor responses to auditory actions are somatotopically organized [10]. Remarkably, recognition of action sounds made by the hand is selectively impaired in patients with limb apraxia whereas recognition of mouth action sounds is deficient in patients with buccofacial apraxia [11]. Despite accumulating evidence of hMNS responsiveness to action related sounds, basic information regarding M1 activity in this context remains sparse. Even if M1 recruitment has been demonstrated through mu frequency modulation in children [2], no study has investigated, to our knowledge, hMNS sensitivity to auditory actions in this population. Also, the time course of M1 activity during action perception is still uncertain, as some recent data suggest an early modulation of M1 activity (less than 100ms) following visual and auditory presentation of action stimuli [12,13].

In the present study, we recorded intracranial EEG in a 12 year-old child undergoing intracranial epilepsy monitoring. We used a multideviant mismatch negativity (MMN) paradigm [14] to investigate auditory responses to action sounds made by the hand and mouth. The experimental protocol strictly matched that described by Hauk and collaborators [15] who showed somatotopically organized ERP responses in motor areas of the brain that were specific to biological actions. In addition, patterns of activity in the functionally defined hand area of motor cortex were examined through wavelet analysis. The current study aimed at determining if the motor cortex is solicited during the perception of action related sounds and establishing the timing of this activity in the immature brain.

3.3. Participant, Material and Methods

Participant. The participant was a 12 year-old right-handed female with intractable epilepsy undergoing presurgical evaluation with an extensive grid/strip coverage of parietal (32 electrodes) and frontal (60 electrodes) cortices of the right hemisphere. The patient had normal vision and hearing and was seizure and medication free during the procedure. Extraoperative study located the epileptogenic focus in the premotor area of the right hemisphere. The experimental protocol was approved by the Notre-Dame Hospital Ethics Board and informed consent was obtained from the patient and her parents.

Stimuli. Biological action sounds and control sounds were based on Hauk and collaborator's study [15]. Sounds were digitally recorded (sampling rate 44.1 kHz) and edited with Cool Edit 96 software (Syntrillium Software Corporation, Phoenix, AZ, USA). Finger clicks were produced by a friction movement of the middle finger on the thumb towards the palm of the hand and tongue clicks were produced by pressing the tongue against the palate, building negative pressure and releasing it by lowering the tongue rapidly against the lower jaw. The resulting two sounds best matched on amplitude and duration were selected as action-related sounds; both were 150ms in duration with a peak frequency of

2226 Hz for the finger and 1060 Hz for the tongue click. Subsequently, acoustically-matched control stimuli were created, replicating properties of both natural sounds on duration, frequency, envelope, onset and peaks latencies. The natural and control finger clicks peak signal intensity arose at 14 ms; for the natural and the control tongue sounds, the first local peak took place at 6 ms, whereas the main peak occurred at 35 ms. In addition, two stimuli with in-between acoustic properties (peak frequency: 1643 Hz; peak latency 24 ms) and a dissimilar envelope were created to resemble the finger and tongue stimuli. One was used as the standard stimulus while the other was used as an additional deviant to faithfully replicate the protocol used by Hauk [15], as a five-deviant design has been established as the optimal MMN paradigm [14].

Procedure. Stimuli were inserted in a multideviant-oddball paradigm where every second sound was the standard stimulus, while the five above-mentioned sounds were presented in a pseudo-random fashion as to never repeat the same deviant sound twice consecutively and so that all deviants would be present in each of 10 consecutive presentations. In the experimental protocol, each deviant sound was presented 256 times at an ISI of 500ms. Stimuli were presented at 75dB sound pressure level through speakers (Logitech X310 model) positioned at 25 cm from the participant's head at auricular height. During the procedure, the participant watched a silent movie (an animated movie showing exclusively animals) with subtitles and was asked to ignore the auditory stimuli. In addition, all deviant sounds were also presented in repetition blocks of 250 trials to further control for acoustical effects. ERPs from deviant sounds were subtracted from their respective ERP produced during the repetition blocks, resulting in a MMN for each deviant sound.

ERP analysis. EEG was acquired from subdural electrodes with a sampling rate of 512Hz and filtered from 0.5Hz to 100 Hz (24 dB/oct). Data were analyzed offline using BrainVision Analyzer (Brain Products, Gilching, Germany) and visually inspected to remove epochs with artifacts and potential epileptic activity. Data were segmented in epochs of

600ms (-100ms to 500ms) with a minimum of 180 trials kept per condition. Each individual ERP for deviant sounds was paired and subtracted from its respective ERP during block presentation to produce a MMN. Criteria to establish the presence of a MMN response on a given electrode site were the following: 1) presence of an auditory response (P1, N1, P2 complex); and 2) increased response *for all deviant sounds* compared to the standard sound (MMN) at any moment in the 100ms-350 ms time window. Comparisons between natural and control sounds were performed only if both sounds elicited a MMN response.

Wavelet analysis. Electrodes were selected on the basis of eliciting motor responses in the effectors associated with the production of the action-related sound (hand and mouth) during the preoperative study. Electrical stimulation at five electrode sites elicited motor responses in fingers of the left hand and none elicited movement of the mouth. Even if no "mouth-area" was defined, wavelet analysis was performed for both pairs of sounds (finger and mouth) on the electrodes corresponding to the hand region in order to assess the specificity of the motor pairing process taking place within M1. Evoked activity was analyzed via complex Morlet wavelet transform ($(t) = A \exp(-t^2/2) \exp(i2\pi ct)$), which has a Gaussian shape in both time and frequency domains around the wavelet central frequency (Frequency steps = 9; Morlet parameters c = 7, frequency range 6-24Hz, linear scale). Before proceeding to wavelet transform, a low frequency filter cut-off (5Hz, 48 dB) was applied to better focus on frequencies of interest (mu bands; 10 and 20Hz). For each condition, resulting wavelet transforms were averaged for each electrode, which were then pooled, and the resulting control-sound wavelets were subtracted from their matched biological counterparts to isolate differences in activity evoked by action-related sounds.

3.4. Results

None of the grid electrodes displayed MMN-like responses when each sound was substracted with its repetition or with the standard used in the multideviant protocol. No further analysis was conducted on ERP responses. Wavelet analysis of the EEG signal

revealed a diminution of power in both mu rhythm frequencies induced by finger-clicks when contrasted with their control sounds. In the alpha band (8-14Hz), there was an early modulation at around 100ms followed by a larger period of decreased activity in the 250-450 ms time window. In the beta band (18-22Hz), a decrease in mu power was found only at the later time window. Hence, there appears to be two distinctive time windows during which motor cortex activity is modulated following the hearing of action related sounds, and these periods also differ with regards to the modulated frequencies. In opposition, no modulation in the 10 or 20Hz band could be observed for the tongue-click pairs, suggesting a selectivity of responses for hand related sounds (Figure 2).

3.5. Discussion

The main finding of the present study is the existence of two distinct time-windows during which primary motor cortex activity is enhanced during passive listening to action-related sounds. This modulation was found in the functionally defined hand area of M1 and was specific to finger sounds. Furthermore, whereas early and late modulation of M1 occurred in the alpha band, beta suppression was only seen at the later time window. In partial agreement with previous reports using subdural recordings, no MMN could be evoked at frontal and parietal sites.

The inability to evoke MMN responses in the present study is not completely surprising, as Rosburg and colleagues [16] reported that only 13 of 29 patients showed responsive subdural electrodes in a protocol designed to elicit MMN responses. In that study, MMN generators were primarily found in the superior temporal lobe, although 2 of 9 patients also produced MMN signals in frontal cortex. As such, the absence of a MMN here may reflect the limited potential of intracranial studies in detecting a MMN and/or the frontal components of the signal generators. Nevertheless, in light of the action-related MMN reported by Hauk and collaborators [15], more data are needed to determine the extent to which action-sound related MMN responses can be observed in primary motor cortex.

As demonstrated through wavelet analysis, hearing a natural finger click, but not a tongue sound, induced a power decrease in both mu rhythm bands for the electrodes located over the hand motor area. The early modulation of alpha rhythms in M1 is reminiscent of recent findings suggesting an early recruitment of M1 following action perception. Hauk and collaborators [15] found the largest ERP difference between action and non-action sounds 100 ms after sound presentation in a MMN design identical to the one used here. Moreover, source estimates suggested that M1 contributed significantly to this effect [15]. This is in line with a recent TMS study that revealed increased corticospinal excitability during passive listening to speech 100ms after stimulus presentation. Interestingly, this early activity was followed by a second increase 200ms to 300ms post-stimulus, presumably reflecting higher cognitive processes [13]. A similar distinction was also stressed in two complementary MEG studies [12, 17] of hand action observation in which the presence of neuromagnetic lateralized readiness fields was found as early as 83ms after movement onset during observation of goal-directed movements. This activity was distinct from a later modulation, which was sensitive to higher order cognitive evaluation such as correctness of the observed action. Much like what was found here, this later activity was observed as a decrease in beta band power and was detected approximately 500ms after movement onset [17]. Taken together, these data suggest the existence of a rapid, automatic mechanism that maps perceived actions onto the observer's own motor system, followed by a second wave of activity that presumably reflects higher order cognitive processes. Because the recording areas were defined through electrical stimulation in the preoperative study, our data add support to the notion that M1 itself is involved in early and late motor resonance.

Despite numerous studies, the relationship between 12Hz and 20Hz mu rhythms remains elusive. As observed here and reported elsewhere, these frequencies can be modulated simultaneously or separately given the context [18]. With regards to action perception, EEG studies have consistently shown alpha suppression [19,20] whereas MEG

studies have generally reported modulations in the 20 Hz range [18]. It has been suggested that alpha mu rhythms reflect somatosensory processing whereas 20Hz rhythms originate from M1 [21]. If this is indeed the case, the early modulation seen at 100 ms could result from an early sensory mapping process that modulates M1 activity through strong reciprocal connections. This would be in line with the early facilitatory effect measured with TMS [13], neuromagnetic lateralized readiness fields [12] and early alpha band power decreases seen here. The late modulation (250-450 ms) seen in both beta and alpha bands could represent the end product of a complex mechanism involving higher-order sensorimotor integration that takes place in different areas of the hMNS.

3.6. Conclusion

Using subdural recordings in a 12 year-old child, we show that the hand representation in M1 is specifically sensitive to the sound of actions executed by the hand. Moreover, our data suggest the presence of two distinct time points at which M1 is activated by action sounds, presumably reflecting low- and high-level motor resonance. While the exact source of this activity remains to be investigated, these data argue in favor of complex primary motor cortex involvement in action perception, even in the immature brain.

3.7. References

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3.8. Figure captions

Figure 1: Sites where electrical stimulation elicited motor activity in the left hand. Top images show sagittal (A) and coronal (B) views of the MRI. Bottom images show a reconstructed picture of the brain and grid (C) and the exposed brain of the subject (D).

Figure 2: Average time-frequency plots from electrodes corresponding to the motor hand area. A) Difference in evoked activity when the control finger-clicks is subtracted from the natural finger-clicks activity. (B) Difference in evoked activity when the control tongue-clicks is subtracted from the natural tongue-clicks activity. Dark areas indicate high power whereas bright areas show low power.

Figure 1.

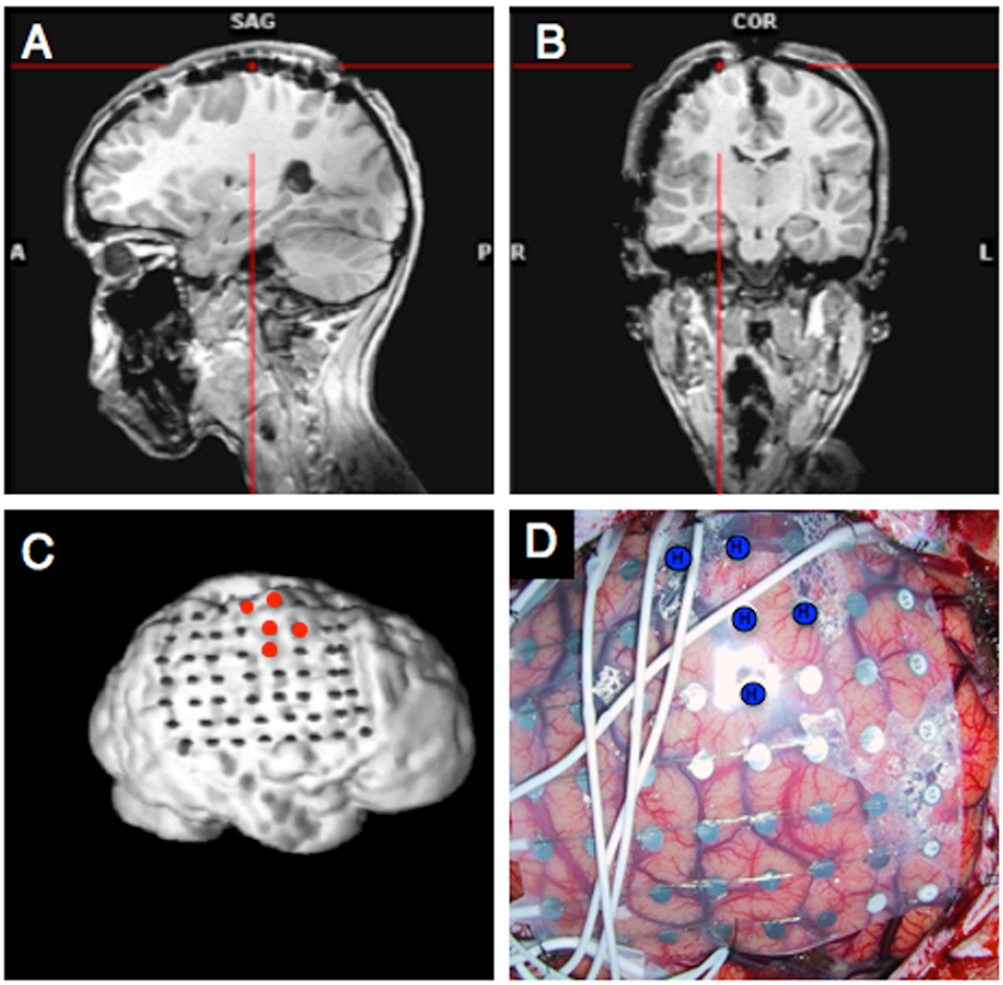
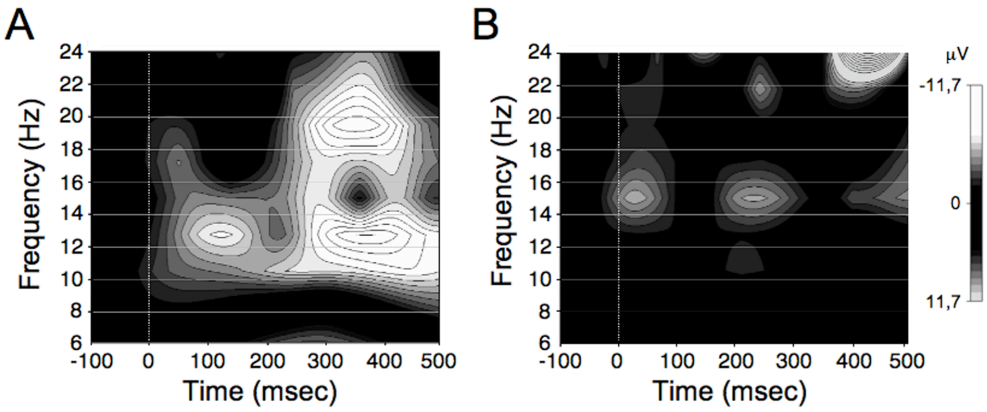


Figure 2.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11,7

Chapitre 4

Article 3

The mirror neuron system : Grasping others' actions from birth?

***Developmental Science*, 2007, 10(5), 512-523.**

The mirror neuron system : Grasping others' actions from birth?

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Article publié dans *Developmental Science*, 2007, 10(5), 512-523.

4.1. Abstract

In the adult human brain, the presence of a system matching the observation and the execution of actions is well established. This mechanism is thought to rely primarily on the contribution of so-called “mirror neurons”, cells that are active when a specific gesture is executed as well as when it is seen or heard. Despite the wealth of evidence detailing the existence of a mirror neuron system (MNS) in the adult brain, little is known about its normal development. Yet, a better understanding of the MNS in infants would be of considerable theoretical and clinical interest, as dysfunctions within the MNS have been demonstrated in neurodevelopmental disorders such as autism spectrum disorder. Arguments in favor of an innate, or very early, mechanism underlying action understanding mainly come from studies of neonatal imitation, the existence of which has been questioned by some. Here, we review evidence suggesting the presence of a MNS in the human child, as well as work that suggests, although indirectly, the existence of a mechanism matching the perception and the execution of actions in the human newborn.

4.2. Introduction

The discovery of mirror neurons in the premotor cortex of the macaque monkey and the growing evidence demonstrating their presence in the human brain has led many to suggest a fundamental role for the mirror neuron system (MNS) in social cognition (Gallese *et al.*, 2003). Specifically, it has been proposed that one of the neural mechanisms underlying the human ability to stand in the shoes of others (the so-called mentalizing behavior) is the MNS. This is particularly important with regards to neurodevelopmental disorders in which mentalizing behavior is impaired. For example, as a failure in attributing mental states to a peer seems to be a core feature in Autism Spectrum Disorder (ASD) symptomatology, abnormal mirror neuron function in ASD has been suggested (e.g. Williams *et al*., 2001) and then recently demonstrated using TMS (Théoret *et al*., 2005), EEG (Oberman et al., 2005), fMRI (Villalobos *et al*., 2005; Dapretto *et al*., 2006) and MEG (Nishitani *et al*., 2004). In light of this evidence, it has become of paramount importance to understand how the MNS develops and whether or not it is present at birth. In this review article, we provide a brief overview of adult MNS properties followed by electrophysiological and behavioral evidence suggesting the presence of a functional MNS early in normal development. As the field of social neuroscience is growing rapidly, it is important to establish where we are at the moment with regards to theories of child development that take into account the MNS and suggest future avenues of research.

4.3. The mirror neuron system

The discovery of mirror neurons ten years ago by Rizzolatti and Gallese (Gallese *et al.*, 1996; Rizzolatti *et al.*, 1996) has created an unprecedent interest for the field of social neuroscience. The existence of a mechanism directly matching action and perception has been the source of numerous propositions regarding the

contribution of the MNS to various phenomena such as language acquisition (Arbib, 2005), imitation (Iacoboni, 2005; Iacoboni *et al.*, 1999; Wohlschlager & Bekkering, 2002), empathy (Carr *et al.*, 2003; Gallese, 2003) and theory of mind (Williams *et al.*, 2001). First observed in area F5 of the macaque frontal cortex, these multimodal cells are activated when an individual *performs* a given action (e.g. cracking a peanut), *sees* a conspecific executing the same action (e.g. observing another monkey cracking a peanut), and sometimes *hears* its action-related sound (e.g. hearing a peanut being cracked) (Kohler *et al.*, 2002). By being simultaneously sensitive to the execution and the perception of actions, it has been suggested that mirror neurons are the basic constituents of a system matching the representation of others onto the representation of the self (Rizzolatti and Craighero, 2004). This idea of shared and common representations is central to the theory of simulation, which stipulates that individuals relate and understand each other by simulating within their own neural networks the pattern of activity that is evoked during the direct experimentation of actions, emotions and thoughts.

A growing body of evidence suggests the existence of a motor resonance mechanism in humans that is highly similar to that found in monkeys. Using a wide variety of brain imaging techniques (EEG, fMRI, MEG, PET, TMS), crucial functional and anatomical similarities between the neuronal circuitry associated with the performance and observation of actions have been demonstrated. The core of this neural system includes the posterior region of the inferior frontal gyrus (IFG) and the rostral part of the inferior parietal lobule (Rizzolatti & Craighero, 2004). These “mirror areas” are part of a complex network that receives afferences from the superior temporal sulcus (STS), a region involved in the processing of biological motion (Puce & Perrett, 2003), and sends efferences to motor cortex.

The vast amount of data collected in the recent years has shed light on the

functional complexity of the adult MNS. MNS activity follows the temporal course of the observed action (Gangitano *et al.*, 2001), is specific to the muscles recruited by the observed action (Maeda *et al.*, 2002), and is sensitive to the orientation of the observed body part (Maeda *et al.*, 2002) and its laterality (Aziz-Zadeh *et al.*, 2002). Although most human studies have relied on actions performed by conspecifics, it is likely that the MNS can also be activated by motor acts executed by other species if they are part of the human motor repertoire (Buccino *et al.*, 2004). Whereas some have suggested that MNS activation is restricted to the observation of biological movements or their schematic representation (Jarvelainen *et al.*, 2004; Tai *et al.*, 2004), others have reported MNS activity triggered by the movement of robotic hands closely matching biological movement (Press *et al.*, 2005). Finally, despite the close correspondence between the human and monkey MNS, they differ on at least one crucial point: whereas the monkey MNS responds only to object-directed actions (transitive movement), the human system is also sensitive to intransitive movements, which are not goal-directed (Buccino *et al.*, 2001).

4.4. Development of the human mirror neuron system

This admittedly succinct description of adult MNS properties highlights the fact that compared to its adult counterpart, very little is known about the MNS of children. Not only are the developing MNS properties mostly unknown, it's mere *presence* is yet to be fully established in young children. This is somewhat surprising since this issue has important theoretical and clinical implications. For one, a better understanding of MNS development would contribute greatly to current theories of language acquisition (Rizzolatti & Arbib, 1998; Westermann & Reck Miranda, 2004) and theory of mind (Trevarthen & Aitken, 2001), both of which afford an important contribution of the MNS to its normal development. From a clinical standpoint, many have suggested MNS impairments as a potential

source of social deficits encountered in various psychopathologies (Gallese, 2003; Williams et al., 2001). The strongest claim for a link between a dysfunctional MNS and social impairments comes from studies reporting functional (Dapretto *et al.*, 2006; Oberman, 2005; Theoret *et al.*, 2005) and anatomical (Hadjikhani et al., 2006) abnormalities within the MNS of individuals with autism spectrum disorder (ASD). A better understanding of the developing MNS is of the utmost importance in the development of diagnostic and therapeutic tools that take into account MNS dysfunction in neurodevelopmental disorders (Fecteau et al., 2006).

The few authors that have addressed developmental aspects of the MNS in humans have supposed the innate character of some of its elements (Meltzoff & Decety, 2003; Rizzolatti *et al.*, 2002). Yet, there has been no direct demonstration of the presence of mirror neurons, or a mirror neuron-like system, in the newborn human, ape, or monkey. Single-unit electrophysiological recordings have only been reported in adult monkeys and human studies directly assessing MNS function have not been carried out in newborns. The idea that a functional MNS could be present at birth is based primarily on the fact that newborns appear to possess imitative capacities (Meltzoff & Moore, 1983; Meltzoff & Moore, 1977), since imitation is thought to be partly based on a direct-matching mechanism mediated by the MNS (Wohlschlager & Bekkering, 2002).

Although the propensity of neonates to imitate has been widely accepted, some have argued that this ability may actually be the result of an innate releasing mechanism (IRM) (Anisfeld, 1996; Anisfeld *et al.*, 2001). According to Anisfeld and collaborators (2001), the orofacial imitation effect reported in Meltzoff and Moore's (1977; see below) seminal study is the result of a single behavior, tongue protrusion. As for the other behaviors that were imitated (mouth opening, lip protrusion, hand waving), it is argued that too few subjects were studied and that

artifacts due to the tongue protrusion behavior may account for the reported effects (Anisfeld, 1996; Anisfeld et al., 2001; Heyes, 2005). Whereas solving this debate is beyond the scope of this review, and even if newborns *can* indeed imitate, it highlights the fact that inferring the presence of a functional MNS from evidence of neonatal imitation is questionable at best. Undoubtedly, neurophysiological evidence is required to establish whether or not fundamental properties of the adult MNS are present in infants and determine how they relate to the normal development of imitative abilities.

Given the scarcity of empirical data on the topic, some have argued that the multimodal nature of the MNS could develop through experience and visuomotor learning (Hurford, 2002). No one would argue that the correspondence between the action of cracking a peanut and the specific sound that it produces is innate, as an infinite number of such pairings would be required at birth. Indeed, many studies have shown that the MNS is flexible and that experience modulates its functioning (Calvo-Merino *et al.*, 2005; Haslinger *et al.*, 2005). For example, mirror neurons have been shown to respond to stimuli to which they were previously insensitive following extensive exposure (Ferrari et al., 2005). Considering its malleability, it is justified to assume that the MNS develops gradually through exposure to actions performed by self and other. According to this view, the MNS would emerge during infancy and go through a number of refinements throughout life, much like other cognitive functions. However, despite acknowledging learning effects in proper MNS development, it seems more likely that an action observation/execution matching system is already present at birth in some form.

4.5. Neurophysiological evidence

Whereas many studies have investigated the perception of motor acts in

children, most have focused on the recognition of biological motion (Cochin *et al.*, 2001; Hirai & Hiraki, 2005; Nakayama, 1985; Pavlova *et al.*, 2001; Pavlova *et al.*, 2005). The earliest electrophysiological demonstration in infants suggests that the neural substrates for processing biological motion are in place by the age of 8 months (Hirai & Hiraki, 2005), which could constitue a prerequisite for the proper development of a motor resonance mechanism. However, despite the wealth of research documenting the developmental aspects of biological motion observation, few studies have looked at the similarities between the patterns of activity during the execution and the observation of motor gestures. Methodological limitations may explain this scarcity of evidence, as many experimental procedures are not suited for infant studies and traditional brain imaging techniques are notoriously difficult to use in infant populations.

Despite these shortcomings, recent efforts aimed at detailing MNS function in younger individuals are beginning to provide useful data. Fecteau and collaborators (2004) recorded activity from a 64-contact subdural grid electrode in a 36 month-old child undergoing surgery for intractable epilepsy. Extraoperating mapping through electrical stimulation was used to define the sensorimotor representation of the right hand. EEG activity was subsequently recorded while the child was 1) passively watching the experimenter draw with his right hand; 2) drawing with her right hand; and 3) resting with her eyes open. Compared to baseline, a decrease in spectral power in the alpha band (8.5-12.5 Hz) was observed in two of the six contact sites overlying the sensorimotor representation of the hand during both *observation* and *execution* of the drawing movement. As previously shown in adults with the same technique (Tremblay *et al.*, 2004), these data provided preliminary evidence for the presence of a mirror-matching mechanism in children.

The presence of an observation-execution matching mechanism in typically developing children was also reported using scalp-EEG. In a group of 15 children aged between 52 and 133 months (mean: 99,3), Lepage & Théoret (2006) measured mu rhythm amplitude during the execution and observation of hand grasping movements. It was found that the typical decrease in mu rhythm amplitude that occurs at central sites (electrodes C3-C4) during action execution was also present during observation of the same movement. Of great interest is the fact that the sensorimotor cortex response in these school-aged children is strikingly similar to that reported in adults (Muthukumaraswamy & Johnson, 2004; Muthukumaraswamy *et al.*, 2004). Furthermore, the absence of correlation between mu rhythm modulation and age (Lepage & Théoret, 2006; Oberman, 2005) suggests a fairly stable mechanism underlying action observation during childhood. If the mu rhythm is truly reflective of MNS activity, this apparent stability suggests that full cortical maturation does not need to occur before the MNS becomes functional.

As EEG desynchronization is a correlate of activated cortical tissue resulting from thalamocortical inputs (Goldman *et al*., 2002), reduction of the mu rhythm in the absence of overt movement is though to reflect the recruitment of neurons in the fronto-parietal circuit involved in sensorimotor processes (see Figure 1). Indeed, the pattern of activity of the mu rhythm during action observation (desynchronization resulting in the reduction of absolute power) and the source of its fluctuation suggest that this electrophysiological measure can serve as a marker for MNS function. This is supported by the fact that the reduction in mu rhythm amplitude that occurs during action observation also occurs when an individual performs a specific motor action. In other words, mu rhythm modulation relates to basic MNS function as both execution and observation of actions reduce its amplitude in sensorimotor cortex. In an extensive review of the topic, Pineda

(2005) suggested that the mu rhythm is reflective of an integrative process which, just like the MNS, “translates seeing and hearing into doing”. This integration from visual/auditory inputs to motoric representations reflected by mu modulation would be the local result of a larger process witnessed in the alpha band in modality specific areas during sensory stimulation.

To this day, a single study has investigated, although indirectly, the MNS of typically developing children using fMRI. Dapretto and collaborators (2006) reported activation of the pars opercularis of the IFG in ten normal children during imitation and passive observation of emotional facial expressions. These children (mean age 12.38 years 2.22) served as controls for 10 children with ASD. In keeping with the MNS theory of social cognition, it was found that activity within the IFG (the main MNS component) was significantly reduced in children with ASD, similarly to what had been reported in adults (Nishitani et al., 2004). Interestingly, in children with ASD, the level of IFG activity during observation of emotional facial gestures was negatively correlated with social adjustment (Dapretto et al., 2006). These data highlight the importance of better understanding the normal development of the MNS, as the link between social cognition impairments and MNS dysfunction in neurodevelopmental disorders becomes increasingly apparent.

Any theory that tries to explain MNS development must take into account the fact that the brain goes through fast and considerable transformations in the first months/years of life. In that regard, the age samples used in the aforementioned studies are small and limited to school-aged children, more than likely overlooking early MNS transformations. Designs that use complex paradigms and directly compare brain activity in children and adults are needed to establish a clear timeline of MNS development. Recent efforts have been made to

probe MNS function in younger populations using realistic protocols and brain imaging techniques more suitable to infant studies. An important first step in that direction has recently been provided by Shimada and Hiraki (2006) who used near infrared spectroscopy (NIRS) to investigate motor resonance mechanisms in adults and 6- to 7-month-old infants. The authors provided the first demonstration of the presence of an action execution/observation matching mechanism in the infant brain by showing an identical pattern of response in the sensorimotor cortex of infant and adults during live observation of hand-object interactions. Specifically, the motor cortical areas that were activated when infants performed hand actions were also active during the passive observation of an experimenter manipulating an object. Surprisingly and contrary to adults, the sensorimotor cortex of infant participants was also activated by the mere observation of an object moving when it was presented on a television screen. Although it is not typical of the adult MNS, there have been reports of increased MNS activity during observation of static objects in adults as well when they *imply* actions (Grafton *et al.*, 1997; Grezes & Decety, 2002). Imaging studies in adults have also shown that the MNS is particularly suited for the coding and understanding of *intentions* (Iacoboni et al., 2005). Shimada and Hiraki (2006) put forth the hypothesis that observation by the immature brain of a moving object on television can reveal an intention and/or simulation of action upon the object. Through experience, infants would gradually realize that the object seen on TV cannot be acted upon, and would learn to refrain from responding to the stimulus as a "real one". Indeed, in adults, the mere observation of an object moving is not sufficient to elicit activity within the core regions of the MNS. Here, the developmental aspects of the MNS come to light, where it can be hypothesized that the basic system present in infants undergoes a series refinements, presumably through experience. When it is understood that an object on a television screen can move without direct human interaction, the automatic MNS response disappears.

These studies constitute a first step towards a clear understanding of the neuronal events that underlie the normal development of the MNS. The reviewed neurophysiological evidence, although still limited, argues in favor of a functional mirror matching mechanism in infancy. If evidence suggesting the presence of a MNS for action as early as 6 months of age is to be replicated and expanded upon, it is tempting to propose that parts of the motor resonance mechanism that exist in adulthood are either innate or develop quickly in the first weeks of life. Still, it is not yet possible to determine from neurophysiological evidence alone if the human infant gradually develops a system matching execution and observation of actions through experience or if, as some have suggested, the schema on which actions are mapped is present at birth (Meltzoff & Decety, 2003). As such, additional research is greatly needed to determine *i)* if humans are *born* with a functional MNS; *ii)* if mirror cells are activated the first time an action is seen; and *iii)* whether the execution of motor acts concurrently with their observation is required for the proper tuning of the matching mechanism that binds them together.

4.6. Behavioral evidence

Not surprisingly, it is towards imitative abilities that neuroscientists first looked for the presence of a MNS in infants (Meltzoff & Decety, 2003). Motor imitation can provide insight into MNS function because it requires the contribution of a neuronal circuitry similar to that solicited by a perceived motor act. In human adults, imitation involves regions traditionally associated with the MNS, particularly the pars opercularis of the inferior frontal gyrus (BA44; Iacoboni et al., 1999). Additionnally, three lines of evidence suggest a role for a direct matching mechanism in imitation: *i)* a dysfunctional MNS has been described in a clinical population with well-documented imitative deficits (Dapretto et al., 2006; Oberman, 2005; Théoret et al., 2005); *ii)* patients with a

lesion in Broca's area (BA44) display imitation impairments (Saygin *et al.*, 2004); and *iii)* repetitive TMS-induced virtual lesions to Broca's area induce imitation deficits (Heiser et al., 2003). Consequently, robust evidence for motor imitation abilities in newborns would support the idea that fundamental MNS properties are present very early in normal development.

Piaget, one of the founders of developmental psychology, gave imitation a key role in the cognitive, as well as social, development of the infant. Piaget believed that motor imitation abilities appeared at around one year of age, co-occurring with volitional control. For Piaget, imitation was the result of a child's tactile exploration of his/her own body and that of others, gradually establishing a correspondence between the two (Piaget, 1945). However, in a series of much discussed studies, Meltzoff and Moore reported the existence of imitative abilities in surprisingly young infants. Newborns as young as 42 minutes were shown to execute orofacial gestures that matched those performed by an adult model (Meltzoff & Moore, 1983; Meltzoff & Moore, 1977). In contrast with Piaget's original proposition (Piaget, 1962), Meltzoff and Moore proposed that visual and motor spaces where not as dissociated as previously believed. Indeed, experimental data argued in favor of closely related representations of executed and observed actions, which could be innately linked together since the mere observation of a movement was sufficient to elicit activation of corresponding motor programs. The active intermodal mapping system (AIM) model that was derived from these experiments assumed that imitation in young infants is the result of a representational system that matches visual input into its proprioceptive and motor equivalent (Meltzoff & Moore, 1997). The exact mechanism underpinning this "supra-representational system" was not explicitely specified, but as we have seen earlier, the discovery of mirror neurons may have bridged this theoretical gap.

The conclusions reached by Meltzoff and his collaborators have not gone unchallenged over the years (Hayes & Watson, 1981; Masters, 1979). Some authors believe that "imitative" behaviors witnessed shortly after birth are reflex-like phenomena that can be explained by a simple innate releasing mechanism (IRM). Moreover, as with many reflexive behaviors, the occurrence of imitative behaviors greatly decreases around the second month of life (Field et al., 1986; Fontaine, 1984), to reappear in more complex fashion near one year of age (Meltzoff & Moore. 1992). The idea that newborns are incapable of truly imitating was at first partly motivated by the belief that newborns were unable to initiate voluntary action, and that arm movements were purposeless and reflexive (Piaget, 1952). However, it now appears that neonates can make directed movements at will (van der Meer, 1997; van der Meer *et al.*, 1995). It has also been suggested that the decrease in imitative behaviors that occurs at around 2 months of age reflects the fact that older infants initiate social interactions more dynamically than newborns that are simply responding to social cues (Meltzoff & Moore, 1992).

When presented with facial gestures, the first reaction of the newborn is to move the homologous regions of his/her own face (Meltzoff & Moore, 1997). According to Meltzoff, newborns will move their lips when observing lip movement and move their tongue when observing tongue movements (Meltzoff & Decety, 2003). When the act is not fully imitated, the corresponding body part is nonetheless activated (Abravanel & Sigafoos, 1984; Meltzoff & Decety, 2003). Interestingly, this activation is accompanied by decreased activity of body parts unrelated to the execution of the observed action (Meltzoff & Moore, 1997). It thus seem that even if newborns cannot put forth a motor program matching the one that is seen, the observed body part is nevertheless correctly identified. If infants can truly imitate facial gestures, the presence of a direct matching

mechanism between observation and execution of actions becomes likely, as facial imitation implies movement of a body part that is out of sight. Even if there are relatively few facial movements that can be carried out by newborns, it indicates that motor pairing does not require the contribution of vision in the establishment of a correspondence between self and other. Proprioceptive information, and that resulting from a corollary discharge or efferent copy, is the only way by which the newborn can get information about his movements, supporting the view that there is a common body schema on which motor actions performed by self and other are mapped. It must be noted, however, that neonatal imitation often has several seconds response latency. It could be argued here again that the human MNS must go through a series of subtle changes after birth to fully develop. In addition to greater spatial resolution, where the correspondence between observed body parts and the infants' own limbs gradually increases, temporal resolution may also increase with age within the mirror-matching system. One possible explanation for this phenomenon would be that the temporal coupling between the sensory and motor components of the system is not yet fully functional in newborns. The activated representations of an observed action may need additional processing stages before a matching motor command can be sent out. Additionally, the observation of an action may be sufficient to produce a motor representation that could be reactivated subsequently by specific cues. This is obviously an important issue that must be carefully examined to fully incorporate neonatal imitation into developmental theories of the MNS.

The vast majority of neonatal imitation studies have used simple stimuli, mostly limited to orofacial movement (Heimann *et al.*, 1989; Meltzoff & Moore, 1983; Meltzoff & Moore, 1977). As previously mentioned, studies of neonatal facial imitation have important limitations. First, there is a high spontaneous production rate that makes it hard to relate the occurrence of the behavior to the

experimental condition (Heimann et al., 1989; Jones, 1996). Second, the "imitation" of mouth movement that has been most reliably reproduced (tongue protrusion) can apparently be elicited by non-biological stimuli, such as pen or ball movement (Jacobson, 1979). Finally, because different methodologies and age groups have led to diverging results, there is still debate, nearly 30 years after the first report of neonatal imitation of facial gestures, as to whether it is reflective of true imitative mechanisms or the result of an IRM (Heyes, 2005).

Very few studies have investigated imitation abilities in newborns with stimuli other than facial gestures. One of those was in the original paper of Meltzoff and Moore (1977), where the number of finger/hand movements in 14 days old infants were more frequent following observation of hand closings and openings. A recent experiment has refined the original design to investigate fine motor imitation abilities in newborns (Nagy *et al.*, 2005). In 39 neonates (aged between 3 and 96 hours) that were presented with index finger protrusions, it was found that newborns made more finger movements, complete and incomplete, following observation of human movement than during a baseline period. In addition, whereas the first imitated movements were incomplete and inaccurate, accuracy gradually increased as the session progressed, similarly to what has been reported during facial imitation (Meltzoff & Moore, 1983; Meltzoff & Moore, 1977). It is unclear whether improvement in imitation accuracy results from practice, exposure to the movement, or both. In adults, TMS induced movements become increasingly similar to an observed movement following repetitive observation (Stefan *et al.*, 2005). Moreover, the execution of a motor gesture combined with the observation of an identical gesture, a paradigm routinely used in imitation studies, strengthens this phenomenon (Celnik *et al.*, 2006). The improvement in movement accuracy found in newborns suggests the existence of a neonatal action-observation pairing system that is flexible, leading to quick

refinements in visuomotor pairings.

One central feature of the MNS is its ability to respond to the visual and auditory representations of a motor act (Kohler et al., 2002). For this reason, studies dealing with the perception and imitation of vocal utterances in the neonate are of great interest. Not surprisingly, simultaneously seeing and hearing someone speak modulates motor cortex activity in adults (Sundara *et al.*, 2001). To a lesser extent, observation of orofacial movements (Mottonen *et al.*, 2005; Muthukumaraswamy *et al.*, 2006), as well as passive listening to speech (Fadiga *et al.*, 2002), also modulate motor cortex activity in somatotopic fashion. Meltzoff and Kuhl pioneered research on vocal perception in the human child in a series of classic experiments (Kuhl & Meltzoff, 1982, 1996; Kuhl *et al.*, 1991). They demonstrated that infants as young as 12 weeks were able to imitate vocal material. Indeed, during presentation of videos where an adult was pronouncing one of three vowels (/a/, /i/ or /u/), participants responded with vocalizations that perceptually matched those that were presented (Kuhl & Meltzoff, 1996). In a prior study using a preferential viewing procedure, Kuhl and Meltzoff (1982) showed that 18-20 week-old infants spent significantly more time watching the utterance /i/ and /a/ when it was accompanied by the matching sound. The effect disappeared when vocalizations were replaced by pure tones that were similar in timing and tonality. Beyond vocal imitation, one important point that emerged from these studies is that infants can correctly recognize motor gestures and their associated sounds at a very early age.

In the aforementioned studies, the visual and auditory stimuli were presented simultaneously, making it impossible to evaluate the contribution of each modality to imitative abilities. To determine the contribution of auditory input in the manifestation of orofacial imitative behaviors in neonates, Chen and collaborators

(2004) studied behavioral responses to the presentation of vocal utterances. Orofacial gestures of twenty-five newborns aged between 24 hours and 7 days (mean=3 days) were monitored while they listened to vocalizations (/a/ and /m/). Infants produced significantly more mouth clutching than mouth opening during the /m/ condition, and significantly more mouth opening than mouth clutching during the /a/ condition. Indeed, newborns performed corresponding mouth movements to both the vowel and the consonant sounds, whether their eyes were opened or closed. As no visual cues were associated with the heard sound, the only available information representing the action was auditory. Going beyond the classic neonatal imitation phenomenon, these data showed that orofacial gestures associated with the production of specific utterances could be elicited by its sole audition. These data are in agreement with electrophysiological results obtained in adults, where listening to speech is associated with activity in motor circuits also recruited during speech production (Fadiga et al., 2002) and support the idea that some rudimentary observation/execution matching system is present shortly after birth in the human brain and that it is modality-independent.

4.7. Perceiving is doing

In light of the evidence reviewed here, it seems more than likely that the human infant possesses the capacity to perform the motoric equivalent of what he sees or hears. Given the fact that the presence of such abilities has been documented very early in normal development, less than an hour after birth for visual imitation and less than a week after birth for auditory-orofacial matching, we can speculate that a dedicated neuronal mechanism underpinning this ability is present at birth. Although neurophysiological evidence supporting this hypothesis is still scarce, it is likely that *i)* the body and motor schema on which actions are mapped are present at birth or shortly thereafter; *ii)* these schema are sollicited during the observation of actions and contribute to the execution of motor

programs matching perceived actions; and iii) the same motor representation can be elicited through different modalities (visual or auditory) from the time of birth or shortly thereafter. Neurophysiologically, EEG, fMRI and NIRS studies support the presence of a sensorimotor matching system as early as 6 months of age.

It would appear that the "behavioral matching" that occurs in newborns during the passive observation of actions results from an *automatic* rather than *reflexive* mechanism. The variety of imitated acts and the fact that behavioral matching can be elicited through different modalities makes it unlikely that a purely reflexive mechanism would account for early imitative abilities. Nevertheless, the infant pairing process that matches the perception and execution of motor acts would not necessarily be under direct volitional control either and, similarly to adults, a behavioral manifestation of the observed action would not necessarily occur (i.e. imitation). In adults, imitation is considered a voluntary action. As we *choose* to perform a given movement, we also decide to execute actions that match those we perceive. Whereas the execution of a motor act is under voluntary control (except for certain pathological conditions such as echopraxia), MNS activation is largely automatic and pre-attentive. In the first moments of the imitative process, the observation/hearing of a motor action automatically activates the motor/bodily representation of the perceiver, presumably through the MNS. Subsequently, the individual can *willingly* reactivate this representation to imitate the observed behavior. Evidence that subthreshold activations occur in response to the passive observation of motor acts in non-imitative situations are plently. For example, observation of emotional facial expressions leads to contraction of face muscles involved in the execution of the observed act which, although not visible to the eye, can be detected by electromyography (Dimberg, 1982; Hess & Blairy, 2001; Sato and Yoshikawa, 2006). In the case of infants, we propose that similar motor matching behaviors are

present and more readily executed because inhibitiory mechanisms may not be adequately developed to suppress motoric activations triggered by the observed movement. In that sense, the question of MNS development may be best viewed as a process by which the child learns to refrain from acting out the automatic mechanism that links perception and execution.

The idea that neonatal imitation is the result of "enactive perception" or "direct transduction" is not new. Kinsbourne (2002) suggests that "infant imitation is infant perception captured on the fly". As a result, the newborn *performs* his perceptions and the behavioral manifestation of this perception, encoded through the MNS, is what comes through as imitation for the adult observer. Although acknowledging a newborn's capacity to perform willed actions (van der Meer, 1995), the infant does not have to match the gesture he perceives *deliberately*, as "the act of perception activates [automatically] the infant's own innate corresponding movement patterns" (Kinbourne, 2002). Following on this, we propose that neonatal imitation, mediated by a rudimentary MNS, comes down to *motor matching behavior as unhibited perception*. In that sense, the reason why neonates perform imitative responses would be that they cannot yet actively suppress the motoric representation associated with the heard sound or gesture and mere perception would be the sole *necessary* condition to imitate.

4.8. Conclusion

Recent advances in the field of social neuroscience have led to unprecedented interest in the neuronal mechanism underlying infant imitation. The discovery of mirror neurons has certainly been instrumental in shifting focus from behavior-based theoretical models to the neurophysiological study of the link between perception and action. Resonance models rooted in MNS activity described here cannot account for all the imitative behaviors that have been

observed in newborns. For example, the fact that infants sometimes imitate gestures that were previously observed, overriding current perceptions (Meltzoff & Moore, 1997), has been cited as evidence against a direct transduction model of infant imitation. Nevertheless, although strict application of simulation models would undoubtedly underestimate the complexity of imitative behaviors, converging data strongly favor models that acknowledge the exsistence of an infant MNS in some form or another. In that regard, a better understanding of MNS function in the newborn and infant and a thorough description of its developmental course is of paramount importance in light of the strong relationship between MNS impairments and neurodevelopmental disorders such as ASD (Nishitani et al., 2004; Oberman et al., 2005; Théoret et al., 2005; Dapretto et al., 2006). Indeed, the establishment of critical periods for proper MNS development would be invaluable for the development of diagnostic and intervention tools that acknowledge the strong link between imitation and mirror matching mechanisms.

Despite accumulating evidence detailing MNS abnormalities in ASD, one still needs to be careful when weighing the contribution of this dysfunction to its general pathophysiology and symptomatology. ASD is a very complex condition that can vary widely in terms of the nature of pervasive symptoms and their severity. Hence, it must be assumed at present that whatever the nature of the MNS dysfunction in ASD, it can only account for a limited number of behaviors, presumably those that specifically deal with social interactions. Indeed, repetitive behaviors and restricted interests, as well as executive dysfunctions, cannot readily be explained by the MNS theory of ASD. In addition, clinical and empirical observations suggest that imititative deficits are not a necessary condition for the development of ASD. Further studies are needed to determine the specific effects of impaired motor-matching mechanisms on the development of social behavior,

and relate MNS dysfunction with other known dysfunctions such as genetic abnormalities.

It is crucial to stress the fact that whatever the nature of the perception-action coupling mechanism present at birth or shortly thereafter, much remains to be established through experience. Adult literature has repeatedly shown the inherent malleability of the MNS, such that learning and experience can modulate MNS response in a drastic fashion. For example, when experts in a specific dance style observe their own dance style performed by others, there is greater activity within the classical MNS areas than during observation of an unpracticed dance (Calco-Merino *et al*., 2005). This example shows that even in adulthood, learning effects and experience cannot be dissociated from the mirror-matching mechanism that we have described. This is especially true with infants, where the rapid changes that occur in the brain, in addition to the multiplication of interactions with the outside world, are certain to play a significant role in the way the MNS develops. This has serious implications for pathologies associated with MNS dysfunction since it suggests that early intervention may direct these changes in a more optimal direction. It is therefore imperative to better understand the effects of experience and learning on MNS development to foster tratment strategies that take into account not only the existence of an infant MNS, but also its malleability.

Finally, one may be tempted to go back to work in monkeys, where mirror neurons were first discovered, to asses the functional properties of mirror mechanisms in the newborn. Recent evidence supports the contention that even Rhesus monkeys, previously thought to lack imitative abilities, are capable of neonatal imitation. Indeed, macaque monkeys can imitate a model's mouth openings on the first day of life (Ferrari et al., 2006). Of great interest is the fact that these neonatal imitative abilities disappear very quickly after birth, at around 1

week of age. In light of the proposal suggesting that neonatal imitation can be viewed in neural terms as a motor matching behavior resulting from unhibited perception, single-cell work in the newborn macaque could specifically explore the inhibitory mechanism that underlies this important developmental step. Whatever the nature of theses mechanisms, we figure that the mystery of neonatal imitation may soon be exposed

4.9. Acknowledgements

We gratefully acknowledge financial support form the Canadian Institutes of Health Research and the Fonds de Recherche en Santé du Québec.

4.10. References

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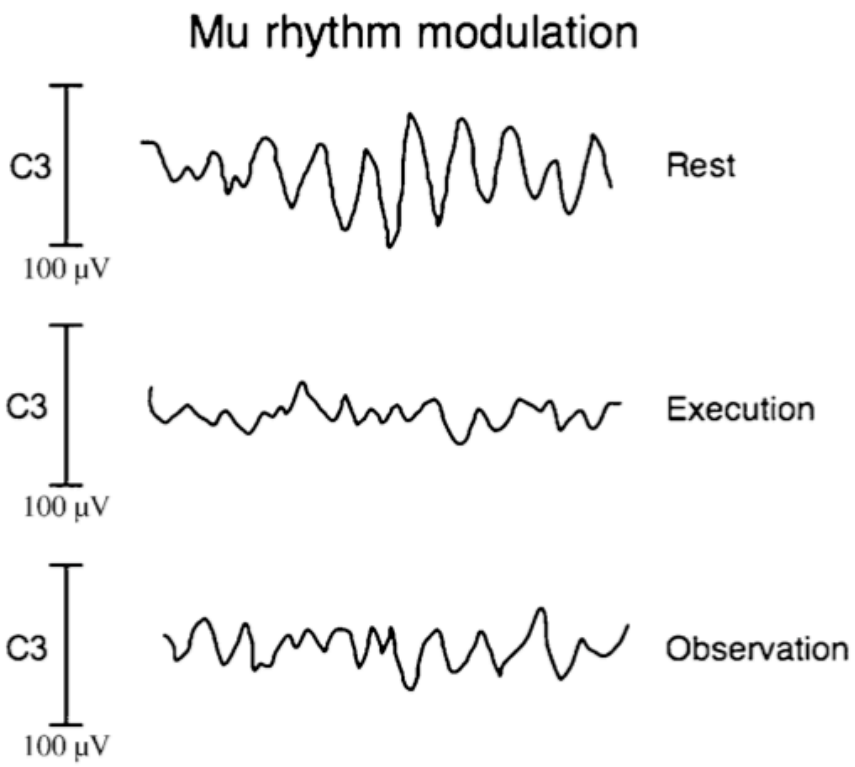
4.11. Figure legends

Figure 1: EEG traces showing mu rhythm modulation during rest, execution of a grasping movement, and passive observation of a human model performing a grasping movement. It can be seen that mu rhythm amplitude decreases during both action execution and action observation at electrode position C3, which overlies sensorimotor cortex.

Figure 1.


Mu rhythm modulation
C3
100 µV
Rest
C3
100 µV
Execution
C3
100 µV
Observation

Chapitre 5

Article 4

Validation of French-Canadian Versions of the Empathy Quotient and Autism-Spectrum Quotient

Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement, 2009, 41, 272-276

Validation of French-Canadian Versions of the Empathy Quotient and Autism-Spectrum Quotient

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Publié dans *Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement*, 2009, 41, 272-276

5.1. Abstract

The primary objective of this study was to validate French-Canadian versions of the Autism spectrum Quotient (AQ) and the Empathy Quotient (EQ) in normal and pathological samples. Translated versions of these scales (AQ-F and EQ-F) were administered to 100 undergraduate university students in the hard science or humanities fields and to 23 individuals diagnosed with autism spectrum disorder (ASD). For both scales, obtained data were partially consistent with English versions. The EQ-F and AQ-F scores were negatively correlated, and the ASD group differed significantly from both control groups, scoring lower on the EQ-F and higher on the AQ-F. These preliminary results support the validity of the AQ-F and EQ-F versions as screening tools in French-speaking populations.

5.2. Introduction

Empathy is a complex ability that allows us to understand the emotions, actions and intentions of our peers. Understanding the thoughts and feelings of another person enables an individual to respond accordingly. Consequently, the individual gifted with such abilities has considerable advantages in initiating and maintaining social relationships (Decety & Lam, 2006). As a core feature of social cognition, many researchers have tried to define and quantify the extent to which an individual is empathic. However, the complexity of the phenomenon has led to the formulation of diverging hypothesis regarding its exact nature (Decety & Jackson, 2004). As a result, many tools have been designed to quantify inter-individual differences in numerous aspects empathy. Unfortunately, most of these scales do not limit their scope to the empathy construct and assess broader concepts such as social skill (Baron-Cohen & Wheelright, 2004)

One of the most widely used measures of trait empathy is the Interpersonal Reactivity Index (IRI) (Davis, 1980), a self-report questionnaire with four subscales assessing the cognitive and emotional aspects of empathy: Fantasy (FS), Perspective Taking (PT), Empathic Concern (EC) and Personal Distress (PD). The cognitive aspect of empathy is measured with the PT and PD subscales, which respectively assess the tendency to adopt the point of view of others and to project oneself into a fictional character. The EC subscale, which measures other-oriented feelings of sympathy, and the PD subscale, quantifying self-oriented negative feelings when experiencing others in distress, evaluate the affective aspects of empathy. Whereas the distinction between the cognitive and emotional aspects of empathy is interesting, the validity of this dichotomy is questionable given the important overlap between both concepts (Baron-Cohen & Wheelright, 2004). Moreover, as pointed out by others (Baron-Cohen & Wheelright, 2004), it is unclear whether the FS and PD subscales are even related to pure empathy.

A recent attempt was thus made to create a measure of empathy that reflects its conceptual heterogeneity while limiting its scope to pure empathy (Baron-Cohen & Wheelright, 2004). The Empathy Quotient (EQ) is a short, self-administered questionnaire comprising 40 items tapping empathy and 20 filler items. The EQ has been shown to have good test-retest reliability (r = .97), high validity (Cronbach's alpha = .92) and replicates previous data demonstrating superiority of females on trait measures of empathy (Baron-Cohen & Wheelright, 2004).

The empathy concept and its measure have added significance when one considers pathological conditions in which it is impaired. Autism spectrum disorder (ASD) is one of the most cited conditions associated with difficulties in empathy. It is characterized by a triad of impairments (repetitive behaviors, social and communication difficulties) in which social dysfunction is a defining feature (APA, 1994). Even with an IQ in the normal range, individuals with ASD have difficulties initiating and maintaining reciprocal social interactions and fail to appreciate the point of view and feelings of others (Baron-Cohen, 1995).

Similarly to the concept of empathy, the importance of a reliable measure of autistic traits has led to the development of numerous instruments. One interesting approach has been to view ASD as lying on a continuum of social impairments (Bolton *et al.*, 1994; Frith, 1991), which allows researchers to quantify autistic traits in any individual of normal intelligence. A short, self-administered questionnaire similar to the EQ has been developed with that idea in mind by Baron-Cohen and collaborators (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). They have created an instrument, the Autism Spectrum Quotient (AQ), comprising 50 items divided into five 10-items subscales: 1) social skills; 2) attention switching; 3) attention to details; 4) communication; and 5) imagination. The AQ has demonstrated good face validity, where average-IQ ASD individuals scored significantly higher than normal controls

(Baron-Cohen *et al*., 2001). Supporting the validity of its use in clinical settings, the AQ has been shown to successfully discriminate between individuals who will later be diagnosed with ASD from those who will not, such that 83% of patients were correctly classified (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005). This is of considerable interest because of the potential use of the AQ as a rapid screening instrument for ASD. It must be pointed out, however, that the AQ has *screening* rather than *diagnostic* value as reflected by the number of false positives that occur with the instrument. Indeed, as stated by Baron-Cohen *et al.* (2001) in the original validation study, "…a high score on the AQ however does not mean an individual has AS or HFA…". In the general population, the AQ has been shown to be sensitive to subtle differences, revealing significant gender and field of study differences (Baron-Cohen *et al.*, 2001). Indeed, this instrument has revealed significant differences between women and men, the latter displaying more autistic traits, in the same fashion as student from science domains showed higher score that individuals from humanities and social sciences (Baron-Cohen *et al.*, 2001).

Not surprisingly, the empathy and ASD constructs have been shown to be strongly related when they are measured with the EQ and AQ scales. There is a strong negative correlation between the EQ and AQ in both typically developing individuals and people with ASD (Wheelwright, Baron-Cohen, Goldenfeld, Delaney, Fine *et al*., 2006). Furthermore, individuals with ASD score significantly lower than typically developing individuals on the EQ (Baron-Cohen & Wheelwright, 2004). Taken together, these data support the validity of the EQ and AQ in clinical and research settings. It must be pointed out, however, that both instruments have *screening* rather than *diagnostic* value since false positive cases occur at a significant level. Nevertheless, because of the short time required to fill out the questionnaires and the ease with which they can be administered, there is a need to make the AQ and EQ available to a broad spectrum of clinicians and researchers.

There currently exists no validated French versions of the AQ and EQ scales. Here, both instruments were translated (the EQ-F and AQ-F) and administered to a group of people with ASD and two groups of typical individuals studying in sciences or humanities. Following the original validation results (Baron-Cohen et al., 2001; Baron-Cohen & Wheelwright, 2004), we hypothesize that for the AQ-F: i) the ASD group will score significantly higher than control groups on the AQ-F; and ii) humanities students will score significantly lower than science students on the AQ-F. Regarding the EQ-F, we believe that iii) the ASD group will score significantly lower than the control groups on the EQ-F; and that iv) female participants from control groups will score higher than male participants on the EQ-F. Lastly, we stipulate that v) scores on the EQ-F and AQ-F will be negatively correlated in the ASD and control groups.

5.3. Method

Participants and Procedure

Ethics approval to conduct the study was obtained from the *Comité d'éthique de la recherche de la Faculté des arts et des sciences* (CERFAS) *de l'Université de Montréal*. All subjects were paid $10 for their participation. Three groups of subjects participated in the study. The *Science group* (SG) included 50 undergraduate students (16 women, 34 men) in hard science disciplines (mathematics, physics, engineering; age range: 18-40 years, M = 22.86, SD = 4.42). The *Humanities group* (HG) included 50 undergraduate students (15 women, 35 men) from social sciences/humanities disciplines (history, philosophy, anthropology, political sciences, literature; age range: 20-30 years, M = 21.96, SD = 2.65). The *ASD group* included 23 individuals with ASD (8 women, 15 men, range: 18-55 years, M = 27.91, SD = 10.70). The ASD group was significantly older than both control groups ($F(2,115) = 8.89$, $p < .001$). To account for this fact, age was used as a covariate in all statistical analyses. All participants were recruited via public announcement and filled the EQ-F and AQ-F in a quiet room. Individuals with

ASD were recruited via the *Fédération Québecoise de l'autisme et des autres troubles envahissant du développement (FQATED)* and *the Société de l'autisme des Laurentides (SARL)*. Both centers are community-based groups that cater to the social needs of individuals with ASD. They provide information, resources and settings in which social activities are planned. Diagnostic evaluations are not performed at the center. All ASD participants reported to have an IQ in the normal range and received a formal diagnosis of ASD from a psychiatrist using DSM-IV criteria for AS/HFA.

Translation

All items from the EQ and AQ were translated by a panel of three bilingual experts in the field of psychology and verified by a certified translator. Each member of the panel translated all scales from English to French. Individual translations were compared and discrepancies were reduced through discussion. Final versions were then back translated into English from French, and discrepancies further discussed and reduced through an iterative review process. At the end, only one translated statement raised concerns about its validity, item 16 of the EQ. However, given that it is a filler item with no impact on the EQ score, it remained in the final version. For all scales, scoring methods were left unchanged from original versions (Baron-Cohen *et al*., 2001; Baron-Cohen & Wheelwright, 2004).

5.4. Results

Five individuals from the SG and 3 from the HG were rejected from the analysis because they either filled the questionnaires incorrectly or reported having been diagnosed with a psychopathology. Mean total scores for EQ-F and AQ-F from each group are presented in Table 1. Distribution of AQ-F and EQ-F scores are shown in Figure 1 and 2. Separate ANOVAs were conducted for the EQ-F and AQ-F with *Group* and *Sex* as between-subject factors and age as covariate.

For the EQ-F scale, ANOVA analysis revealed significant main effects of *Sex* ($F(1,112) = 19.13$, $p < .001$) and *Group* ($F(2,112) = 15.46$, $p < .001$) with no interaction between factors ($F(2,112) = .87$, $p = .42$). Post hoc comparisons (Bonferonni) revealed that EQ-F scores were significantly lower for the ASD group compared to the SG ($p < .001$) and HG ($p < .001$) control groups. There was no significant difference between the SG and HG groups ($p = .132$). Finally, women scored significantly higher than men in all groups (all $p < .05$). To determine a useful cutoff score to differentiate clinical from typical groups, the percentage of individuals scoring at or above each score was calculated. A score of 33 points generated the largest difference between the ASD and control groups, such that 79.2% of individuals with ASD scored at or below this score compared to only 29.8% of control individuals.

For the AQ-F scale, ANOVA analysis revealed significant main effects of *Sex* ($F(1,112) = 5.90$, $p = .02$), and *Group* ($F(2,112) = 34.80$, $p < .001$) with no interaction between factors ($F(2,112) = .202$, $p = .82$). Post Hoc comparisons (Bonferonni) revealed that AQ-F scores were significantly higher for the ASD group compared to the SG ($p < .001$) and HG ($p < .001$) groups. Given the absence of significant differences between the SG and HG groups, data were collapsed for the remaining analyses. There was a significant sex difference (men scoring higher than women) in the collapsed SG\HG group ($F(1,90) = 12.71$, $p = .01$) but not in the ASD group ($F(1,21) = .43$, $p = .52$). On all five AQ-F subscales, the ASD group scored significantly higher than the SG/HG group (t-tests, all $p < .05$). To determine a useful cutoff score to differentiate clinical from typical groups, the percentage of individuals scoring at or above each score was calculated. A score of 22 points generated the largest difference between the ASD and control groups, such that 75% of individuals with ASD scored at or below this score compared to only 14.4% of control individuals.

To determine the relationship between the EQ-F and AQ-F, correlation analysis was performed between individual scores for all groups. A significant negative correlation was obtained in the SG ($r(43) = -.47$, $p = .001$) and HG ($r(45) = -.34$, $p = .02$) groups. However, presumably due to the small sample size, the correlation in the ASD group failed to reach significance ($r(21) = -.39$, $p = .07$). Finally, the internal consistency of the EQ-F and AQ-F (including its five subscales) was assessed by computing Cronbach's alpha coefficients (Table 2). Given the small sample size data from the three groups was collapsed. Satisfactory levels of internal consistency were obtained for the EQ-F (.83) and AQ-F (.81) scales. The AQ-F subscales, containing only 10 items each, yielded somewhat lower alpha coefficients, ranging from .41 (Imagination) to .75 (Social Skills). Pearson correlations between each AQ-F subscales and total score were also calculated (Table 3).

5.5. Discussion

The purpose of the present study was to validate French-Canadian versions of the EQ and AQ, two self-administered scales tapping important aspects of social cognition. Overall, data are consistent with those reported in the original English versions. Namely, *i*) people with ASD scored significantly lower than typical individuals on the EQ-F, whereas they scored significantly higher on the AQ-F; *ii*) EQ-F and AQ-F scores were inversely correlated in all groups; *iii*) gender differences were found in control groups on the EQ-F and AQ-F. A significant difference between the *sciences* and *humanities* groups was not found. Taken together, these data suggest that the EQ-F and AQ-F scales can be used in research settings. Further validation studies are needed to clearly establish the clinical value of the AQ-F, but in line with previous reports (Baron-Cohen *et al.*, 2001; Woodbury *et al*., 2005), it appears that it may have some utility as a screening tool to determine the need for additional evaluation or referral. Furthermore, the AQ seems to have good cross-cultural validity, as a recent large-sample study conducted in Japan reported values and group differences that were similar to the original English version

and the French translation described here (Wakabayashi, Baron-Cohen, Uchiyama, Yoshida, Kuroda, & Wheelright, 2006).

Despite the close concordance, there were some discrepancies between the French and English versions of both instruments. Whereas the cutoff score that best discriminates between the ASD and control groups on the EQ-F is comparable in both versions (33 vs 30), its discriminative power is lower in the EQ-F, as 70% of individuals with ASD scored below the cutoff point compared to 81.1% in the English sample (Baron-Cohen & Wheelwright, 2004). A similar pattern was also found with the AQ-F, as 75% of individuals with ASD in our sample scored above the cutoff point, compared to 79% in the original version. The cutoff score on the AQ-F was also much lower than that reported in the original English sample (22 vs 32). However, a subsequent study using the AQ[8] also reported that a lower cutoff score (26) differentiated best individuals later diagnosed with ASD from others. On the other hand, the small sample size used in this study may explain part of the discrepancies, which may also reflect selection bias. Indeed, participants with ASD were recruited through organizations that set up and promote social contact. It is therefore plausible that individuals taking part in these activities display increased social abilities and interest compared to typical ASD persons. In addition, the sex ratio in our ASD group (1,9:1) was different from that used in the original sample (2,6:1) (Baron-Cohen & Wheelwright, 2004). The inclusion of a larger proportion of female participants with ASD in our sample may also have contributed to the differences with the English version. Finally, male participants with ASD scored significantly higher than females with ASD on the AQ-F. Although there was a significant trend to that effect in the Japanese and English versions of the AQ, it did not reach statistical significance (Baron-Cohen *et al*, 2001; Wakabayashi *et al*., 2006). More studies are needed to determine the significance of this minor discrepancy, as cross-cultural differences are unlikely to explain the data. A weakness of the current study is the lack of strict diagnostic and matching procedures. IQ was not formally tested

in the ASD and control groups, and diagnosis was based on DSM-IV criteria. Although these factors may have contributed to the discrepancies between the current results and those of the original validation study (Baron-Cohen *et al*., 2001), we tried to follow their procedure as closely as possible. Now that French versions of the instruments are available, it is of significant importance to address these issues by testing patients using standardized instruments for diagnosis and IQ.

5.6. Conclusion

It appears that the AQ-F and EQ-F are valuable instruments in research settings dealing with French-speaking populations, both normal and pathological. Despite the small sample size, the present data were remarkably similar to those obtained on Japanese and English versions of both scales. In light of the recent resurgence of interest for social neuroscience, tools probing different aspects of social behavior are greatly needed. Because of its validity in establishing the level of autistic and empathic traits in normal individuals, as well as those with ASD, French-speaking researchers in many research fields will undoubtedly benefit from the availability of short, easy to administer instruments probing fundamental aspects of the social brain.

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5.8. Tables and Figures captions

Table 1 : Means and SDs for AQ-F and EQ-F total scores by group and gender.

Table 2: Cronbach's alpha (α) of EQ-F, AQ-F and AQ-F subscales.

Table 3: Correlations between each AQ-F subscales and AQ-F total score.

Figure 1: Distribution of AQ-F scores in percentage for the Science (n=45), Humanities (n=47) and ASD (n=23) groups.

Figure 2: Distribution of EQ-F scores in percentage for the Science (n=45), Humanities (n=47) and ASD (n=23) groups.

Table 1.

Groups		AQ-F	EQ-F
Humanities			
All (n= 47)	M	14,63	39,98
	SD	9,34	4,97
Males (n=32)	M	15,41	38,36
	SD	5,01	9,23
Females (n=15)	M	12,87	43,53
	SD	4,53	5,51
Science			
All (n=45)	M	17,04	36,42
	SD	5,41	8,89
Males (n=32)	M	17,94	34,18
	SD	5,66	6,83
Females (n=13)	M	14,69	41,92
	SD	3,68	10,13
ASD			
All (n=23)	M	27,36	26,65
	SD	5,73	9,79
Males (n=15)	M	29,87	21,40
	SD	5,33	7,69
Females (n=8)	M	26,50	33,75
	SD	4,72	9,75

Table 2.

Scales	α
EQ-F	0.83
AQ-F	0.81
AQ-F Subscales	
Social skills	0.75
Attention switching	0.53
Attention to details	0.58
Communication	0.70
Imagination	0.41

Table 3.

	Social Skills	Attention switching	Attention to details	Communication	Imagination
Social Skills	-	-	-	-	-
Attention Switching	0.50*	-	-	-	-
Attention to details	-0.006	0.13	-	-	-
Communication	0.70*	0.49*	0.11	-	-
Imagination	0.38*	0.17	0.10	0.37*	-
AQ-F total score	0.80*	0.71*	0.41*	0.82*	0.59*

*$p<0.001$

Figure 1.

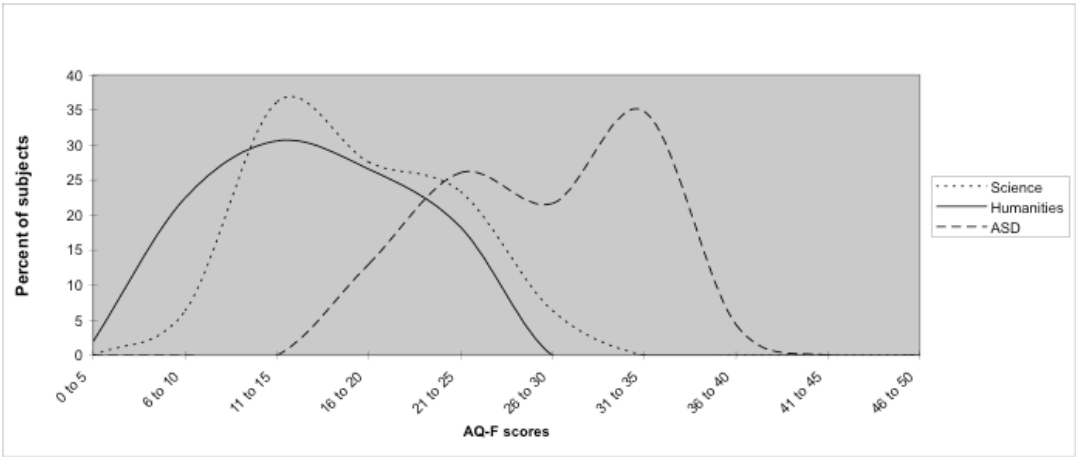
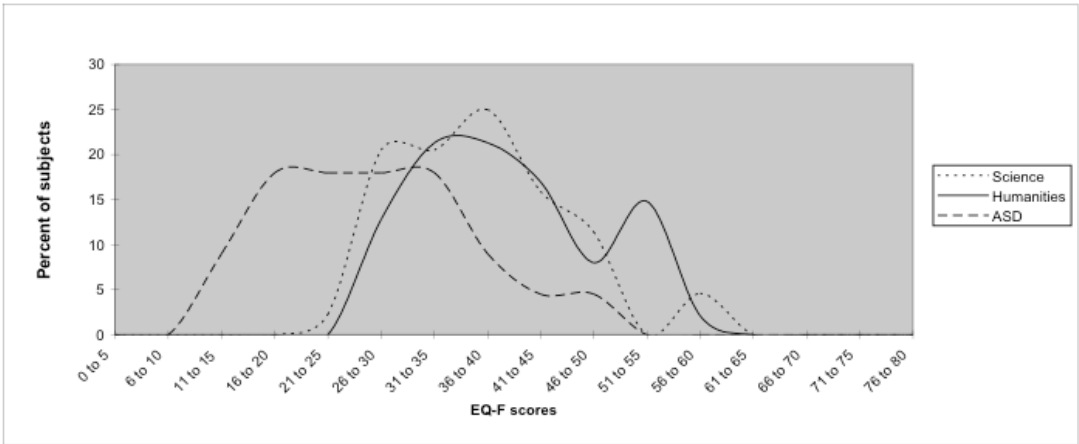

Percent of subjects
40
35
30
25
20
15
10
5
0
0 to 5
6 to 10
11 to 15
16 to 20
21 to 25
26 to 30
31 to 35
36 to 40
41 to 45
46 to 50
AQ-F scores
Science
Humanities
ASD

Figure 2.


Percent of subjects
30
25
20
15
10
5
0
0 to 5
6 to 10
11 to 15
16 to 20
21 to 25
26 to 30
31 to 35
36 to 40
41 to 45
46 to 50
51 to 55
56 to 60
61 to 65
66 to 70
71 to 75
76 to 80
EQ-F scores
Science
Humanities
ASD

Chapitre 6

Article 5

Early non-specific modulation of corticospinal excitability during action observation

European Journal of Neurocience, 2010, 31(5), 931-937

Early non-specific modulation of corticospinal excitability during action observation

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Article publié dans *European Journal of Neuroscience*, 31(5), 931-937, 2010

6.1. Abstract

Activity of the primary motor cortex (M1) during action observation is thought to reflect motor resonance. Here, we conducted three studies using TMS-induced motor evoked potentials (MEPs) of the first dorsal interossus muscle (FDI) during action observation to determine 1) the time course of M1 corticospinal excitability during the observation of a simple finger movement; 2) the specificity of M1 modulation in terms of type of movement and muscle; and 3) the relationship between M1 activity and measures of empathy and autistic traits. In a first study, we administered single TMS pulses at 30ms intervals during the observation of simple finger movements. Results showed enhanced corticospinal excitability occurring between 60 and 90ms after movement onset. In a second experiment, TMS induced MEPs were recorded from the FDI and abductor digiti minimi (ADM) muscles while pulses were delivered 90ms after movement onset during observation of simple finger movement and dot movement. Increased corticospinal excitability was restricted to finger movement and was present in both muscles. Finally, in an exploratory experiment, single TMS pulses were administered at 30, 90 and 150ms after movement onset and participants were asked to complete the Empathy Quotient (EQ) and the Autism Spectrum Quotient (AQ). Correlational analysis revealed a significant link between motor facilitation at 90 ms and the EQ and AQ scores. These results suggest that corticospinal excitability modulation seen at M1 during action observation is the result of a rapid and crude automatic process, which may be related to social functioning.

Keywords: TMS, motor cortex, mirror neurons, motor resonance mechanism, action observation

6.2. Introduction

Since the discovery of mirror neurons (MN; Gallese *et al.,* 1996; Rizzolatti *et al.,* 1996) in the monkey brain, numerous studies have sought to describe a similar system in the human brain. An impressive body of literature now points to striking similarities in brain activity during the performance and the observation and/or hearing of motor acts. This motor resonance mechanism, often called the human mirror neuron system (hMNS), is hypothesized to play an important role in various cognitive and social processes, ranging from imitation to intention understanding (Rizzolatti & Craighero, 2004). In humans, one of the first demonstrations of motor cortex involvement in action perception was made using transcranial magnetic stimulation (TMS) (Fadiga *et al.,* 1995). When applied over primary motor cortex (M1), single-pulse TMS induces a corticospinal volley that results in an involuntary muscle contraction that can be measured with electromyography (motor evoked potential; MEP). MEPs can be used to quantify the motor output resulting from the depolarization of cortical neurons through TMS stimulation. When intensity is held constant across experimental conditions, the variation in MEP amplitude is thought to reflect heightened or diminished M1 corticospinal excitability (Pascual-Leone *et al.,* 1998). Using this technique, Fadiga and collaborators (1995) showed that MEP amplitudes recorded from the hand significantly increased when participants passively observed hand movements, supporting the idea that the perceived action was mapped onto the onlooker's motor system. Motor facilitation during action observation has since been replicated numerous times (Aziz-Zadeh *et al.,* 2002; Maeda *et al.,* 2002; Strafella & Paus, 2000; Urgesi *et al.,* 2006) and it is now well established that motor resonance effects found in motor cortex are muscle-dependent rather than direction dependent (Alaerts *et al*., 2009), are highly modulated by experience (Catmur *et al*., 2007) and are causally linked to activity in premotor cortex (Avenanti *et al*., 2007). Finally, single-pulse TMS studies of motor resonance may

reveal direct facilitation of motoneurons or reflect downstream modulation from known MN areas such as premotor cortex (Fadiga et al., 2005).

Despite the fact that M1 recruitment during action observation is widely accepted and that single-pulse TMS is commonly used to assess various properties of human motor resonance, basic information regarding the time course of this activity is relatively sparse (see Hauk et al., 2008 for review). It has been shown with TMS that motor cortex facilitation follows the temporal course of the observed action. For example, corticospinal excitability increases with larger finger aperture during a grasping movement whereas it progressively decreases as the hand closes (Gangitano *et al.,* 2001). Furthermore, modulation of corticospinal excitability is strictly in phase with an observed cyclic movement, such that the time course of MEP increases and decreases follows the same pattern as the observed hand action (Borroni *et al.,* 2005). Another important issue with regards to timing is determining when the earliest motor cortex response to action observation occurs in M1. This is of considerable interest to assess the level of automaticity of the M1 response and to develop optimal TMS paradigms that take into account the specific temporal pattern of its activity. It has been reported that activity in primary motor cortex during observation of hand (Nishitani & Hari, 2000) and lip (Nishitani & Hari, 2002) actions occurs relatively late in the activation sequence. It was found that M1 activation occurred after that of occipital, superior temporal, inferior parietal and inferior frontal cortex, roughly 350ms after movement initiation (Nishitani & Hari, 2000, 2002). A recent MEG study, however, reported the presence of fast resonance effects in M1 through the use of neuromagnetic lateralized readiness fields, which occurred as early as 83ms after movement initiation (van Schie *et al.,* 2008). Arguing in favor of the existence of a fast resonance mechanism, it has also recently been shown with TMS that corticospinal excitability increases in the motor cortex representation of tongue muscles as early as 100ms after auditory presentation of peudo-words containing consonants requiring tongue movements (Roy *et al.,* 2008).

Whether observation of simple hand movements, a classical MNS task, also produces rapid corticospinal excitability modulation detectable with TMS is an open issue.

Beyond simple motor-mapping taking place through direct matching mechanisms, the hMNS has received considerable attention for its hypothesized relationship with skills related to the social domain. Shortly after their discovery, Gallese and collaborators (1996) suggested that MN could be at the core of social understanding. According to the motor theory of empathy, a basic action mapping system would contribute to higher order cognitive processes such as emotional sharing and empathy. In healthy individuals, brain activity during the execution and observation of hand and mouth actions greatly overlaps. Interestingly, the extent to which these regions are activated during action observation positively correlates with subscales of the Interpersonal Reactivity Index (IRI; Davis, 1983), a widely used measure of empathy (Gazzola *et al.,* 2006; Kaplan & Iacoboni, 2006; Pfeifer *et al.,* 2008). Furthermore, evidence from clinical populations in which social deficits are prevalent, such as autism spectrum disorders (ASD), also suggests a link between empathy and the hMNS (Bernier *et al.,* 2007; Dapretto *et al.,* 2006; Oberman *et al.,* 2005; Théoret *et al.,* 2005; Williams *et al.,* 2006). Of particular interest is an fMRI study conducted in children with ASD in which activity of the inferior frontal gyrus, a core region of the hMNS, was negatively correlated with the severity of social symptoms (Dapretto *et al.,* 2006). These studies support the idea that social cognition is related to hMNS functioning, and that its activity can be measured through simple action observation paradigms. However, despite the increasing number of studies addressing this topic, the relationship between hMNS activity and an individual's psychological characteristics remains uncertain. Indeed, most studies showing a hMNS-social cognition link relied on measures of empathy derived from the IRI, which has been questioned by some for its validity and interpretation (Baron-Cohen & Wheelwright, 2004; D'orazio, 2004).

Here, we conducted three complementary studies specifically designed to assess 1) the time course of M1 activity during action observation; 2) the specificity of M1 activity during action observation; and 3) the relationship between M1 activity and empathic and autistic traits in a non-pathological sample. In a first study, we used a chronometric single-pulse TMS approach to assess the time-course of M1 activity following the observation of a simple finger movement. TMS-induced MEPs were acquired at 30ms intervals during the presentation of videos showing either a single index-finger movement of the right hand or a control video showing a static hand. Based on timing data obtained from the first study, we then determined whether M1 modulation was specific to the muscle involved in the action and restricted to biological movement. Finally, we investigated the link between M1 activity and measures of empathy (Empathy Quotient; Baron-Cohen & Wheelwright, 2004) and autistic traits (Autism Spectrum Quotient; Baron-Cohen *et al.,* 2001).

6.3. Experiment 1

6.3.1. Materials and methods

Participants. Data were obtained from 10 right-handed volunteers (5 females, mean age = 23.0 years, sd = 1.3) recruited via public announcement. All subjects reported being in good physical and mental health, having normal vision and not being on psychoactive medication. Written informed consent was obtained and the experimental protocol was approved by the *Comité d'éthique de la recherche de la Faculté des arts et des sciences* of the Université de Montréal.

Stimuli. Participants were asked to watch two different videos showing: 1) a rapid movement of the index finger of the right hand towards a colored dot and back to its original position; and 2) an immobile hand. Videos were identical until the onset of the movement occurring at 2008 ms after the beginning of the clip. One type of movement and one static hand were depicted and both were in the egocentic view. Each

video presentation was followed by a seven second interval where a grey screen was presented. Videos were presented 100 times each in random order. In order to maintain a good level of attention, the color of the dot was digitally changed in one quarter of the trials and participants were asked to count the number of colored dot presentations.

Procedure and task. The experiment took place in a Faraday room. Participants were comfortably seated one meter away from a 17" high-resolution computer screen set at eye level for the duration of the procedure. Participants were instructed to passively watch the videos and count the number of colored-dot presentations. Prior to video presentation, baseline corticospinal excitability was assessed by acquiring ten MEPs while the participants passively watched a fixation cross on the computer screen. TMS-induced MEPs from the right FDI were acquired once per video presentation, at one of ten randomly selected time-points ranging from 0 to 270ms, starting at movement onset and separated by a 30ms interval. The same time-points were used for the control video showing a static hand. A total of ten MEPs were acquired at every time point for each video. The procedure was divided in two 18-minute sessions with a 10-minute rest interval. The presentation of stimuli and the timing of TMS stimulation were managed by PsyScope X running on a MacBook Pro computer (Apple, Cupertino, USA).

TMS stimulation and MEP recording. TMS was delivered with a Medtronic Magpro X 100 TMS device (Medtronics, Minneapolis, USA) with a 80-mm-diameter figure-of-eight coil. The current waveform was biphasic and the coil was angled 45^{o} from the midline with the handle pointing backward. Pulses were delivered over the left primary motor cortex corresponding to the hand region. MEPs were recorded from electrodes placed over the contralateral first dorsal interosseus (FDI) muscle and a circular ground electrode was placed over the participants' wrist. The electromyographic signal was amplified using a Powerlab 4/30 system (ADInstruments, Colorado Springs, USA), filtered with a band pass 20-1000Hz and digitized at a sampling rate of 4 KHz.

MEPs were recorded using Scope v4.0 software (ADInstruments, Colorado Springs, USA) and stored offline for analysis. Prior to the experimental procedure, the stimulation site eliciting MEPs of maximal amplitude was determined. The intensity of stimulation was individually defined to reliably elicit MEPs of approximately 1mV in the FDI at rest. To ensure stable coil positioning throughout the experiment, a Brainsight neuronavigating system (Rogue Research Inc., Montréal, Canada) marking the site of stimulation was used. For each condition, peak-to-peak amplitudes of the collected MEPs were measured and averaged at each time point. Ratios were then computed using the fixation cross as baseline. In order to reduce the number of comparisons without losing information, we averaged consecutive time-points. A repeated measures ANOVA was conducted on the ratios with *condition* (movement, static) and *time* (0-30ms, 60-90ms, 120-150ms, 180-210ms, 240-270ms) as factors.

6.3.2. Results

Sphericity of the data was verified prior to performing statistical analysis (Mauchly's test, $p > 0.05$). A repeated measures ANOVA with *condition* (movement and static) and *time* (0-30ms, 60-90ms, 120-150ms, 180-210ms, 240-270ms) as factors was performed. This analysis revealed a main effect of *time* ($F = 2.68$; $p = 0.047$), no main effect *condition* ($F = 0.85$; $p = 0.38$) and a significant interaction between factors ($F = 3.38$; $p = 0.019$). Post-hoc comparisons (Bonferroni corrected) showed that the 60-90ms time cluster differed significantly between conditions with the movement condition inducing greater MEP values that the static condition ($p = 0.006$; Figure 1).

6.4. Experiment 2

6.4.1. Materials and methods

Participants. Data were obtained from 10 right-handed volunteers (6 females, mean age = 22.5 years, sd = 1.71) recruited via public announcement. All subjects

reported being in good physical and mental health, having normal vision and not being on psychoactive medication. Written informed consent was obtained and the experimental protocol was approved by the *Comité d'éthique de la recherche de la Faculté des arts et des sciences* of the Université de Montréal.

Stimuli. Participants were asked to watch three different videos showing: 1) a rapid movement of the index finger of the right hand towards a colored dot and back to its original position (same as in Experiment 1); 2) an immobile hand (same as Experiment 1); and 3) Movement of a red dot on a black background matching the kinematics of a simple finger movement.

Measures and procedure. The apparatus was the same as in Experiment 1 except for the fact that MEPs were recorded simultaneously from the FDI and abductor digiti minimi (ADM). Based on data obtained in Experiment 1, single TMS pulses were delivered at the time point at which the condition effect was maximum (90 ms after movement onset). Each video was presented 10 times in random order. A ratio was computed using the fixation cross as baseline (MEP at 90ms / MEP baseline).

6.4.2. Results

Sphericity of the data was verified prior to performing statistical analysis (Mauchly's test, $p > 0.05$). A repeated measures ANOVA with *condition* (finger movement, dot movement, static) and *muscle* (FDI, ADM) as factors was performed. This analysis revealed a main effect of *condition* ($F = 3.56$; $p = 0.050$), where corticospinal excitability was greater in the finger movement condition compared to dot movement and static hand (Figure 2). No other main effect or interation was significant (all $p > 0.05$).

6.5. Experiment 3

6.5.1. Materials and methods

Participants. 12 right-handed volunteers (5 females, mean age = 22.5 years, sd= 2.21) participated in this experiment. In order to maximize variability in the sample, participants were selected on the basis of their score on the Empathy Quotient obtained from a validation study of this scale in French (Lepage *et al.,* 2009), and those scores were used in the current study. None of the participants were aware of the aim of the study nor took part in the first experiment.

Stimuli, measures and procedure. French-versions of the Empathy Quotient (EQ) and the Autistic Spectrum Quotient (AQ) were used (Lepage *et al.,* 2009). The apparatus was the same as in Experiment 1, but the static and non-biological-movement conditions were not presented. Single pulse TMS was administered at 90ms after movement onset, as well as 30ms and 150ms after movement onset. Ten MEPs were acquired at each time point presented in random order. A ratio was computed using the fixation cross as (MEP at 90ms / MEP baseline). Pearson's correlations were conducted between normalized MEP amplitude, EQ total score, and AQ total score.

6.5.2. Results

Pearson's correlations revealed a significant link between motor cortex modulation at 90ms and both the EQ ($r = 0.663$; $p = 0.019$) and AQ ($r = -0.689$; $p = 0.013$) scales (Figure 3). There was no significant correlation between motor cortex activity at 30 or 150ms and total scale scores (both $p > 0.05$)

6.6. General Discussion

As expected, our results replicated previous findings showing increased corticospinal excitability during the passive observation of hand actions (Aziz-Zadeh *et al.,* 2002; Izumi *et al.,* 1995; Mercier *et al.,* 2008; Urgesi *et al.,* 2006). The chronometric

approach used here allowed to precisely map the time course of M1 activity during this process, revealing a rapid modulation occurring between 60 and 90ms after movement onset. A second experiment showed that although increased corticospinal excitability was present only during observation of biological movement, the effect was non specific as it was found in both recorded muscles. Furthermore, a third experiment showed that modulation of M1 corticospinal excitability is associated with empathic and autistic traits, supporting the hypothesis that the hMNS is involved in social cognition.

Fast motor resonance

Few studies have directly investigated the time course of M1 corticospinal excitability during action observation. While suggesting a close temporal coupling between M1 activity and the sequence of an observed action (e.g. Borroni *et al.,* 2005; Gangitano *et al.,* 2004), most studies did not directly address the question of when M1 activity *first* occurs. The rapid M1 activity reported in the present study contrasts with what would be expected from classical hMNS descriptions (Rizzolatti & Craighero, 2004). Besides what is believed to be 'mirror areas', namely the premotor cortex (Di Pellegrino et al., 1992), the inferior parietal lobule (Rozzi *et al.,* 2008) and arguably the primary motor cortex (Tkach *et al.,* 2007), the hMNS receives contributions from the superior temporal sulcus (STS), a region known to be sensitive to biological motion (Perret *et al.,* 1990). Usually, activity within this network is though to be sequential and this view has received support from Nishitani and colleagues (2000, 2002, 2004), who looked at the sequence of cortical activation during action observation with MEG. Their results are in accordance with an orderly and sequential organization of hMNS activity, as visual regions were activated first (≈118ms), followed by the STS (≈193ms), the inferior parietal lobule (≈224ms), the inferior frontal gyrus (≈255ms), and finally M1 (≈345ms). The timing of M1 activity reported by Nishitani and collaborators suggests that motor mapping taking place at M1 is the end result of a relatively long process. This

late activity contrasts sharply with our results, which suggest the existence of a more direct route that bypasses the 'classical' pathway from visual cortical areas to M1.

Interestingly, early modulation of corticospinal excitability occured in the ADM muscle although it was not directly involved in the observed movement. This is at odds with previous findings that found muscle-specific MEP increases during obsevation of simple finger movements (e.g, Fadiga et al., 1995; Maeda *et al*., 2002; Catmur *et al*., 2007). In light of the fact that corticospinal facilitation was not found during observation of a still hand or dot movement, the data presented here suggest that early resonance relies on crude mapping of action information. This is consistent with two recent studies that reported early motor facilitation that differed from later modulations in terms of complexity. Using TMS, Roy and collaborators (2008) showed motor facilitation of phonological properties during speech perception 100ms after stimulus presentation. This rapid increase in corticospinal excitability was distinct from later modulations that were related to higher-order cognitive processes such as lexical and semantic interpretation (Roy *et al.,* 2008). A distinction between early-automatic and late effects was also suggested by van Schie and collaborators (2008) who reported the presence of neuromagnetic lateralized readiness fields 83ms after movement onset during observation of goal-directed movements. Significantly, this early effect was the same whether or not the observed finger movement was made to a correct or incorrect target, suggesting the existence of a fast, low-level resonance that is independent of higher-order considerations. Along with the present data, these studies suggest that motor resonance relies on at least two different mechanisms. First, as shown here, crude mapping of the observed action may occur rapidly and be independent of the involved muscle. A second, slower computation would then provide a more refined matching, taking into consideration specific muscle activity, goal inference and action understanding. The present data thus suggest that the properties of motor responses to observed actions differ according to the processing stage. Further experiments are

needed to precisely detail the time course of muscle-specific responses that occur during the observation of hand actions and to determine whether muscle specificity is present at the body-part level.

Finally, it should be noted that the temporal dynamic of early M1 activity during action observation remains to be fully determined. Van Schie and collaborators (2008) have suggested that fast modulation of M1 is the product of a specialized mechanism devoted to biological motion perception that would rely on the contribution of the STS. Given the speed of at which M1 is modulated, however, one may argue in favor of a more direct route, perhaps involving direct thalamo-M1 projections. Furthermore, although it has been established that MEP modulation during action observation is not related to changes in spinal excitability (Baldissera et al., 2001; Patuzzo et al., 2003), much remains to be learned about spinal influences on *early* motor resonance effects. In that respect, further studies are necessary to fully understand the neurophysiology of fast motor resonance.

Motor resonance and social cognition

Although the idea that social cognition is linked to hMNS function in not new (Gallese *et al.,* 1996), it has only recently gained experimental support (Dapretto *et al.,* 2006). The present exploratory study adds to recent experimental evidence by showing a strong correlation between corticospinal excitability increases during simple action observation and measures of social function. Increasing evidence points to a link between the hMNS and social competence. Most of this evidence comes from studies of individuals with ASD in which social deficits are a defining feature. It has been shown that hMNS response during action observation is different from that of neurotypical individuals (Bernier *et al.,* 2007; Martineau *et al.,* 2008; Oberman *et al.,* 2008; Théoret *et al.,* 2005; but see Avikainen *et al.,* 1999). Furthermore, the severity of social impairment in individuals with ASD appears to be negatively correlated with hMNS

activity, such that less activity in inferior frontal gyrus during observation of emotional expressions is associated with greater social impairment (Dapretto *et al.,* 2006). The data reported here suggest that this relationship also holds true in neurotypical individuals. Indeed, our data show that subclinical displays of autistic traits are related to diminished hMNS activity at the motor cortex level. To our knowledge, this is the first study to link the presence of autistic traits in the healthy population with corticospinal excitability during action observation. In line with these data, a previous TMS study using a similar action observation paradigm revealed reduced corticospinal excitability in individuals with ASD during finger movement observation (Théoret *et al.,* 2005). In this population, reduced motor facilitation was found when the observed hand was in the egocentric position and not when in was in allocentric view. Whether or not a link between autistic traits and motor facilitation in healthy participants is also present when the observed hand is presented in allocentric view is an open question that warrants further investigation.

Despite accumulating evidence, the association between hMNS activity and ASD has been questioned on conceptual and methodological grounds (Southgate & Hamilton, 2008; Dinstein *et al.,* 2008). Particularly relevant is the question of the specifity of hMNS dysfunctions in explaining social impairments in ASD and the fact that a presumed deficit in motor resonance cannot account for the entire spectrum of ASD symptomatology (Dinstein *et al.,* 2008). While many of the criticisms that have been put forward with regards to the hMNS/ASD link are certainly valid, the current data suggest that autistic traits can be *related* to a basic motor resonance mechanism involving simple action observation. Whether there exists a causal relationship between the two concepts, however, remains to be fully determined.

Although it has been frequently discussed, there have been relatively few demonstrations of a functional link between motor resonance and psychological

constructs such as empathy in healthy individuals. The most convincing evidence in favor of such a relationship comes from a series of fMRI studies where activity in hMNS was found to correlate with subscales of the IRI such as the Empathic Concern scale, which measures other-oriented feelings of sympathy and concern (Gazzola *et al.,* 2006; Kaplan & Iacoboni, 2006; Pfeifer *et al.,* 2008). While theses studies did not report M1 activity, they nonetheless suggest that activity within parts of the hMNS is related to empathy. It should also be noted that the relationship between personality traits such as anxiety (Wassermann et al., 2001) and psychopathic traits (Fecteau et al., 2008) has been shown previously. In the present study, corticospinal excitability was positively correlated with EQ scores, which is not surprising since the EQ and AQ scales are *negatively* correlated and tap into overlapping concepts (Wheelwright *et al.,* 2006). This strengthens the idea that efficiency of early motor resonance is related to psychological traits, abilities and preferences, related to social functioning. Of course, empathy is a very complex phenomenon and it can hardly be reduced to a pairing process taking place at M1. Understanding actions, emotions and thoughts requires higher-order cognitive processes that can be dissociated from the automatic, low-level matching mechanism described here. Nevertheless, it would appear that early hMNS function might provide some of the information that is required to build an empathic response based on the actions and emotions of others. Finally, it must be noted that the emergence of a significant correlation between M1 activity and empathy in this specific design may be accounted for by methodological factors that were overlooked in previous studies. First, there may be a limited time-window at which M1 is specifically responsive to motor resonance mechanisms. Secondly, previous studies may have selected a more homogenous sample than the one used here. For example, we previously failed to demonstrate a correlation between corticospinal excitability and empathy using a similar design where participants were mostly undergraduate psychology students (Désy & Théoret, 2007). In the present study, however, care was taken to select participants with a wide distribution of AQ and EQ scores, which may explain the positive results.

Finally, some methodological limitations related to the demonstration of an EQ/AQ-action observation link should be pointed out. The absence of a static hand control weakens the conclusions that can be drawn from the present data. Indeed, expectancy effects related to seeing the hand move as well as anticipation of the TMS pulse may have modulated corticospinal excitability. Furthermore, a phenomenon akin to the "visual enhancement of touch" (Fioro & Haggard, 2005) may also explain corticospinal excitability increases in that observation of an immobile body could increase motor cortex activation. Following on this, individuals with higher EQ/lower AQ scores may simply be more susceptible to expectancy or body effects. On the other hand, it may still be argued that the reported relationship does reflect resonance mechanisms since correlations between corticospinal excitability and EQ/AQ scores were only found at 90ms following movement onset (not at 20ms or 150ms). This is the specific time point where resonance effects were found in motor cortex and corticospinal excitability in the static hand condition was not modulated by time. Despite this caveat, the present data suggest a link between psychological constructs and corticospinal excitability. Further studies with larger samples are needed to determine to what level empathy and autistic traits in healthy populations can modulate corticospinal excitability during action observation.

6.7. Acknowledgements

This work was supported by grants from the National Sciences and Engineering Research Council of Canada and the Fonds de la Recherche en Santé du Québec (HT). JFL is supported by a Canada Graduate Scholarship Doctoral Award from the Canadian Institutes of Health Research

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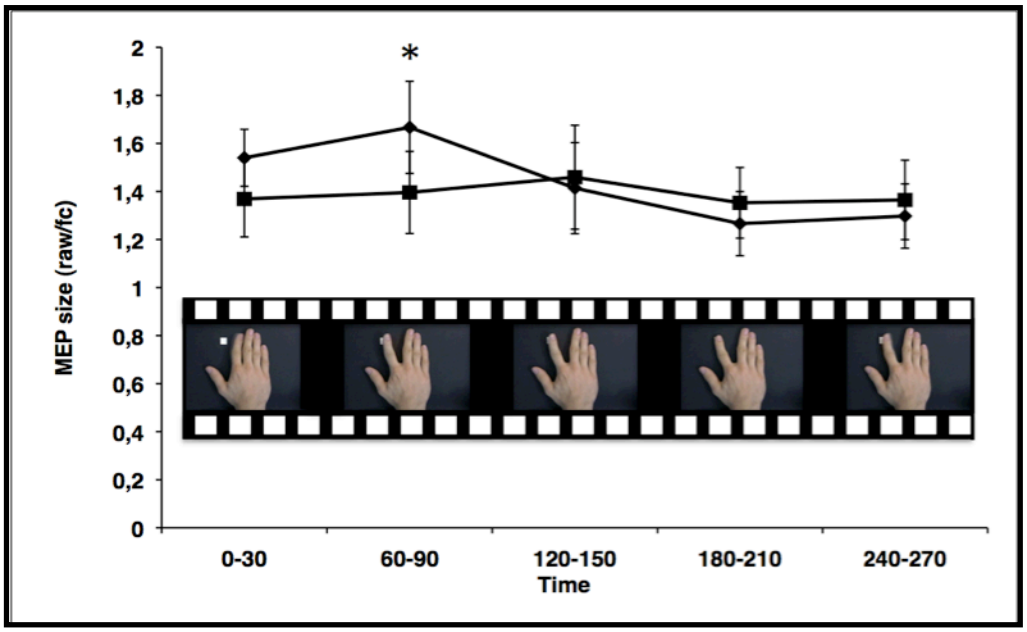
6.9. Figure legends

Figure 1. Average normalized MEP values for each condition (movement and static) and time-frame (0-30, 60-90, 120-150, 180-210, 240-270ms). Only the 60-90ms time cluster differed significantly between conditions. Error bars represent standard error of the mean.

Figure 2. Average normalized MEP values for each condition (dot movement, hand movement, still hand) for the FDI and ADM muscles.

Figure 3. A) Correlation between normalized MEP values at 90ms and the Empathy Quotient ($r= 0.663$ $p = 0.019$). B) Correlation between normalized MEP values at 90ms and the Autistm Spectrum Quotient ($r = 0.689x$; $p < 0.013$).

Figure 1.


MEP size (raw/fc)
2
1,8
1,6
1,4
1,2
1
0,8
0,6
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0,2
0
*
0-30
60-90
120-150
180-210
240-270
Time

Figure 2.

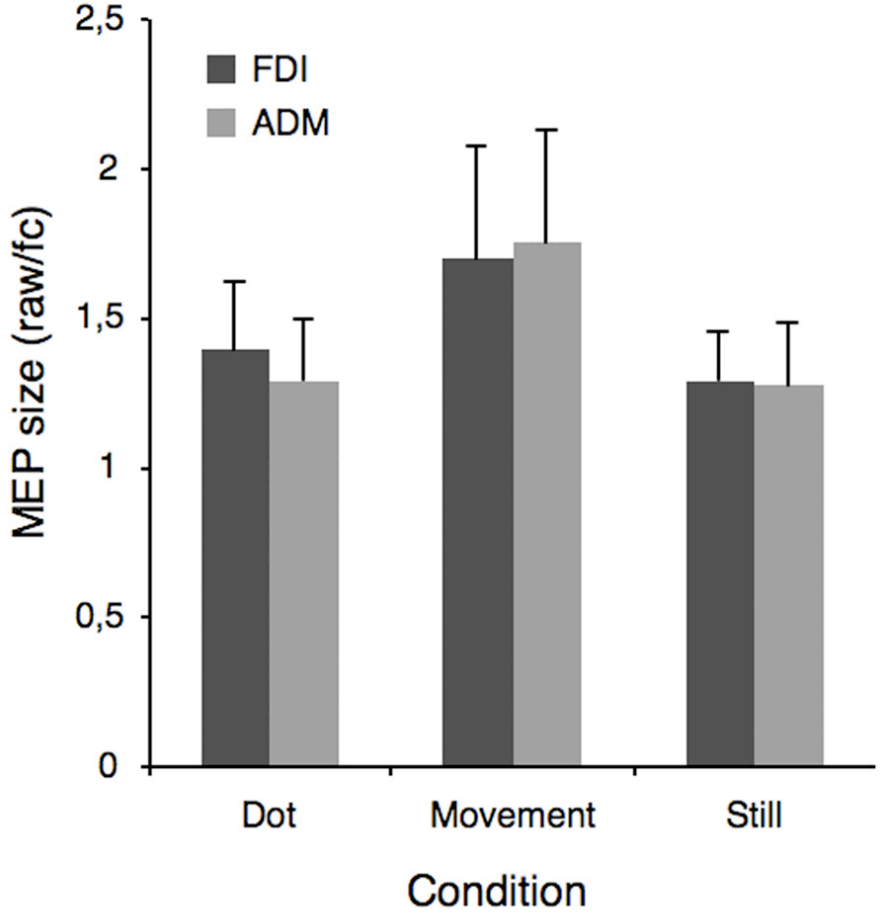
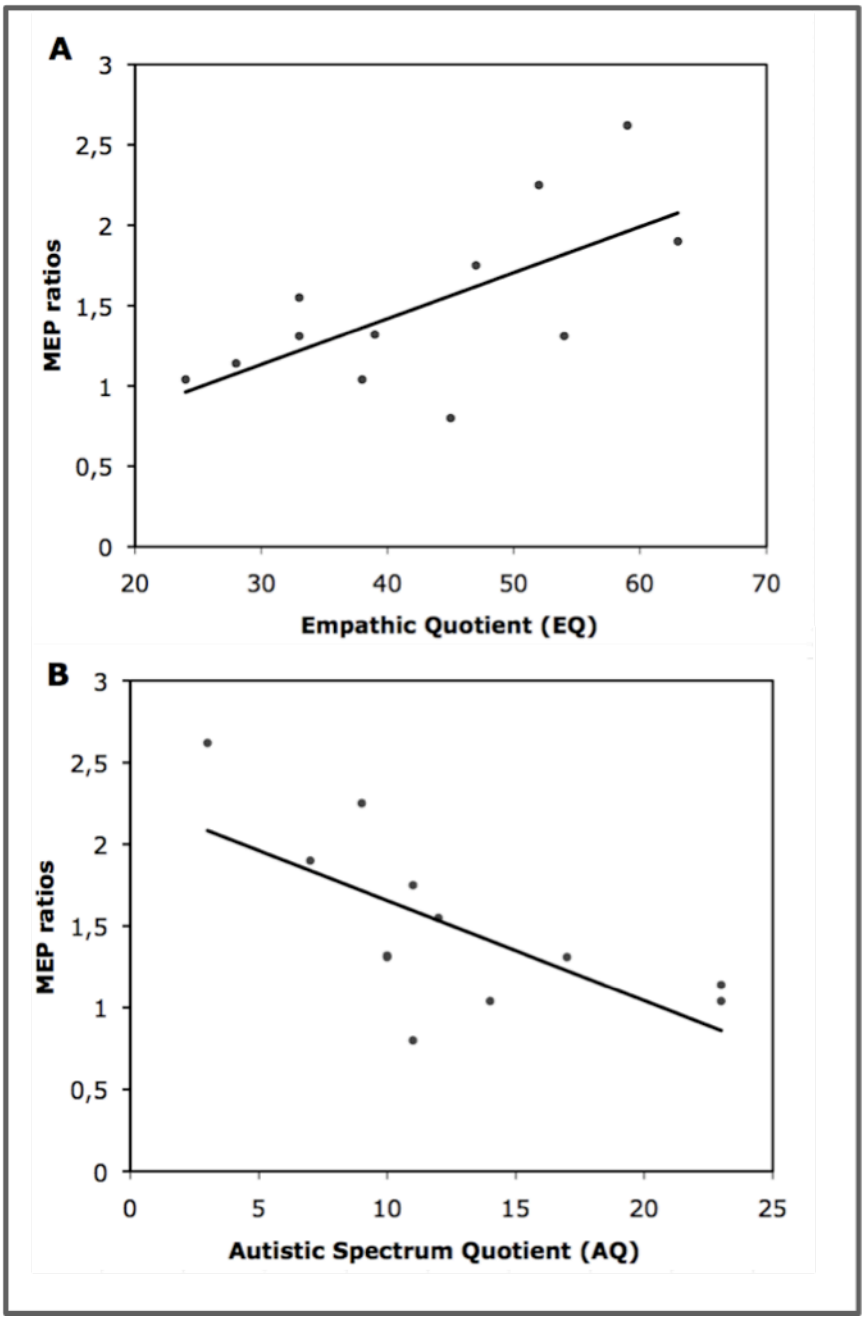

2,5
2
1,5
1
0,5
0
FDI
ADM
MEP size (raw/fc)
Dot
Movement
Still
Condition

Figure 3.


A
MEP ratios
3
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Empathic Quotient (EQ)
B
MEP ratios
3
2,5
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1,5
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0
0
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25
Autistic Spectrum Quotient (AQ)

Chapitre 7

Article 6

EEG and neuronavigated single-pulse TMS in the study of the observation/execution matching system: are both techniques measuring the same process?

***Journal of Neuroscience Methods*, 2008, 175(1), 17-24**

EEG and neuronavigated single-pulse TMS in the study of the observation/execution matching system: are both techniques measuring the same process?

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Article publié dans le *Journal of Neuroscience Methods*, 2008, 175(1), 17-24

7.1. Abstract

It is now well established that the human brain is endowed with a system that matches the observation of actions with their execution. At the motor cortex level, EEG mu rhythm modulation (8-12Hz) and TMS-induced motor evoked potentials (MEPs) are two techniques commonly used to assess brain activity during action observation. While both techniques have reliably demonstrated similarities in the pattern of activity induced by action production and action observation, the relationship they bear with each other remains elusive. In the present study, we combined ongoing EEG recordings and single pulse TMS during the execution, imagination and observation of simple hand actions. Relationship between MEPs and EEG frequency bands at the individual level was investigated. Our results replicate those obtained independently with both techniques: a significant increase in MEP amplitude and a significant attenuation of the mu rhythm during action observation, imagination and execution compared to rest. Surprisingly, we found no significant correlation between MEP amplitude and mu rhythm modulation. However, modulation in the low to midrange beta (12-18Hz) was related to MEP size during the rest and execution conditions. These results suggest that although mu rhythm and TMS-induced MEPs are sensitive to motor resonance mechanisms, they may reflect different processes taking place within the observation/execution matching system.

7.2. Introduction

In the last decade, the primary motor cortex (M1) has been associated with a number of cognitive processes that go well beyond simple motor production (Carpenter et al., 1999; Molnar-Szakacs et al., 2005; Richter et al., 2000). Indeed, it now seems that what was once thought to be a unimodal motor production area is also recruited by higher-order cognitive processes where no motor output is required. One of the newly discovered properties of M1 that has garnered the most attention is its ability to respond to the passive observation of motor acts as though the observer was actually performing the action (Tkach et al., 2007). Using a variety of brain imaging techniques, studies have pointed out striking functional similarities between the patterns of M1 activity seen during the execution and passive observation of motor acts (Fadiga et al., 2005). In both instances, common regions are not only activated but the mapping is surprisingly refined, such that enhanced activity seen in M1 during action observation is specific to the muscles recruited in the observed action (Fadiga et al., 1995; Strafella and Paus, 2000). Moreover, there is a close temporal coupling between the seen action and the muscle-specific increase in cortical excitability (Gangitano et al., 2001). These findings, combined with the discovery of cells in the macaque brain that respond to the execution and observation of actions (mirror neurons; Rizzolatti et al., 1996), have led to the formulation of the motor resonance hypothesis (Rizzolatti and Craighero, 2004). While the exact role of this system is still a matter of debate, it is thought to contribute to action understanding and imitation (Rizzolatti and Craighero, 2004).

When applied over M1, single-pulse transcranial magnetic stimulation (TMS) induces a corticospinal volley that produces an involuntary muscle twitch in the corresponding body part of the motor homunculus that can be reliably measured with electromyography (the motor evoked potential; MEP). TMS-induced MEPs can be used to quantify the motor output resulting from the depolarization of cortical neurons through TMS stimulation. MEP amplitude varies as a function of TMS intensity, but it is

also sensitive to factors that influence corticospinal excitability (Pascual-Leone et al., 1998). When intensity is held constant across experimental conditions, the variation of amplitude observed in MEPs is thought to reflect heightened or diminished M1 excitability. Using this technique, Fadiga and collaborators (1995) provided the first evidence of an observation/execution matching mechanism in human M1. They showed that MEP amplitudes recorded from the hand significantly increased during conditions in which participants passively observed hand movements. This motor facilitation during action observation has since been replicated in numerous studies (Aziz-Zadeh et al., 2002; Maeda, et al., 2002; Strafella and Paus, 2000; Urgesi et al., 2006). It also seems that observation of action is not necessary to elicit motor facilitation, as mere imagination of a movement can be sufficient to increase corticospinal excitability. Indeed, studies investigating motor visualization (or motor imagery), in which the individual is asked to rehearse within working memory a dynamic movement, also showed increased MEP size compared to baseline conditions (Izumi et al., 1995; Mercier et al., 2008; Stinear et al., 2006). These data strongly suggest that different motor embodiments, externally as well as internally generated, are mapped onto the cortical representation of an onlooker's motor system.

Another indicator of sensorimotor activity that is increasingly used in the study of motor resonance mechanisms is the EEG mu rhythm (Bernier et al., 2007; Lepage and Théoret, 2006; Muthukumaraswamy et al., 2004; Oberman et al., 2005; Oberman et al., 2008; Stroganova et al., 2007). Located in the alpha band (8-12 Hz) and of maximal amplitude over central sites (C3-C4) at rest, the mu rhythm is strongly suppressed during the performance of controlateral motor acts (Pineda, 2005). Desynchronisation of the mu rhythm over central sites during motor performance is believed to reflect M1 recruitment through thalamocortical input. The hypothesis that decreased mu rhythm power is related to cortical activation is supported by simultaneous EEG and fMRI studies showing a negative relationship between EEG alpha rhythms power and the fMRI

BOLD signal (Laufs et al., 2006). Recent studies have shown that observation (Muthukumaraswamy et al., 2004) and imagination (Pfurtscheller and Neuper, 1997) of motor actions are sufficient to attenuate rolandic mu rhythm amplitude. In the absence of overt movement, diminution of this sensorimotor rhythm is thought to be the product of fronto-parietal networks that map a perceived action onto the motor system, which ends up modulating activity within motor regions (Pineda, 2005). The pattern of M1 activity during both the execution and the observation of motor acts is congruent with the hypothesis that mu rhythm modulation reflects the activity of motor resonance mechanisms in the human brain. Moreover, much like single-pulse TMS studies have shown, it seems that mu rhythm modulation within sensorimotor areas is specific to the cortical region corresponding to the body part recruited in the observed or imagined movement (Pfurtscheller et al., 2006).

Modulation of oscillatory brain activity has been linked to changes in cortical excitability (Pfurtscheller, 2001) and although increased amplitude of the TMS-induced MEP and blocking of the mu rhtyhm during action observation/execution/imagination has been well-documented, the link between both measures has not been directly investigated. In the visual system, individuals who display lower alpha band power at rest over posterior areas also show higher visual cortical excitability as indexed by phosphene threshold (Romei et al., 2008). Furthermore, at a trial-by-trial level, low prestimulus alpha band power has been associated with increased visual cortex excitability (Romei et al., 2007). In motor cortex, however, the link between oscillatory fluctuations and corticospinal excitability is less clear. In a recent study, Mitchell and collaborators (2007) reported only weak correlation between EEG activity and size of the TMS-induced MEP during a precision grip. In the present study, we combined continuous EEG recordings and single-pulse TMS to investigate motor resonance mechanisms. Both measures were acquired during the performance, the imagination and the observation of actions to determine whether both methods, which are widely used in

the study of motor resonance, would correlate at the individual level. One crucial prerequisite to allow the establishment of a relationship between TMS-induced MEPs and EEG oscillations is the stability of measurements. With this in mind, we used a neuronavigating system to ensure stable coil positioning throughout the experimental procedure.

7.3. Materials and methods

Participants

Data were obtained from 16 right-handed volunteers (8 females, 8 males, 20-28 years-old; mean age = 24.75 years, s.d. = 2.86) with no history of neurological disorders. All subjects reported being in good health, having normal vision and not being on psychoactive medication. Written informed consent was obtained and the experimental protocol was approved by the *Comité d'éthique de la recherche de la Faculté des arts et des sciences* of the Université de Montréal.

EEG

The experimental procedure took place in a Faraday room. EEG was acquired from four 8mm carbon electrodes (Easycap, Herrsching-Breitbrunn, Germany) located on C3-Cz-C4 and Oz sites of the International 10-20 system of electrode placement. While only electrodes over central sites (C3, Cz, C4) are indicative of sensorimotor cortex activity, the Oz location over occipital cortex was used as a control site. EEG was recorded using Scan 4.2 Acquisition Software (Neuroscan, Charlotte, USA) running on a PC computer and amplified using a Neuroscan NuAmps system (Neuroscan, Charlotte, USA). EEG was digitized at 1000 Hz, with a bandpass filter of 0.1-100Hz. All electrode impedances were inferior to 5 kΩ. A grounding electrode was placed on the forehead of the participant with the reference averaged from electrodes located on the left and right ears.

TMS

TMS was delivered with a Medtronic Magpro X 100 TMS device (Medtronics, Minneapolis, USA) with a 80-mm-diameter figure-of-eight coil. To minimize electromechanical noise on the EEG recordings, a customized shielding device made of 5mm-thick rubber-foam was positioned between the coil and the subject's head during stimulation sessions. The current waveform was biphasic and the coil was angled 45^{o} from the midline with the handle pointing backward. Pulses were delivered over the left primary motor cortex corresponding to the hand region. MEPs were recorded from electrodes placed over the contralateral first dorsal interosseus (FDI) muscle and a circular ground electrode was placed over the participants' wrist. The electromyographic signal was amplified using a Powerlab 4/30 system (ADInstruments, Colorado Springs, USA), filtered with a band pass 20-1000Hz and digitized at a sampling rate of 4 KHz. MEPs were recorded using Scope v4.0 software (ADInstruments, Colorado Springs, USA) and stored offline for analysis. Prior to the experimental procedure, the stimulation site eliciting MEPs of maximal amplitude was determined. The intensity of stimulation was individually defined to reliably elicit MEPs of approximately 1mV in the FDI at rest. To ensure stable coil positioning throughout the experiment, a Brainsight neuronavigating system (Rogue Research Inc., Montréal, Canada) marking the site of stimulation was used.

Stimuli and experimental procedure

Participants were comfortably seated one meter away from a 17" high resolution computer screen set at eye level for the duration of the procedure. EEG recordings and TMS-induced MEPs from FDI were acquired during four different conditions randomly presented in blocks, each lasting approximately seven minutes. Conditions were made of 40 trials, each lasting four seconds with a seven second inter stimulus interval. Participants were asked to 1) *Observe* a video showing a real-sized hand applying pressure on a stress ball with the index and thumb; 2) *Visualize* what it feels like to

actually perform this same movement; 3) *Perform* the action with the right hand; and 4) *Rest* and imagine the front of their home. Participants were asked to keep their eyes open during the imagery condition. To increase compliance during the visualization condition, and to better match the speed of execution during the *perform* and *visualize* conditions to the video shown in the *observe* condition, a cue indicating the beginning and the end of the movement was presented for the length of the trial on the computer screen. EEG was acquired continuously while TMS pulses were delivered over on the left primary motor cortex randomly between 2000 and 3000 ms after the beginning of each trial. The presentation of stimuli (videos and cues), the timing of TMS stimulation and the marking of the events on the EEG recording were managed by PsyScope X running on a MacBook Pro computer (Apple, Cupertino, USA) (Figure 1).

Electrophysiological data analysis

Offline analyses of EEG data were performed using BrainVision Analyzer (Brain Products, Gilching, Germany). EEG was segmented in epochs of 2000 ms preceding the trigger indicating the TMS pulse. Obtained segments were inspected visually to eliminate epochs with artefacts. A minimum of 30 segments of sufficient quality for each condition was required for further analysis. If this criterion was not met for one of the conditions, the participant was discarded. Fast Fourier Transformation (FFT) was performed for each electrode on kept segments (2000 points Hanning window) and resulting power magnitudes (V^2) were averaged for each condition. The frequency band corresponding to mu rhythm for each subject was defined by subtracting the *perform* condition from the *rest* condition. The resulting 2Hz bandwith best resembling mu desynchronization was selected as the individual's mu frequency band (Babiloni et al., 1999). Logarithmic transformations were performed on EEG data to achieve Gaussian distributions. A repeated measures ANOVA was conducted with *electrode* (C3, Cz, C4, Oz) and *condition* (perform, visualize, observe and rest) as factors. For MEP data, peak-to-peak amplitudes of the collected MEPs (40 per condition) were measured, averaged

for each condition, and log transformed to achieve a Gaussian distribution. A repeated measures ANOVA was conducted with *condition* as factor. The relationship between mu rhythm modulation and MEPs in each condition was assessed by correlating mu rhythm and MEP amplitude (Pearson's test). In addition to the mu rhythm, variations in other frequency bands in relationship with MEP amplitude were investigated in exploratory analyses. The EEG spectrum was divided in 2Hz frequency bands ranging from 4 to 40Hz and correlated with MEP amplitude in each condition.

7.4. Results

Four subjects were rejected from analysis, two due to an insufficient number of clean segments to perform spectral analysis, and two because we were unable to define a mu band (no desynchronization occured in the alpha band during the *perform* condition compared to *rest*). Twelve subjects were thus included in the analysis. The average mu frequency band was 9-11 Hz. Sphericity of the data was verified (Mauchly's test, $p > 0.05$) and a repeated measures ANOVA with *electrode* (C3, Cz, C4, Oz) and *condition* (perform, observe, visualize and rest) as factors was performed. There were main effects of *condition* ($F(3,9) = 10.76$; $p < 0.001$) and *electrode* ($F(3,9) = 6.28$; $p < 0.005$) (Figure 2a). The interaction was also significant ($F(9,3) = 3.31$; $p < 0.001$). To correct for multiple comparisons, a Bonferroni correction was applied to all subsequent contrast analyses (= 0.0087) of the interaction. Differences between each level of the *condition* factor were further investigated with separate ANOVAs for each electrode (Bonferroni corrected, = 0.0125). All four ANOVAs were significant (all $p < 0.003$). Subsequently, paired t-tests were performed between conditions for each electrode (Bonferroni corrected, = 0.0087). These analyses revealed that in all three electrodes situated over central sites (C3, Cz, C4), mu rhythm amplitude was significantly higher during *rest* compared to the *observe*, *visualize* and *perform* conditions (all $p < 0.004$). All other comparisons were not significant. The Oz electrode displayed a slightly different pattern, where only the *observe* and *visualize* conditions differed from *rest* (both $p < 0.004$).

Indeed, unlike what was witnessed over central sites during the performance of a hand movement, namely a significant reduction of mu rhythm amplitude, the *perform* condition did not induce a significant decrease of activity in Oz when compared to *rest* ($p > 0.05$).

For TMS data, a repeated measures ANOVA with *condition* as factor revealed a significant effect ($F(3,33) = 141.07$, $p < 0.001$) (Figure 2b). Post-hoc t-tests were carried out (Bonferroni corrected, $= 0.0087$), which showed that MEPs at rest were significantly lower than those of all other conditions (all $p < 0.003$). In addition, MEPs in the *perform* condition were significantly larger than every other condition (all $p < 0.001$). Finally, there was no significant difference between the *observe* and *visualize* conditions.

The relationship between MEP amplitude and mu rhythm modulation was evaluated using bivariate correlations between both measures for each condition. Given that electrodes over central sites displayed highly similar patterns of activity in all conditions, the three electrodes were pooled together to minimize the number of correlations carried out and enhance statistical power. All correlations turned out to be not significant, ranging from -.186 (*observe*) to -.322 (*perform*) (rest, -.302; visualize, -.227). Moreover, the absence of significant correlation persisted even when we adopted a less stringent definition of the mu rhythm (the whole 8-13Hz alpha band; Bernier et al., 2007; Oberman et al., 2005). To further rule out the presence of any significant relationship between MEP amplitude and mu power, three additional correlations were computed: *i*) MEP size and mu power at electrode C3 (contralateral to right-hand MEPs); *ii*) after correction for the possible effects of variability in alpha-power/MEP-size by computing relative changes with respect to baseline (*rest* condition); and *iii*) with a shorter, 1-second window prior to the TMS pulse. All additional correlations were non-significant.

Finally, to look if the activity in other frequency bands could be related to MEP amplitude, exploratory analyses were carried out without correcting for multiple comparisons. Power spectrum between 4 and 40Hz of the pooled electrodes was segmented into twenty-2Hz frequency band. Resulting power for each band was correlated with MEP amplitude for each condition (Figure 3). Only the *perform* and *rest* conditions showed significant correlation coefficients ($p < 0.05$, uncorrected). In both conditions, these correlations were found for frequency bands situated between 12-18Hz.

7.5. Discussion

Our results show that although TMS-induced MEPs and EEG mu rhythm are modulated during action observation, visualization and execution, these two measures do not correlate with each other at the individual level. This lack of relationship is found despite faithful replication of previous results using these techniques in similar paradigms; namely, a significant increase in MEP amplitude and a significant attenuation of mu rhythm during action observation, imagination and execution (Fadiga et al., 1995; Li, 2007; Muthukumaraswamy et al., 2004; Pfurtcheller et al., 2006). This finding is surprising given that both measures are though to reflect sensorimotor activity during motor matching processes.

Corticospinal excitability

As expected, observation, visualization and execution of a goal-directed hand movement increased M1 excitability compared to baseline. This is in agreement with a wealth of studies (e.g. Aziz-Zadeh et al., 2002; Izumi et al., 1995; Mercier et al., 2008; Urgesi et al., 2006), which indicates that the experimental procedure successfully elicited M1 activity in the absence of overt movement, presumably reflecting direct-matching mechanisms (Fadiga et al., 2005). Not surprisingly, the actual performance of

the hand action induced larger MEPs than every other condition, as muscular contraction prior to TMS stimulation is known to facilitate motor output by increasing the number of descending volleys and lowering the threshold of spinal motoneurons (Di Lazzaro et al., 1998). It was also found that visualization and observation of a hand action modulated M1 excitability to a comparable degree. This is interesting, given that although many studies have looked at motor facilitation induced by action observation and visualization separately, few have directly compared the degree to which they modulate M1 activity. However, in cases where both tasks were performed by the same participants, M1 activity was found to be highly similar with respect to both amplitude of the response and spatial overlap (Clark et al., 2003; Léonard and Tremblay, 2007; Munzert et al., 2008). Our data are consistent with these findings and suggest that externally and internally generated motor acts are equivalent at the level of M1, in line with the simulation theory of Jeannerod (2001). This is an important issue in light of the well-known effects of motor imagery on motor rehabilitation (see Mulder et al., 2007) and the possiblity that action observation may also improve rehabilitation in stroke patients (Ertelt et al., 2007).

Mu rhythm modulation

Our EEG data are also in line with previous studies suggesting that mu rhythm desynchronization can be viewed as a neural marker of motor matching mechanisms at the sensorimotor level (Pfurtscheller, 1997; Muthukumaraswamy et al., 2004; Pineda, 2005). Indeed, mu rhythm over central sites (C3, Cz, C4) was decreased compared to baseline when participants either watched, visualized or performed a goal-directed hand movement. Moreover, at control site Oz, mu power decreases were limited to the observation and visualization conditions. The absence of mu desynchronization during execution at Oz shows that the effect is spatially specific, as increases in activity during both execution and observation is a necessary condition for the direct matching of actions. This pattern of response at Oz was expected since observing and actively

visualizing movements involves visual cortical areas (Cui et al., 2007; Hari et al., 1997). It may be argued that the perform condition should also have elicited diminished activity at Oz since it was conducted with eyes open, in addition to the possibility that some participants were actively visualizing while they executed the action. The lack of change of change at Oz suggests that looking at the fixation cross during the perform condition refrained participants from engaging in imagery and produced negligible reductions in alpha power due to visual stimulation

It could be argued, however, that the rest condition should not differ from the visualization condition given that it also consists of mental imagery. Other processes at work during mental imagery could explain this result. One of them is the attention devoted to the task, as attention has been shown to modulate alpha brain rhythms in the occipital cortex during simple visual perception (Yamagishi et al., 2003). Visualization a dynamic hand movement is more engaging, and possibly more demanding, that imagining the front of a house, hence soliciting additional attentional resources. The nature of the imagined stimuli may also explain the difference between rest and visualization conditions at the Oz site. It has been shown that primary visual cortex is activated during mental imagery tasks requiring detailed image representation (Kosslyn et al., 1999) or involving active evaluation of object characteristics (Klein et al., 2000). It is therefore possible that imagery of the dynamic properties of the hand action explains the greater activity found at Oz compared to the static imagery of a house. Following on the issue of the rest condition, the absence of a non-motor control condition involving non-biological movement in the present study may hinder the claim that mu suppression can be specifically attributed to a motor action. This is unlikely, however, since prior studies compared mu responses to biological and non-biological movement at central sites and reported specific power decreases for the observation of biological actions (e.g. Cochin et al, 2001; Pineda et al., 2007). Finally, it is important to stress the fact that motor imagery can either involve the visual representation or the

mental simulation of an action. In the present study, participants were asked to imagine 'what it felt like' to perform the movement (kinetic imagery; KI), rather than produce a visual representation thereof (visual imagery; VI). Numerous studies have shown that KI more closely resembles the actual performance of a motor act (see Solodkin et al., 2004). Accordingly, it appears that increases in corticospinal excitability during motor imagery are limited to KI (e.g. Fadiga et al., 1999), as are sensorimotor activations (Solodkin et al., 2004). These data suggest that the imagery task used here was the most likely to produce patterns of motor activity reflected by both EEG and TMS. The relationship between visual imagery, corticospinal excitability and EEG oscillations, however, is an open issue that remains to be formally addressed.

Unlike M1 responses found with TMS, mu rhythm modulation during the execution of a motor act did not significantly differ from the visualization or observation conditions. Most studies using comparable paradigms have obtained similar results (e.g. Bernier et al., 2007; Oberman et al., 2005; see also Lepage et al., 2006; Muthukumaraswamy et al., 2004), where the execution condition produces mu power decreases highly concordant with those found during observation or imagery. One of the significant differences between both techniques is that electrophysiological recordings during TMS testing are obtained at the level of the muscle, whereas EEG measures reflect central activity directly. Hence, the fact that the muscle whose representation is probed in motor cortex is contracted when during TMS certainly increases the response amplitude.

Oscillatory activity and motor cortex excitability

One possible explanation for the absence of relationship between MEPs and mu rhythm is that one technique would not reflect M1 activity as it is commonly believed. That is, despite the fact that both measures seem to be reliable, the validity of one of them may be questioned. The most likely candidate for this is the mu rhythm, given that

it is highly improbable that MEPs recorded in this paradigm would be elicited by any other mechanism besides M1 stimulation. On the other hand, the source of mu rhythm as measured from scalp EEG is much more difficult to assess. Whereas most researchers tend to qualify the mu rhythm as "somatomotor" (Pineda, 2005), many MEG studies suggest a preponderance of somatosensory origins, situating its source in the post-central bank (S1) (Cheyne et al., 2003; Hari et al., 1997; Simões et al., 2004). Considering this, it is possible that mu rhythm modulation witnessed over central sites does not emanate from M1, but from the adjacent somatosensory cortex. As movements are inherently linked with their somatosensory feedback, the decrease in mu rhythm may not be due to the motor component of the performed or perceived action, but rather be associated with its sensory equivalent. This hypothesis is supported by the fact that 1) diminished sensory input is related to enhanced mu rhythm (Cheron et al., 2006); and 2) sensory stimulation over the hand strongly suppresses mu power, even in the absence of movement (Cheyne et al., 2003). Alternatively, it is possible that even if mu rhythm does originate from S1, its modulation could still be due to the "motoric" features of resonance mechanisms. As M1 and S1 bear important cortico-cortical connections (Classen et al., 2000), mu rhythm modulation taking place in S1 may be a by-product of upstream activity in M1, where the motor matching process is occurring.

Another explanation for the absence of a relationship between TMS-induced MEPs and mu oscillations may be related to the inherent variability of the measures. Indeed, the strength of correlation between two measures is limited by the reliability of the instruments used. If a given technique is correlated with itself, this degree of correlation cannot be expected to improve when that same technique is put in relationship with another instrument quantifying the same object of study. In other words, the internal reliability of the techniques used limits the strength of the correlation that can be expected. In the present study, one of the techniques used to assess cortical activity was the transcranial MEP. Although we have knowledge of no study that

investigated the reliability of MEPs in the study of motor resonance mechanisms, there is no reason to believe that the measurement of M1 activity is unreliable. It is well known that MEPs induced transcranially show high sweep-to-sweep variability (Ellaway et al., 1998; Kiers et al., 1993). However, when averaged, TMS measurements of motor cortex excitability have demonstrated good reliability. Indeed, in a test-retest design, motor threshold measured at the optimal site has been shown to be highly consistent from session to session, with an intraclass correlation ranging from .90 to .97 (Lefebvre et al., 2004; Malcolm et al., 2006). Regarding EEG, there is also no reason to believe that it is unreliable. Spectral analysis patterns have been shown to be highly reproducible over months and years when recorded at rest (Maltez et al., 2004; Vuga et al., 2006). Moreover, the intra-individual variability of most parameters, namely absolute power and alpha mean frequency, is less than the inter-individual variability found in the normal population, allowing identification of individuals based on their EEG signature (Näpflin et al., 2007; Poulos et al., 2002). Modulation of the alpha band during cognitive tasks also seems to be highly reliable. Evaluating the alpha fluctuation in different working memory and psychomotor tasks, McEvoy and collaborators (2000) reported correlation coefficients between sessions ranging from .90 to .97. Not surprisingly, the stability of EEG power bands seems higher than that obtained during event-related synchronization/desynchronization (ERS/ERD) periods (Neuper et al., 2005). This may be attributed to the summation of error of the measures required to compute ERS/ERD. Despite this, ERS/ERD measured from the alpha band (8-12Hz) at central sites show good reliability in individual participants, even across different tasks (Cronbach's alpha coefficient ≈ .77; Neuper et al., 2005). In the light of these data, it seems unlikely that the lack of relationship reported in the present study between mu rhythm and TMS-induced MEPs is due to the techniques' imprecision, as both measures show sufficient reliability to permit the detection of significant correlational relationships. It should be mentionned, however, that MEP size can be modulated by processes taking place outside the brain. For example, spinal contributions to MEP size that would likely not be

reflected in EEG may partly explain the lack of correlation between the two measures. As argued by Mitchell and collaborators (2007), electromyographic (EMG) activity may be a better predictor of TMS response amplitude than EEG oscillations since it reflects selected activity from regions of the motor cortex projecting to the muscle of interest. As such, it would be of great interest to determine whether EMG oscillations at the muscle level also reflect MEP size druing the observation and imagination of actions.

As mentioned previously, the source of rolandic alpha rhythms, which comprise mu oscillations, has been attributed to the somatosensory system, whereas beta oscillations appear to originate from primary motor cortex (Ploner et al., 2006; Salmelin and Hari, 1994; Salmelin et al., 1995). In a simultaneous EEG-fMRI study, it was found that spectral power negatively correlated with the fMRI BOLD signal in postcentral cortex for mu oscillations and precentral cortex for beta oscillations (Ritter et al., 2008). Furthermore, reductions in motor cortex excitability have been associated with the 20 Hz beta rebound that occurs after median nerve stimulation (Chen et al., 1999). Taken together, these data suggest that it is beta bands that should best correlate with TMS response amplitude (Rossini et al., 1991). Our exploratory analyses support this claim, as significant correlations between TMS-induced MEPs and spectral power were found for beta frequencies (12-18 Hz) only. It could thus be argued that TMS-induced MEPs reflect motor activity whereas mu oscillations represent the sensory aspects of the motor resonance system. This would explain the lack of a direct linear relationship between both measures at the individual level, since the two methods probe distinct systems within the brain. Interestingly, the relationship between beta oscillations and motor cortex excitability was limited to the rest and perform conditions. The additional mechanisms recruited during the observation or imagination of a hand movement may modify the balance between cortical excitability and oscillatory power, resulting in diverging patterns of activity at the motor cortex level. In light to the exploratory nature of these findings, further studies are necessary to determine the exact nature of beta

oscillations and motor cortex excitability relationships during motor resonance.

7.6. References

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7.7. Figure legends

Figure 1. A) Experimental setup. Position sensors placed on the participant's forehead and on the coil handle ensured stable coil positioning throughout the stimulation sessions using a frameless stereotaxic system. EEG was acquired from electrodes at C3, Cz, C4 and Oz while MEPs induced by TMS stimulation over the left primary motor cortex were recorded from electrodes located on the right hand (positive over FDI muscle). B) Timeline of the experiment. Videos lasted three seconds with a seven-seconds ISI. The TMS pulse was delivered randomly between 2000 and 3000 ms after the beginning of each trial. FFT was performed on the 2-second period preceding the TMS-pulse.

Figure 2. A) Average mu rhythm power (log V^2) for electrodes located at C3, Cz, C4 and Oz. For all electrodes, mu rhythm was significantly suppressed during both *visualize* and *observe* conditions compared to *rest*. However, unlike electrodes over central sites, the control electrode (Oz) was not significantly modulated during the *execute* condition. Error bars represent standard error of the mean. B) Average MEP amplitude (Log mV) for each condition (*perform, observe, visualize, rest*). *Execute* and *rest* elicited larger and smaller MEPs, respectively, than all other conditions while *observe* and *visualize* did not differ from each other. Significant differences ($p<0.01$) are marked by an asterisk. Error bars represent standard error of the mean.

Figure 3. Exploratory analyses showing the correlational strength between MEP amplitude and 4 to 40Hz EEG band power for each condition (2Hz frequency bins). For both *rest* and *execute*, EEG power was significantly correlated ($p<0.05$, uncorrected) for bins situated in low to midrange beta (12 to 18 Hz). Shaded areas represent mu rhtyhm frequencies.

Figure 1.

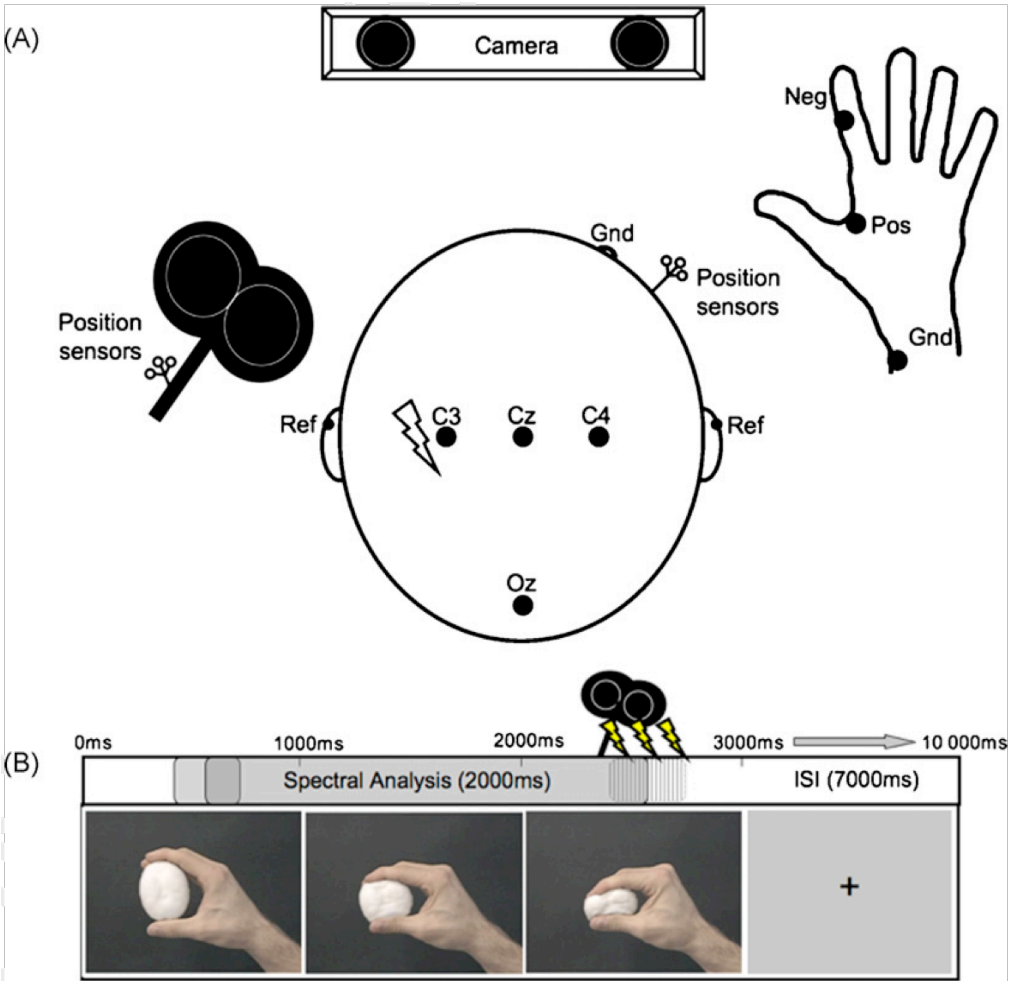

(A)
Camera
Neg
Pos
Gnd
Position sensors
Position sensors
Gnd
Ref
C3
Cz
C4
Ref
Oz
(B)
0ms
1000ms
2000ms
3000ms
10 000ms
Spectral Analysis (2000ms)
ISI (7000ms)
+

Figure 2.

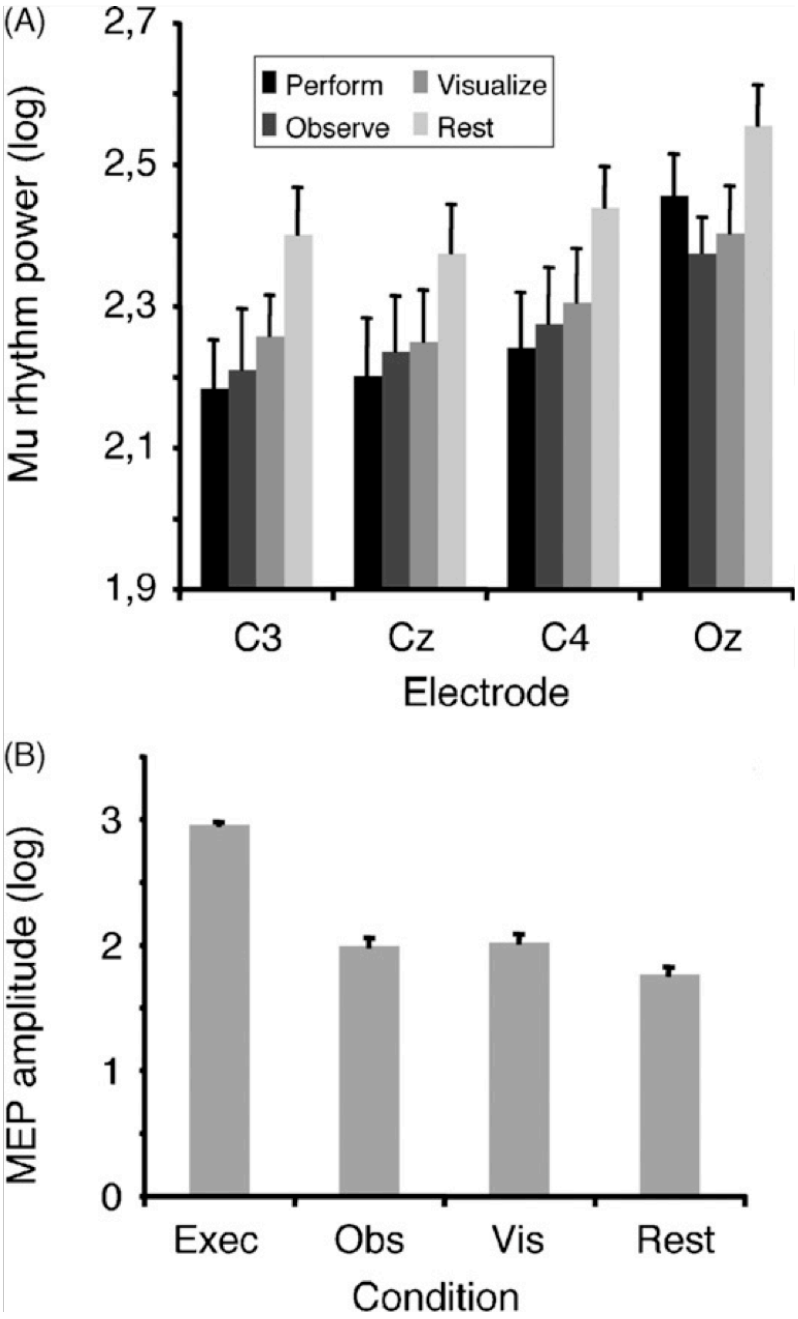
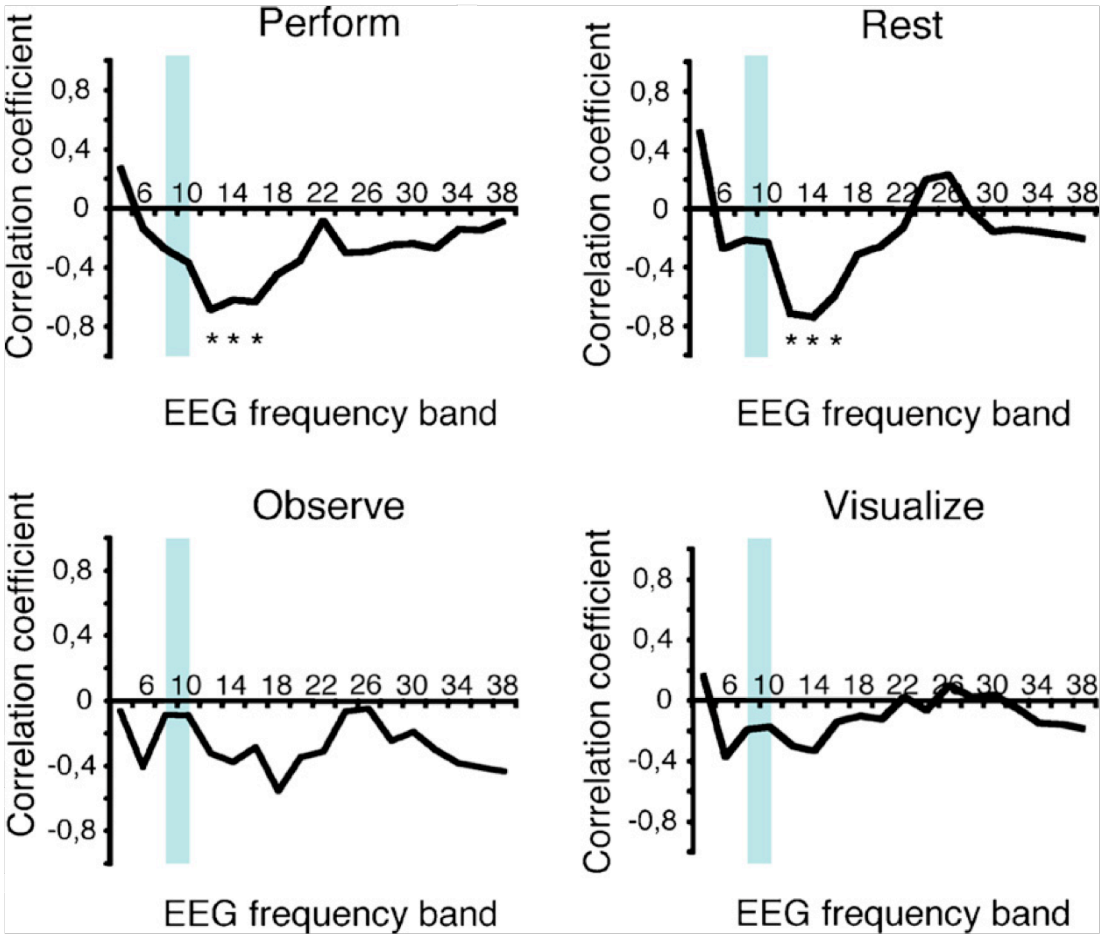

(A)
Mu rhythm power (log)
2,7
2,5
2,3
2,1
1,9
Perform
Visualize
Observe
Rest
C3
Cz
C4
Oz
Electrode
(B)
MEP amplitude (log)
3
2
1
0
Exec
Obs
Vis
Rest
Condition

Figure 3.


Perform
Rest
Observe
Visualize
Correlation coefficient
0,8
0,4
0
-0,4
-0,8
6 10 14 18 22 26 30 34 38
* * *
EEG frequency band

Chapitre 8 : Discussion

8.1. Discussion générale

Le but premier de la présente thèse consistait à documenter l'existence et le fonctionnement du SNMh chez l'enfant normal lors de l'observation d'actes moteurs dans les modalités visuelle et auditive. Cet objectif est au centre des études et des données présentées dans les articles 1, 2 et 3, où l'on présente des données neurophysiologique soutenant l'existence d'un système de résonance motrice plurimodal chez l'enfant. Le second objectif de cet ouvrage visait à déterminer le décours temporel de l'activité observé à M1 lors de l'observation d'actions et d'établir un lien avec la présence de traits autistique et empathique chez des individus normaux (études 4 et 5). Finalement, le troisième objectif de cette thèse consistait à déterminer la correspondance entre les processus neurophysiologiques mesurés par la SMT et l'EEG dans différents contextes de production et d'observation d'actions.

Cette discussion a pour but de revisiter les hypothèses émises et les résultats obtenus dans les six articles présentés, de les comparer avec les données récentes et de souligner les contributions faites par ces études à la littérature scientifique. Dans un premier temps, les articles documentant l'existence du SNMh chez l'enfant normal (articles 1, 2 et 3.) seront abordés. Subséquemment, les articles 4 et 5, qui traitent du lien entre les caractéristiques psychosociales et le système de résonance motrice seront visités. Il sera notamment question du rôle du SNMh dans les aptitudes sociocognitives de l'adulte sain et des caractéristiques spécifiques associées aux mécanismes de résonance de haut et de bas niveau. Finalement, les aspects méthodologiques liés aux outils d'investigation neurophysiologiques employés, la SMT et l'EEG, seront discutés.

8.2. Objectif 1: Le système de résonance motrice chez l'enfant

Comme nous avons vu dans la première étude (article 1) réalisée chez un groupe d'enfants d'âge scolaire, l'activité du cortex moteur est modulée lors de l'observation passive de mouvements de la main. Cette activité est spécifique au mouvement de préhension, alors qu'une main en extension seule n'induit pas une diminution significative du rythme mu aux sites centraux comparativement à une condition de repos. Par contre, à l'instar de la production motrice active, l'observation passive d'actions recrute la participation du système moteur et plus spécifiquement le cortex moteur primaire. L'analyse corrélationnelle effectuée entre l'âge des enfants et le niveau de désynchronisation de la bande de fréquence mu n'a pas mis en évidence une relation entre l'âge et l'activité du système de résonance motrice telle que quantifiée par l'EEG.

La première constatation qui peut être faite à l'égard de ces résultats est qu'ils répliquent fidèlement ce qui a été documenté chez l'adulte avec la même technique (Muthukumaraswamy et Johnson, 2004a). En effet, tout comme chez l'adulte, c'est la bande de fréquence mu, et non la bande delta comme certains l'ont suggéré (Cochin, Barthelemy, Roux, et Martineau, 2001), qui reflète l'activité des régions somatomotrices. Par delà la concordance des fréquences cérébrales liées à l'activité de M1 entre les populations infantile et adulte, ce sont surtout les similitudes fonctionnelles quant aux patrons de désynchronisation qui sont frappantes. En effet, on observe une gradation dans le niveau de désynchronisation mesuré dans les différentes conditions, soit, dans l'ordre, l'exécution d'action, l'observation d'un mouvement de préhension, l'observation d'une main ouverte en mouvement et la condition de repos ; une gradation comparable a été rapportée chez l'adulte (Muthukumaraswamy et Jonhson, 2004a).

À la lumière de ces faits, il paraît donc vraisemblable que le rythme mu peut être utilisé comme indicateur du niveau d'activité de M1 dans un contexte de perception d'action chez l'enfant. D'ailleurs, plusieurs études parues subséquemment supportent cet énoncé, alors que ces résultats ont été répliqués par des groupes indépendants (Martineau et al., 2008 ; Oberman et al., 2008). Cette technique a d'ailleurs été mis à profit afin de mettre en évidence des anomalies au sein du système de résonance chez des enfants présentant un trouble du spectre autistique (Martineau et al., 2008 ; Oberman et al., 2008).

Dans un deuxième temps, l'absence de lien entre l'âge de l'enfant et le niveau de diminution de la bande mu suggère que les mécanismes neuronaux qui y sont associés subissent peu ou pas de changement quantitatif au cours de ces années. Cependant, il est plausible que la taille restreinte de l'échantillon n'ait pu permettre l'émergence d'une corrélation significative. Advenant la confirmation ultérieure de l'absence d'un tel lien, cela soutiendrait l'idée que le SNMh d'enfants en bas âge est aussi sensible et apte à représenter l'action observée que celui de l'adulte. Il est important de souligner cependant que l'absence de changement quantitatif n'exclut d'aucune façon la présence d'altérations qualitatives du système. Il est probable, par exemple, que le SNMh d'enfants plus âgés présente une sensibilité accrue au mouvement d'autrui comparativement aux enfants plus jeunes envers certains types de mouvements. Hypothétiquement, l'utilisation de mouvements complexes, intransitifs ou abstraits, pourrait mettre en lumière une évolution quant au spectre de sensibilité du SNMh chez l'enfant au cours de son développement. Cette hypothèse est soutenue par la démonstration récente que le rythme mu parait être modulé en fonction des apprentissages et des compétences moteurs de l'enfant. Notamment, Elk et collaborateurs (2008) ont montré un lien entre le nombre de mois écoulés depuis l'acquisition de la marche et le niveau de diminution de la bande alpha chez de jeunes enfants durant l'observation de mouvements similaires. L'efficacité du pairage moteur

qui s'effectue au sein du SNMh, tel que mesuré par l'EEG quantitatif, semble ainsi être influencé par l'étendue du répertoire moteur et de la pratique. Il est donc concevable que l'expérience motrice chez les enfants plus âgés et les adolescents ait une influence similaire sur les patrons de réponse EEG lors de l'observation de mouvements complexes.

Ceci cadre d'ailleurs avec des études conduites chez l'adulte, où il a été démontré à maintes reprises que l'expérience motrice influençait l'activité du SNMh durant l'observation d'actions (Calvo-Merino et al., 2005 ; Cross, Hamilton, et Grafton, 2006; D'Ausilio, Altenmuller, Olivetti, et Lotze, 2006; Haslinger et al., 2005 ; Margulis, Mlsna, Uppunda, Parrish, et Wong, 2009). En effet, il a été montré que les sujets qui possèdent une expertise pour certains types de mouvements montraient une plus grande désynchronisation des rythmes alpha et beta lors de leur observation (Orgs et al., 2008). En lien avec ceci, des observations en IRMf montrent une activité accrue du SNMh lors d'observation de mouvements se situant dans leur domaine d'expertise (Calvo-Merino et al., 2005). En fait, la plasticité du SNMh est telle qu'il est possible de modifier relativement rapidement, et de façon importante, le patron de résonance suite à un entrainement intensif (Catmur, Walsh, et Heyes, 2007). Bref, même si le SNMh est fonctionnel chez l'enfant normal, il est vraisemblablement sculpté par les expériences motrices de l'individu, et se raffine sans aucun doute au cours du développement.

La deuxième étude (article 2), effectuée auprès d'une adolescente portant des électrodes sous-durales implantées, illustre la sensibilité du SNMh aux représentations sonores d'actions. Toujours en utilisant les rythmes cérébraux comme marqueurs de l'activité corticale, on y démontre le recrutement du cortex moteur lors de la perception de sons produits par la bouche ou par la main. Cette activité est spécifique à la région motrice impliquée dans la production motrice de l'action entendue, à savoir la

représentation de la main lors de l'audition de claquement de doigts. Grâce à l'analyse par ondelettes, on note deux périodes distinctes de modulation de la bande alpha : une modulation hâtive et brève autour de 100 ms, et une plus tardive et soutenue vers 350-450ms. Cette dernière période d'activité est accompagnée par une diminution de la puissance spectrale dans la bande beta (18-22Hz), qui est également reliée aux processus moteurs (Hari et al., 1998).

Les résultats de cette étude complémentent ceux de l'article 1 de plusieurs façons. D'une part, elle valide l'utilisation du rythme mu comme indicateur de recrutement cortical impliqué dans la perception d'actions. Ils démontrent aussi que le SNMh de l'enfant présente une propriété cruciale des NM telle que documentée chez le singe macaque, à savoir une sensibilité à la représentation d'actions dans plusieurs modalités sensorielles. Cette démonstration comble une lacune importante de la littérature, alors que la majorité des études conduites chez l'adulte, et la totalité des études portant sur le SNMh chez l'enfant publiéees à ce jour, n'utilisent que des stimuli visuels pour investiguer l'activité du SNMh. Elle constitue également un ajout important à l'étude précédente en fournissant des informations spatiales et temporelles quant aux mécanismes d'appariement moteur au sein de M1. En effet, on note que la modulation de rythmes cérébraux dans la région motrice de la main est spécifique aux sons produits par la main, alors que les sons buccaux n'engendrent aucune réponse dans cette même zone. Cette spécificité spatiale est en accord avec d'autres observations obtenues avec l'utilisation de la SMT, où la facilitation motrice était spécifique aux muscles recrutés dans l'action perçue (Maeda et al., 2002).

Au niveau temporel, la présence précoce d'activité dans M1 est surprenante, considérant les recherches antérieures portant sur la question. En effet, parmi les

quelques études portant sur le décours temporel de l'activité au sein du SMNh, Nishitani et collaborateurs rapportaient un patron d'activité hautement séquentiel, où M1 montrait une activation 345ms après le début du mouvement (Nishitani et al., 2004). Les données de la présente thèse suggèrent plutôt l'existence d'un mécanisme d'appariement sollicitant rapidement la contribution de M1.

Bien que les données actuelles ne permettent pas de se prononcer quant aux rôles et aux circuits reliés aux différentes périodes d'activité au sein de M1, il est tentant de spéculer quant à leurs fonctions et substrats physiologiques. Concernant le rôles différentiel de ces activités, une série d'études en MEG réalisées par van Schie et collaborateurs (Koelewijn, van Schie, Bekkering, Oostenveld, et Jensen, 2008; van Schie et al, 2008) suggère des implications distinctes pour les différentes périodes d'activité. Toujours dans un contexte d'observation d'actions, ceux-ci rapportent la présence de deux périodes de modulation dans M1, l'une à 83ms et l'autre plus tardive, soutenue, et associée à une diminution simultanée des bandes alpha et beta. Fait intéressant, seule la période d'activité tardive se voyait modulée par des facteurs cognitifs de haut niveau, telle l'acuité du mouvement effectué (Koelewijn et al., 2008). À l'inverse, la première période d'activité se montrait insensible à ces facteurs (van Schie et al., 2008). Similairement, Roy et collaborateur ont montré à l'aide de la SMT une dissociation temporelle entre l'effet de facilitation motrice relié aux aspects purement moteurs (100 ms) et ceux davantage cognitifs (200-300 ms).

À la lumière de ces résultats, il est possible de concevoir les différentes périodes de modulation chez le sujet de l'article 2 comme reflétant deux mécanismes complémentaires ayant cours consécutivement au sein du système d'appariement moteur. Le premier constituerait un appariement grossier et rapide de l'activité perçue sur le patron moteur de l'observateur, alors que le second serait plutôt associé aux

aspects cognitifs de la représentation d'action, possiblement l'identification de la source sonore. Étant donné que le moment de cette dernière période d'activité correspond à celui rapporté par Nishitani et collaborateurs (2002) (345ms), elle résulte possiblement du réseau identifié par ces chercheurs, à savoir le circuit pariéto-frontal du SNMh. Il est plus hasardeux de se prononcer quant au circuit physiologique associé à la modulation précoce. Van Shie et collaborateurs (2008) suggèrent que cette activité est le reflet d'un sytème spécialisé dans la perception de mouvement biologique, et dont le STS serait une région cruciale (van Schie et al., 2008). À notre avis, même s'il est vrai que le cerveau humain possède probablement un système spécialisé dans la détection et le traitement du mouvement biologique (Pruce et Perret, 2003), la rapidité avec laquelle l'activité parvient à M1 suggère une route alternative. En effet, les données fournies par Hari et collaborateurs quant au décours temporel de l'activité au sein du SNMh suggèrent une activité à 176 ms au STS durant l'observation passive de mouvements (Nishitani et Hari, 2002). Une hypothèse alternative serait que cette activité rapide résulte d'une connexion directe entre le thalamus et M1. D'intenses projections thalamocorticales reliant plusieurs noyaux thalamiques et les régions motrices primaires et supplémentaires ont d'ailleurs été répertoriées chez le singe (Gharbawie, Stepniewska, Burish, et Kaas, sous presse ; Morel, Liu, Wannier, Jeanmonod, et Rouiller, 2005). Ainsi, bien que l'architecture d'un réseau court-circuitant la route du SNMh « classique » puisse être en place dans le cerveau humain, nous ne disposons pour le moment d'aucune information exacte quant aux aspects fonctionnels qui pourraient lui être associé.

En résumé, les résultats expérimentaux des articles 1 et 2 suggèrent la présence d'un système qui apparie la perception d'actes moteurs avec leurs productions dans le cerveau de l'enfant. À l'image des cellules qui le constituent, ce système de résonance motrice se montre sensible à la représentation d'actions dans plusieurs modalités sensorielles. De plus, l'ensemble de ces données montre d'importantes similarités quant au fonctionnement du SNMh de l'enfant et de l'adulte. En fait, comme le suggèrent les

données comportementales présentées dans l'article 3, il est possible que ce système soit présent dès la naissance sous une forme plus ou moins rudimentaire.

8.3. Objectif 2: Mécanismes de résonance motrice précoces et cognition sociale

Tel que discuté précédemment, il semble qu'un pairage rapide puisse prendre place au sein du système de résonance motrice humain. De même, quelques études suggèrent un lien entre l'activité du système de résonance motrice et les aptitudes sociocognitives chez des individus sains (Fecteau, Pascual-Leone, et Théoret, 2008; Avenanti, Minio-Paluello, Bufalari, et Aglioti, 2009; Gazzola et al., 2006; Kaplan et Iacoboni, 2006; Pfeifer et al., 2008). Cependant, on ignorait toujours la nature du lien entre l'activité de M1 et l'empathie, de même que le lien entre l'activité motrice précoce et certains traits psychosociaux. C'est avec ces questions en tête que les études composant l'article 5 ont été élaborées. Celles-ci visaient deux objectifs principaux : 1) définir le décours temporel de l'activité de M1 durant l'observation d'actions; et 2) établir la présence d'un lien entre cette activité et certaines habiletés sociocognitives chez des sujets sains.

En utilisant la SMT dans une approche chronométrique, la première étude a démontré une modulation précoce du cortex moteur primaire (90-120ms) suivant la présentation d'un mouvement rapide du doigt. Cette modulation est en accord avec ce qui avait été observé chez un enfant à l'aide d'enregistrements intracrâniens (article 2), à savoir une modulation survenant vers 100 ms lors de la perception de sons d'actions. Il semble ainsi que l'activité de M1 suive un parcours temporel similaire lors de l'observation et de l'audition de stimuli d'actions, soulignant le caractère multimodal du

SNMh et sa stabilité développementale. Cette période précoce de modulation est aussi en phase avec ce qui a été rapporté récemment dans les modalités visuelle (van Schie et al., 2008) et auditive (Roy et al., 2008).

Cependant, contrairement à ce qui avait été répertorié chez l'adulte (Maeda et al., 2002), et contrairement à l'hypothèse de départ, la seconde étude de cet article montre que l'augmentation d'excitabilité corticospinale n'est pas spécifique aux muscles recrutés dans le mouvement observé. En effet, une augmentation de l'excitabilité corticospinale est observée à la fois dans la représentation corticale des muscles du petit doigt et de l'index, bien que le mouvement observé n'implique que l'index. . Cette absence de spécificité pourrait être interprétée comme un indicateur du fait que l'appariement moteur s'effectue de façon grossière tôt dans la séquence de pairage, pour ensuite être raffiné. Cette hypothèse est soutenue par des études récentes qui montrent une dissociation entre l'activité précoce et tardive de M1 dans des contextes de perception d'action (Roy et al., 2008; van Schie et al., 2008; Koelewijn et al., 2008). Celles-ci montrent que la première phase d'activité est moins sélective quant à différents aspects du stimulus biologique présenté comparativement à celle plus tardive, qui semble au contraire plus sensible à l'influence de processus de haut niveau.

La troisième étude présentée dans cet article s'attarde au lien entre l'activité précoce du SNMh et certains traits sociocognitifs. Tel que mentionné précédemment, plusieurs théoriciens et chercheurs ont suggéré l'existence d'un lien entre certaines capacités sociales, notamment l'empathie, et le fonctionnement du SNMh. Cette supposition découle en partie du fait que des individus avec des troubles neurodéveloppementaux, caractérisés par la présence de difficultés sociales, montrent une altération du fonctionnement du SNMh (Dapretto et al., 2006; Oberman et al., 2008; Théoret et al., 2005). Cependant, aucune étude n'avait montré l'existence d'une telle

relation entre le fonctionnement du SNMh mesuré par la SMT et la présence de traits empathiques et autistiques dans une population neurotypique. Ici, en sélectionnant les participants afin de maximiser la variance aux échelles psychométriques (validées dans l'article 4), nous avons démontré un lien entre l'activité corticospinale précoce et le niveau d'empathie et de traits autistiques. Il est important de noter que les questionnaires utilisés, les versions françaises du Quotient d'Empathie et du Quotient de Traits Autistiques, ont fait l'objet d'une étude de validation (article 4). Les résultats de cette étude répliquent fidèlement ceux obtenus avec les échelles originales (Baron-Cohen et al*.,* 2001; Baron-Cohen & Wheelwright, 2004) et mettent en evidence des difference significatives entre le groupe contrôle et celui d'individus avec un trouble du spectre autistique, ce dernier obtenant des résultats moins élevés à l'échelle d'empathie et plus élevés à l'échelle de traits autistiques. Ce patron de réponses confirme notre hypothèse et suggère la validité des échelles psychométriques utilisées dans l'article 5.

Cette démonstration est porteuse de plusieurs éléments nouveaux concernant le lien entre les mécanismes de résonance motrice chez l'humain et les capacités sociocognitives. D'une part, il s'agit d'une des premières démonstrations d'un tel lien chez une population neurotypique dans un contexte de résonance motrice. En effet, bien qu'une étude IRMf ait rapporté une relation positive entre l'activité du GFI, une région centrale du SNMh, durant l'observation d'action et les capacités empathiques dans une population normale (Pfeifer et al, 2008), cette étude est marquée par certaines questions quant à l'interprétation de la mesure psychométrique de l'empathie, dont la sommation des sous-échelles de l'Index de Réactivité Interpersonnelle (D'Orazio, 2004). De plus, même si quelques études SMT ont montré l'existence d'un lien entre des concepts psychologiques et des mécanismes de résonance (Fecteau et al., 2008; Avenanti et al., 2009), aucune étude SMT n'avait montré l'existence d'un lien entre les capacités empathiques et l'activité du SNMh. Dans notre étude, deux éléments principaux ont contribué à la mise en évidence de cette relation. Premièrement, la sélection des

participants sur la base de leurs réponses obtenues lors de la validation des outils (article 4) a contribué à maximiser la variance aux tests, permettant ainsi de mettre en évidence un large spectre de sensibilité quant aux mécanismes neurophysiologiques qui sous-tendent la résonance motrice. L'autre élément potentiellement crucial est en lien avec le décours temporel de l'activité de M1 durant l'observation d'actions. En ciblant de façon précise le moment de modulation maximum de M1, nous avons été capables de circonscrire le moment précis où l'appariement moteur prend place et ainsi mettre en lumière la relation de cette activité avec des traits psychologiques. Ceci est souligné par le fait que la mesure de l'activité de M1 à d'autres moments (60 et 150 ms) n'est pas corrélée avec les échelles sociocognitives.

Deux études récemment publiées soutiennent d'ailleurs la validité des résultats obtenus. La première, utilisant le rythme mu comme indicateur des processus de résonance dans M1, montre une corrélation négative entre le niveau de réduction de la bande alpha et le score obtenu à l'échelle du Quotient d'Empathie durant l'observation d'action chez l'individu sain. (Perry, Troje, et Bentin, 2010). Ainsi, plus l'activité du SNMh mesurée à M1 est forte, plus l'individu présente de traits empathiques. La seconde étude, réalisé par Puzzo et collaborateurs (2009), montre que la présence de traits autistiques chez des individus est corrélée avec la modulation des PÉM induits par SMT dans un protocole d'observation d'actions. En effet, les personnes avec de forts traits autistiques montrent une augmentation relativement faible des PÉM comparativement aux individus avec peu de traits autistiques. Bien que ces études n'abordent pas la question temporelle des mécanismes de résonance, elles suggèrent néanmoins l'existence d'un lien entre l'activité corticale à M1 durant la perception d'action, l'empathie et les traits autistiques.

8.4. Objectif 3: Rythme mu et potentiels évoqués moteurs : deux facettes d'une même pièce?

Après avoir utilisé le rythme mu et les PÉM induits par SMT comme indicateurs de l'activité du SNMh mesurée à M1, il était légitime de se questionner quant à leur spécificité dans la mesure du système de résonance motrice chez l'humain. En effet, bien que ces deux techniques soient largement utilisées dans des protocoles de perception d'actions, la relation qu'elles entretiennent entre elles, de même que leurs substrats neuronaux exacts, sont étonnamment méconnus. Ainsi, bien que toutes deux soient conçues comme étant le reflet de l'activité de M1, cette assomption est questionnable considérant l'absence de données empirique sur le sujet.

Afin d'établir la concordance et la spécificité de l'EEG et de la SMT dans l'étude des mécanismes de résonance, nous avons utilisé ces deux techniques simultanément dans des contextes d'observation, d'imagination et de production motrice, de même qu'au repos chez des sujets sains. D'une part, nous répliquons fidèlement les résultats antérieurs quant à l'utilisation de ces techniques dans des situations similaires, à savoir une diminution de la puissance du rythme mu dans toutes les conditions expérimentales comparativement à la condition de repos, ainsi qu'une augmentation des PÉM induits par SMT dans ces mêmes situations (Fadiga et al., 1995; Li, 2007; Muthukumaraswamy et Jonhson, 2004a; Pfurtcheller, Brunner, Schlögl, et Lopes da Silva, 2006). Ces résultats suggèrent que la manipulation expérimentale s'est avérée efficace pour engendrer l'activité du SNMh telle que reflétée par l'activité des régions sensorimotrices. Étonnamment, à l'encontre de l'hypothèse originale, la modulation de ces deux marqueurs ne semble pas corrélée, bien que les analyses exploratoires montrent la

présence d'un lien entre la puissance de la bande beta et les PÉM dans les conditions d'exécution et de repos.

Une explication possible de l'absence de relation entre les PÉM et le rythme mu est qu'une des deux techniques ne reflèterait pas l'activité de M1. Étant donné qu'il est hautement improbable que les PÉM enregistrés dans ce paradigme soient reliés à un autre processus que la stimulation de M1, il est vraisemblable que ce soit le rythme mu qui capte l'activité corticale émanant d'une autre source que M1. En effet, il est difficile d'établir avec précision la source du rythme mu telle que mesurée à partir du cuir chevelu.

Bien que la plupart des chercheurs ont tendance à qualifier le rythme mu de rythme «sensoritomoteur» (Pineda, 2005), de nombreuses études MEG situent son origine au niveau du gyrus postcentral, siège du cortex somatosensoriel primaire (S1) (Cheyne et al., 2003; Hari, Salmelin, Mäkelä, Salenius, et Helle, 1997; Simões, Salenius, et Curio, 2004). Considérant ceci, il est possible que la modulation du rythme mu observée aux sites centraux n'émane pas de M1, mais de la région somatosensorielle adjacente. Comme les mouvements sont intrinsèquement liés à une rétroaction somatosensorielle, la diminution du rythme mu pourrait ne pas être associée à la composante motrice de l'action observée, mais plutôt avec son équivalent sensoriel. Cette hypothèse est soutenue par le fait que 1) une diminution d'entrées sensorielles est liée à une puissance accrue du rythme mu (Cheron et al., 2006); et 2) la stimulation sensorielle de la main supprime fortement la puissance du rythme mu, même en l'absence de mouvement (Cheyne et al., 2003). Alternativement, il est possible que, même si le rythme mu provient de S1, sa modulation pourrait être due à l'aspect moteur des mécanismes de résonance. Comme M1 et S1 ont d'importantes connexions corticocorticales (Classen et al., 2000), la modulation du rythme mu émanant de S1 peut

être un sous-produit de l'activité en amont dans M1, où le processus de jumelage moteur prend place.

Tel que mentionné précédemment, des études MEG suggèrent que le rythme alpha émane du cortex somatosensoriel, alors que les oscillations beta semblent provenir du cortex moteur primaire (Ploner, Gross, Timmermann, Pollok, et Schnitzler, 2006; Salmelin et Hari, 1994; Salmelin, Hämäläinen, Kajola, et Hari, 1995). Ces observations sont appuyées par une étude utilisant l'EEG et l'IRMf conjointement, où il a été constaté que le signal BOLD est négativement corrélé avec la puissance spectrale de la bande alpha dans le cortex postcentral et avec les oscillations beta dans la région précentrale (Ritter et al. 2009). Ces données suggèrent que ce sont les fréquences beta qui devraient mieux corréler avec l'amplitude de la réponse motrice induite par SMT (Rossini, Desiato, Lavaroni, Caramia, 1991), ce qui expliquerait l'absence de lien entre la puissance du rythme mu et l'amplitude des PÉM. Nos analyses exploratoires appuient d'ailleurs cette hypothèse, alors que des corrélations significatives entre les PÉM et la puissance des fréquences 12-18 Hz ont été observées.

Fait intéressant, la relation entre les oscillations beta et l'excitabilité du cortex moteur est limitée aux conditions d'exécution et de repos. Il est possible que les mécanismes supplémentaires recrutés durant l'observation ou l'imagination de mouvements viennent modifier l'équilibre entre l'excitabilité corticale et la puissance oscillatoire de cette bande de fréquence, induisant une nouvelle dynamique entre les rythmes oscillatoires set le niveau d'activité du cortex moteur. Cependant, compte tenu du caractère exploratoire de ces résultats, des études complémentaires sont nécessaires pour déterminer la nature exacte de la relation entre l'activité de la bande de fréquence beta et l'excitabilité de cortex moteur dans les processus de résonance motrice.

8.5. Le système neurones-miroirs : inné ou acquis?

L'ensemble des données présentées sur le SNMh chez l'enfant suggère que celui-ci est déjà fonctionnel chez bien avant la fin de la maturation cérébrale. Ces études constituent un premier pas vers une meilleure compréhension du SNMh de l'enfant. Cependant, l'âge moyen des échantillons utilisés dans ces études neurophysiologiques ne permet pas de statuer quant au fonctionnement, ou même à la simple présence de ce mécanisme chez l'enfant naissant ou en bas âge.

Le cerveau humain est en grande partie immature à la naissance et se transforme durant les deux premières décennies de son existence, et ce tant au niveau de l'architecture structurale que de l'organisation fonctionnelle (Casey, Tottenham, Liston, et Durston, 2005). Bien que la prolifération cellulaire et la migration neuronale soient en grande partie complétées durant la période fœtale, la différenciation neuronale, la synaptogénèse et l'apoptose se produisent majoritairement après la naissance (Rabinowicz, 1979). De plus, cette maturation corticale s'effectue à différents rythmes d'une région à l'autre (Gogtay et al., 2004). Alors que les régions sensorimotrices sont les premières à se développer, la maturation du cortex préfrontal est beaucoup plus tardive (Casey et al., 2005). Les circuits occipito-temporaux et fronto-pariétaux, notamment au niveau du sulcus temporal supérieur, subissent des modifications considérables jusqu'à la mi-adolescence (Watkins et al., 2002). Étant donné l'importance de ces régions dans le fonctionnement du SNMh, il serait hasardeux d'inférer son fonctionnement chez l'enfant en bas âge sur la seule base des études actuelles. De plus, même si l'on sait que l'expérience a un impact sur le fonctionnement du SNMh (Calvo-Merino et al., 2005; Haslinger et al., 2005), on ignore si, à l'instar du langage avec lequel il semble intimement lié (Arbib, 2005), le SNMh possède une

période charnière durant laquelle son développement serait particulièrement sensible aux stimulations externes.

En l'absence d'études sur le sujet, les données expérimentales ici présentées, bien qu'obtenues chez des populations relativement âgées, ouvrent une voie importante et permettent d'envisager l'existence d'un système de résonance motrice fonctionnel tôt dans le développement. De plus, comme il en a été mention dans l'article 3, plusieurs indices comportementaux soutiennent l'existence d'un système de résonance motrice fonctionnel dès la naissance. La présence de comportements d'imitation manuels et faciaux chez le nouveau-né (Meltzoff et Moore, 1977; Nagy et al., 2004), jumelée à l'existence de comportements d'appariement moteur dans la modalité auditive sont en accord avec cette idée.

Récemment, quelques auteurs ont argumenté contre l'hypothèse du caractère inné du SNMh (Heyes, 2010; Del Giudice et al., 2009), en prenant majoritairement comme point d'appui la malléabilité du SNMh observée dans différents contextes expérimentaux (Calvo-Merino et al., 2005; Haslinger et al., 2005). Ces auteurs proposent que les NM résultent d'un processus d'apprentissage hebbien, en partie relié à l'auto-observation de mouvements effectués par l'enfant et qui engendrerait graduellement un pairage entre l'observation et l'action (Del Giudice et al., 2009). Cette hypothèse est parcimonieuse et permet d'expliquer la malléabilité du système ainsi que sa sensibilité en fonction des expériences motrices antérieures. Cependant, même si celle-ci s'avère vraie, elle complète plus qu'elle ne contredit l'hypothèse du caractère inné du SNM chez l'humain.

D'une part, l'apprentissage hebbien ne permet pas d'expliquer l'imitation néonatale, particulièrement dans le cas d'imitation de mouvements faciaux, où l'observation de son propre visage est impossible pour le nouveau-né. Deuxièmement, ce n'est pas parce qu'un système neuronal est inné que ce qu'il encode et traite l'est également. Il serait en effet surprenant que l'appariement entre le son d'une arachide qui craque et sa représentation motrice soit inné; étant donné qu'un nombre incalculable de tels pairages devraient être présents. Toutefois, cela n'exclut en rien le fait que la correspondance motrice entre soi et autrui puisse être implantée dès la naissance. L'existence d'un tel pairage entre soi et l'autre est en mesure d'expliquer les phénomènes d'appariement moteur présents à la naissance, alors que l'apprentissage hebbien rend compte des changements fonctionnels qui surviennent au sein de ce système au cours du développement.

8.6. Conclusion

Les résultats des études mentionnées précédemment semblent supporter l'hypothèse de la présence d'un SNM rudimentaire à la naissance. En effet, les études sur l'imitation motrice, vocale, ainsi que le transfert intermodal d'information chez le nourrisson, suggèrent la présence d'un système de reconnaissance et d'appariement d'action inné. Cependant, les données neurophysiologiques chez ces sujets sont manquantes, puisque la totalité des études investiguant directement la présence d'un SNM chez l'enfant porte sur des sujets plus âgés. Bien que celles-ci soient concluantes et supportent le fait que le SNMh soit fonctionnel avant la fin de la maturation corticale, elles ne permettent pas d'inférences quant au fonctionnement en bas âge et n'écartent pas la possibilité que le SNM résulte de l'expérience. Similairement, l'idée d'un raffinement du mécanisme d'appariement moteur avancée par Fecteau et collaborateurs (2004), quoique séduisante, manque actuellement de soutien empirique.

À cette fin, l'utilisation d'enregistrements cellulaires dans le cerveau du singe macaque nouvellement né pourrait fournir d'importantes indications sur la présence et le raffinement du SNMh au cours du développement. Cependant, même si cela était fait, il faudrait être prudent quant à la généralisation de ces résultats à l'humain. En effet, l'ontogénie cérébrale varie considérablement d'une espèce de primates à l'autre, et l'humain constitue sans aucun doute un cas particulier. Cependant, la possibilité d'effectuer de telles investigations chez le primate constituerait un avantage majeur.

Pour élucider directement la question chez l'humain, l'utilisation de l'EEG quantitatif ou de l'imagerie optique, étant donné leur caractère non invasif sont les solutions les plus envisageables à court terme. L'EEG s'est en effet avérée probante dans l'étude du SNMh chez l'adulte (Muthukumaraswamy et Johnson, 2004a, 2004b) et l'enfant d'âge scolaire (Oberman et al., 2008). Cependant, outre les conditions techniques plus ardues avec les nouveaux nés, l'activité cérébrale de cette population est qualitativement très différente des enfants plus âgés et d'importants changements surviennent d'une semaine à l'autre (Paterson, Heim, Friedman, Choudhury, et Benasich, 2006). De plus, la fréquence utilisée pour rendre compte du SNMh, le rythme mμ, se situe entre 8 et 12Hz, une bande de fréquence dont la puissance est peu développée en bas âge. Ces constats rendent difficiles les études de groupe et pourraient miner l'obtention de résultats significatifs. Alternativement, l'imagerie optique pourrait s'avérer le moyen idéal de démontrer l'existence et le fonctionnement du SNMh dès la naissance; son utilisation s'est d'ailleurs montrée probante à cet effet chez le nourrisson (Shimada & Hiraki, 2006). Quoi qu'il en soit, l'importance clinique de la question du développement du SNMh dans le traitement et le diagnostic de certaines pathologies infantiles est un facteur important qui motive très certainement l'entreprise de telles investigations.

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Annexe 1

Autism Spectrum Disorder: Seeing Is Not Understanding

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Publié dans *Current Biology* (2006) 16(4) : 131-3.

Abstract

Impairments in social and emotional skills are a defining feature of autism spectrum disorder (ASD). Recent research shows that structural and functional abnormalities within the neural system that matches observation and execution of actions, the mirror neuron system, may explain the social aspects of ASD pathophysiology.

Commentary

The discovery of mirror neurons in the ventral premotor cortex of macaque monkeys and the growing evidence suggesting their presence in the human brain has led many to suggest a fundamental role for the mirror neuron system (MNS) in social cognition. Specifically, the MNS appears to be an essential component of not only action understanding (Rizzolatti et al., 2001 ; 2004) and imitation (Iacoboni et al., 2004; 2005), but also fundamental cognitive functions such as social interaction (Gallese et al., 1998), empathy (Gallese, 2003), language (Gallese, 1998 ; Arbib, 2005), mind reading (Williams et al., 2001), theory of mind (Rizzolatti, 2001 ; Gallese, 1998), and emotional processing (Gallese, 2004) Specifically, mirror neurons mediate understanding of actions performed by others in the following way: each time an individual sees an action performed by a peer, neurons that represent that action are activated in the observer's premotor cortex. The same process seems to occur with higher cognitive functions: for instance, the neural networks normally activated during an experienced emotion allow us to understand the same emotion experienced by a peer. This process seems to underlie the basic aspects of social cognition by creating a link between others and ourselves (Wiliams, 2001).

The MNS is formed by a cortical network composed of the pars opercularis of the inferior frontal gyrus and the rostral part of the inferior parietal lobe (Rizzolatti, 2001). Importantly, the neural system that resonates in the observer's brain networks depends on the mirror function elicited (i.e. the observed action). In the case of emotional processing, for example, observation of a face expressing fear may engage the amygdala (Carr et al., 2003), whereas observation of a face expressing disgust recruits the insula (Wicker et al., 2003), in conjunction with the classical MNS.

As several functions believed to be subserved by the MNS are impaired in autism

spectrum disorder (ASD), ranging from imitation to empathy, abnormal mirror neuron function has been suggested as a possible neural substrate of social impairments characteristic of this condition (Gallese, 1998, 2003 ; Williams, 2001 ; Théoret et al., 2005). Deficits in imitation are well documented behaviorally in ASD but it has only recently been suggested that brain activity related to these deficits is abnormal, as shown by converging data from magnetoencephalography (Nishitani et al., 2004). functional magnetic resonance imaging (MRI) (Williams et al., 2005), and functional connectivity MRI (Villalobos, 2005). In what may be the strongest demonstration of a MNS dysfunction in ASD as of yet, Dapretto and colllaborators (Dapretto et al., 2005) recently reported the functional MRI activation patterns of children with ASD while they imitated facial expressions. Whereas imitation perfomance of children with ASD was equal to that of typically developing children behaviorally, only the typically developing children showed enhanced bilateral activity in the pars opercularis of the inferior frontal gyrus (the main mirror neuron area). In fact, children with ASD showed no activation within the pars opercularis of either hemisphere during imitation. Moreover, similar differences in patterns of activation were found when participants passively observed facial expressions, suggesting that the deficit in imitation is due to a deficit in observation. This strengthens the claim that individuals with ASD have difficulties in reading the emotional state of others because of a failure in adequately activating some of the brain areas that would normally be active if they were experiencing the emotion themselves. Of great importance is the fact that Dapretto and collaborators also found that activity within the pars opercularis of the inferior frontal gyrus was inversely correlated with severity of social dysfunction, underlining the link between social behavior and MNS function.

In a strikingly complementary study, Hadjikani and collaborators (2006) then reported that adults with ASD displayed significantly reduced cortical thickness in the main mirror neuron areas, namely the bilateral pars opercularis of the inferior frontal gyrus (also in the inferior parietal lobule and superior temporal sulcus). These areas are the same that failed to activate when children with ASD imitated facial expressions

Dapretto et al., 2005). Again in agreement with functional data, cortical thinning in these areas was correlated with severity of communication and social symptoms. It appears, then, that the neurophysiological dysfunction found in the mirror areas of individuals with ASD may be rooted in more general structural abnormalities giving rise to complex anatomical-functional interactions. These could potentially explain some of the variability observed in the social-behavioral symptoms of ASD. Taken together, these studies make a strong case for the mirror neuron hypothesis of ASD, particularly if one considers that even passive observation of meaningless hand movement elicits weaker MNS activity in individuals with ASD, as measured by transcranial magnetic stimulation (Théoret et al., 2005) and electroencephalography (Oberman, 2005), suggesting that MNS dysfunction in ASD is not restricted to emotional processing.

One could argue that abnormal MNS-related activations are explained by impaired visual recognition of biological motion (see Dakin et al., 2005 for a discussion of visual perception in ASD). However, a clear dissociation in neural activity related to visual recognition of biological movement and imitation has been reported, where abnormal neural activity in ASD was restricted to action observation (Nishitani, 2004). Specifically, in early cognitive processing, individuals with ASD and healthy controls showed similar patterns of activation involving occipital cortex, superior temporal sulcus and inferior parietal lobule, suggesting normal visual analysis of biological motion. In later stages, however, differences were observed between ASD and normal participants, where weaker and delayed activity was found in the inferior frontal cortex and primary motor cortex of individuals with ASD.

If the existing body of evidence is to be believed, behavioral phenotypes that would emerge as a result of abnormal development of MNS function should lead to social and communicative deficits similar to those seen in ASD. Indeed, the correspondence between ASD phenotype and MNS function is striking. Specifically, failures in MNS development should result in action understanding and imitation deficits which, in turn, would lead to impaired self-other representation, social and

communicative deficits, and ultimately empathic, language, and emotional failures. Despite this promising take on ASD etiology, the abnormal direct-matching mechanism described here is obviously one among many presumably abnormal processes in ASD. Indeed, the MNS hypothesis of ASD does not exclude the possibility that other cognitive processes also participate in the complex pathophysiology of ASD. Although the integrity of the MNS seems to be critical for action understanding, MNS failures probably do not account for all of the reported social impairments of ASD. Moreover, MNS function and its neural network are not entirely abnormal in ASD. As shown by Dapretto et al. (2005), children with ASD are able to imitate facial expressions and display patterns of activity in the amygdala similar to those of healthy participants.

It is important to note that despite enormous efforts in the last decade to pinpoint the specific causes of ASD, the gold standard in diagnosing ASD still rests on behavioral observation; no biological or genetic marker exists as of yet. As such, abnormalities in MNS neural substrates - the inferior frontal and parietal areas - may be important cues in the diagnosis of ASD. From this knowledge, diagnostic markers, and ultimately therapeutic targets for treatment that would allow for early intervention, could be developed. The critical step that needs to follow these exciting results is to establish whether the reported abnormalities in MNS function have any clinical value.

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Annexe 2

Action-coding neurons in primary motor cortex: making sense of M1 activity during action perception

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Publié dans *Journal of Neuroscience*, 2008, 28(9) : 1995-1996

Commentary

In the last decade, considerable efforts have been devoted to the description of "motor resonance", a process by which observation of an action triggers brain activations highly similar to those associated with its execution. The seminal discovery at the root of the resurgent interest in the neural mechanism underlying the direct matching of action observation and execution was the description of mirror neurons (MNs) in area F5 of the macaque monkey. MNs are cells that discharge both when an individual performs and sees a goal directed action (see Rizzolatti and Craighero, 2004) and are part of a complex fronto-parietal "mirror" network that includes area F5 of the ventral premotor cortex and area PF of the inferior parietal lobule.

Until now, the primary motor cortex (M1), despite its crucial role in motor performance, was not considered to be part of this mirroring system because it was though not to respond to the passive observation of actions. It now appears to be otherwise. In a study recently published in The Journal of Neuroscience, Tkach and collaborators (2007) provide the first demonstration of the existence of single-neurons in monkey M1 that exhibit remarkably similar patterns of activity during the execution and the passive observation of a familiar motor task. The authors recorded single-neuron activity in M1 during a task requiring trained monkeys to guide a cursor to a target location using a robotic manipulandum. Subsequently, the animals passively watched a replay of the cursor-to-target action sequence. Results showed that M1 neurons encode a considerable amount of information regarding several aspects of action production that are also present during the passive observation of the action sequence. Mainly, spike responses clearly demonstrate that the observation of cursor movement towards the target modulates neural activity in the same way as the execution task [Figure 1, Tkach et al. (2007), their Fig. 2 (http://www.jneurosci.org/cgi/content/full/27/48/13241/F2)].Importantly, control observation tasks revealed that the presence of a target was necessary for M1 neurons to display similar firing patterns to those elicited by execution of the task.

An interesting, albeit briefly discussed, aspect of the data is the analysis of oscillatory power, which allows comparisons between local field potentials and scalp EEG recordings in humans. It is difficult, from the data shown, to draw firm conclusions regarding the correspondence between beta band (10-25Hz) activity reported in the Tkach et al. (2007) study and human EEG findings. Integrated power during all observation conditions, including the simultaneous observation of cursor and target, was larger than the active movement condition. It is unclear, however, whether observation of the target or cursor movement alone produced significantly different beta activity than cursor-to-target interactions, a pattern that would appear to be necessary to replicate human EEG findings (e.g. Muthukumaraswamy and Johnson, 2004) This inconsistency is probably due to the large frequency band (10-25Hz) that was selected for analysis [Figure 2, Tkach et al. (2007), their Fig. 5 (http://www.jneurosci.org/cgi/content/full/27/48/13241/F5)]. Indeed, human studies have consistently showed decreased spectral power during action execution/observation in relatively narrow and specific frequency bands (EEG: 8-12Hz; Muthukumaraswamy and Johnson, 2004; MEG: ≈20 Hz; Hari, 2006).

Traditionally, MN properties have been studied in situations where monkeys observe biological movement performed by a human model or conspecific (typically object-oriented grasping). Hence, a novel aspect of the Tkach et al. (2007) experiment was to substitute a naturalistic setting in which the effector that executes the action is passively observed by an indirect surrogate that originates in learned cursor-to-target dynamics. Interestingly, the authors argue that such a design prevents the classification of M1 cells as “mirror neurons” because of the absence of an object-effector interation. It is unclear why this should the case since, for example, visual description of an action is not necessary for MNs to fire. Indeed, Umiltà and collaborators (2001) have shown that a mental representation of what the observed action means is sufficient in eliciting activation of MN circuits. In the present case, we would suggest that MN property requirements are fulfilled since i) the cells respond to both the execution and observation

of the results of an action; and ii) a clear interaction between the action and its goal (the target) is necessary for congruent activity to occur in M1. It is however clear that confirmation of M1 spiking patterns during observation and execution of naturalistic biological actions would considerably strengthen the contention that MNs are indeed found in primary motor cortex.

Congruent patterns of action execution/observation activity in human primary motor cortex have been detailed in humans, most notably with transcranial magnetic stimulation (TMS; see Fadiga et al., 2005). Up until now, however, the origin of this activity remained elusive. It had been suggested that M1 corticospinal facilitation resulting from passive observation of biological actions was tributary to cortico-cortical connections originating in MN-rich premotor cortex (Fadiga et al., 2005). Although it is probably true that frontal MN areas exert a modulatory influence on M1 excitability during action observation, it now appears likely that at least some of this activity is due to a local, active motor-matching process. Temporally-sensitive imaging methods such as MEG can offer insight into the time course of this activity while at the same time providing important clues about the specific role of M1 in the complex chain of neural events that underlies action understanding. Indeed, Nishitani and Hari (2000) have shown that activity in human primary motor cortex during observation of hand actions occurs later than inferior frontal gyrus activation (presumably the homologue of monkey F5). This suggests that the contribution of M1 to the understanding of others' actions may be near the end of the activation sequence that accompanies action observation. Although additional studies are needed to pinpoint the exact role of M1 in this complex process, especially at the single-neuron level, it is tempting to speculate that specific information about the dynamics of effector selection and use when observing a conspecific performing an action is computed in the newly-discovered cells of Tkach et al. (2007). Finally, these new data show that exciting times are ahead for M1 research and only time will tell what new functions (going beyond simple motor command) will end up being associated with primary motor cortex.

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Annexe 3

Brain connectivity : Finding a cause

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Publié dans *Current Biology*, 2010, 20(2):R66-7

Commentary

A new study combining double-coil transcranial magnetic stimulation (TMS) with TMS-induced 'virtual lesions' of the brain shows that the anterior intraparietal cortex causally influences interactions between ventral premotor and primary motor cortex during grasping.

It is common knowledge that all aspects of human behavior rely on an elaborate network of interconnected brain areas. One of the main challenges of modern neuroscience is understanding how discrete brain regions interact with each other to form complex perceptual, cognitive and motor representations. Until fairly recently, neuroscientists relied on a limited number of anatomical tract-tracing techniques to reveal the intricate pathways that make up the human brain. Unfortunately, these methods have not seen widespread use since they require post-mortem tissue and cannot trace long distance connections unless a stain is applied to degenerating fibers [1,2].

Modern magnetic resonance imaging tools now permit the study of white matter fibers *in vivo* through techniques such as diffusion tensor imaging (DTI) [3]. Moreover, recent advances in transcranial magnetic stimulation (TMS) make it possible to get precise information about the timing and inhibitory/excitatory nature of cortico-cortical connections. TMS is a non-invasive technique that can measure corticospinal excitability through the recording of motor evoked potentials (MEPs) elicited by stimulation of primary motor cortex (M1) [4]. A single TMS pulse applied to a brain area functionally connected to M1 can modulate the amplitude of MEPs elicited by the subsequent stimulation (again by TMS) of M1 itself. Because TMS has great temporal resolution, varying the interval between pairs of TMS pulses can reveal the exact timing of inter-regional interactions. In addition, depending on whether the conditioning TMS pulse increases or decreases the MEP response to the conditioned M1 stimulus, it is possible to determine if the interaction is inhibitory or excitatory.

A simple example may better illustrate how paired-stimulation can reveal M1 connectivity patterns. In a classic study, Civardi *et al.* [5] positioned a TMS coil over premotor cortex while a second coil was placed over M1 in such a way that single TMS pulses elicited robust MEPs in contralateral hand muscles. It was found that MEP amplitudes were suppressed when a single, low intensity TMS pulse was delivered over premotor cortex 4–6 milliseconds prior to M1 stimulation. This effect was found to be both spatially and temporally specific: no MEP suppression was present at earlier and later time points while slight displacement of the PMd coil abolished MEP inhibition. Paired-stimulation has become a valuable addition to the arsenal of tools neuroscientists use to map functional connectivity of the human motor system. It has been used extensively to study a variety of intra- and interhemispheric pathways including M1–M1[6], posterior parietal–M1 [7] and cerebellum–M1 [8]

In this issue of *Current Biology*, Davare *et al.* [9] report a significant advance in the way functional connectivity of human motor systems can be studied *in vivo*. Using a new 'triple coil' approach, they provide compelling neurophysiological evidence for the involvement and interdependency of three distinct cortical areas in grasping movements. The novel methodological aspect of this study is the use TMS-induced 'virtual lesions' in combination with the double-stimulation technique described above. When TMS is applied repetitively (rTMS) over a given area, its excitability can be reduced for durations that go beyond the end of the stimulation period. The result is altered cortical activity that can impact physiological mechanisms and behavioral performance, allowing *causal relationships* to be established between brain and function [10]. In continuous theta-burst TMS (cTBS), for example, short bursts of high frequency stimulation (three pulses at 50 Hz) are applied every 200 milliseconds for up to 40 seconds [11]. The resulting effect is a robust reduction in cortical excitability that can last up to 60 minutes.

In this new study [9], triple coil stimulation was used to investigate how the transient disruption of anterior intraparietal cortex (AIP) modified premotor ventral(PMv)–M1

interactions while participants were preparing to perform precision or whole-hand grasping movements. It is well established that the three aforementioned areas are involved in specific aspects of sensorimotor computations that transform visual information about a graspable object into a precise motor command. Briefly, studies in humans and monkeys suggest a sequence of events that occur along the AIP–PMv–M1 pathway as follows: first, visual information about a graspable object is encoded in AIP; second, PMv transforms this information into a motor program; and third, M1 organizes the final output in a muscle specific manner to perform the grasping movement.

The novel triple coil technique of Davare *et al.* [9] revealed that PMv–M1 interaction strength was reduced following 40 seconds of cTBS over AIP. More specifically, whereas TMS applied to PMv increased the amplitude of MEPs evoked by a second TMS pulse over M1, the facilitatory effect of PMv stimulation was suppressed following cTBS to AIP. Since precision grasping primarily involves index finger muscles and whole-hand grasping is achieved in part by abduction of little finger muscles, the authors were able to show how precise the effects of AIP disruption were on PMv–M1 interactions. A 'virtual lesion' of AIP specifically reduced the facilitatory effect of PMv stimulation on the MEPs elicited by M1 stimulation of the index finger representation. The opposite effect was seen during whole hand grasping: PMv facilitation of M1 was exclusively reduced in the M1 representation of the little finger. Strikingly, the disruptive effects of cTBS were also reflected during the execution of the grasping movement and followed a similar muscle-specific pattern: activity in the index finger was selectively reduced during precision grasping whereas little finger muscle activity was abated during whole-hand grasping.

With this report, Davare *et al.* [9] introduce 'causal connectivity' as a new way to probe inter-regional influences in the human brain and provide significant insight into the sequence of events that underlie some aspects of motor control. Beyond the remarkable potential of the methodological approach, the conclusions that can be drawn from the data are limited by the fact that a single direction of information flow was investigated. AIP and PMv, for instance, share dense reciprocal connections, and one can assume that

backprojections that do not follow the AIP–PMv–M1 hierarchy also play an important role in grasping movements. Indeed, the fact that no overt behavioral deficit was seen following disruption of AIP raises the question of what exactly is the contribution of the AIP–PMv–M1 circuit, in that order, to grasping behavior. This is obviously not an insurmountable problem and combining this new approach with EEG, which is already being used in conjunction with TMS to study cortico-cortical connectivity [12], may help disentangle the relative contribution of each area within a specific network and provide much needed information about directionality.

Only time will tell what impact causal connectivity studies will have on our understanding of the human motor system. The widespread potential of triple coil stimulation to probe functional connectivity *outside* motor areas is at present limited. This is because cortical areas such as M1, where TMS produces a robust and measurable index of excitability (the MEP), are scarce. The visual system may be a good starting point to venture outside motor areas to probe causal connectivity patterns. Although based on subjective reports, TMS of primary visual cortex can produce flashes of light known as phosphenes that can serve as a reliable measure of excitability [13]. Furthermore, a double-coil stimulation approach has been used to investigate the role of feedback projections from area V5 to area V1 in conscious awareness [14]. But as mentioned above, it is probably through its combination with sophisticated imaging techniques that triple coil stimulation can be used successfully at the whole-brain level. Whatever the case may be, one thing is certain: it will require less patience than traditional post-mortem tracing techniques.

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