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Interactions interhémisphériques dans le contrôle du mouvement unilatéral

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Résumé

L'exécution d'un mouvement purement unilatéral nécessite le recrutement d'un vaste réseau de régions corticales et sous-corticales, qu'il est possible de regrouper sous le terme de *réseau de transformation non-miroir*. Ce réseau doit contrer la tendance naturelle du cerveau à exécuter des mouvements de manière bilatérale et synchronisée, en miroir. Malgré l'efficacité de ce réseau, une activité miroir subtile est observée au niveau de la main qui doit demeurer inactive lors de mouvements unilatéraux chez l'humain en santé. Ce débordement moteur doit être inhibé grâce aux interactions interhémisphériques transitant par le corps calleux (CC), la plus grande commissure du cerveau servant de pont entre les hémisphères. Ainsi, la commande motrice peut être acheminée efficacement du cortex moteur primaire (M1) controlatéral à la main devant exécuter une l'action par l'entremise de la voie corticospianle (VCS). En plus du CC, le cortex prémoteur (CPM) joue un rôle important dans ce réseau puisque son interférence via la stimulation magnétique transcrânienne (SMT) entraîne une augmentation de l'activité miroir dans la main devant normalement demeurer inactive lors d'un mouvement unilatéral. Ainsi, toute modification dans ce réseau ou dans les processus interhémisphériques peut provoquer l'augmentation des mouvements miroirs (MM). À ce jour, aucune étude n'a tenté de moduler ces interactions pour réduire la présence de MM.

Ainsi, les études cliniques et méthodologiques qui composent la présente thèse comportent deux objectifs principaux : (1) déterminer si la stimulation électrique transcrânienne à courant direct (SÉTcd) permet l'étude du réseau de transformation non-miroir, et si cette technique est en mesure de diminuer l'intensité des MM chez des individus en santé; (2) caractériser l'anatomie et le fonctionnement du cerveau dans deux populations d'individus porteurs de mutations génétiques affectant le développement de structures impliquées dans la latéralisation du mouvement, le CC et la VCS.

L'article 1 décrit les assisses théoriques de la présente thèse grâce à une revue de la littérature portant sur les interactions interhémisphériques dans le mouvement unilatéral.

L'article 2 suggère que la SÉTcd est un outil efficace dans l'étude du réseau de transformation non-miroir puisque le protocole de stimulation bilatérale a permis d'augmenter la présence et l'intensité des MM physiologiques (MMp) chez des individus en santé. Cependant, il n'a pas été possible de moduler à la baisse les MMp malgré différents protocoles de stimulation.

Dans l'article 3, l'étude d'individus nés sans CC a mis en lumière une augmentation de l'épaisseur corticale au niveau des aires somatosensorielles (S1) et visuelles (V1) primaires, de même qu'au niveau de la représentation de la main dans M1. Ces différences demeurent toutefois légères considérant l'importance du CC.

L'article 4 a démontré que les individus porteurs d'une mutation sur le gène *DCC* présentent un phénotype similaire à celui de porteurs d'une mutation sur le gène *RAD51*. Ces mutations affectent la migration de la VCS au niveau des pyramides. La VCS projette ainsi aux deux mains, causant des mouvements miroirs congénitaux (MMC). Cette pathologie est également accompagnée d'anomalies neurophysiologiques, telle qu'une inhibition interhémisphérique (IIH) réduite.

En somme, les études composant cette thèse ont permis d'approfondir notre connaissance de certaines structures responsables de la latéralisation adéquate du mouvement, tout en décrivant de nouvelles méthodes pour en étudier le fonctionnement.

Mots-clés : mouvements miroirs, mouvements miroirs congénitaux, stimulation magnétique transcrânienne, stimulation électrique à courant direct, inhibition interhémisphérique, corps calleux, agénésie du corps calleux, cortex prémoteur, voie corticospinale, gène *DCC*.

Abstract

The execution of purely unilateral hand movements requires the recruitment of vast cortical and subcortical brain areas known as the *non-mirroring network*. This network counteracts the natural tendency of the brain, which tends to execute movements in a bilateral and synchronized manner. Despite the efficacy of the non-mirroring network in restricting motor output to contralateral limbs, subtle mirroring can be observed in the inactive hand of healthy individuals when performing a unilateral task. This motor overflow needs to be inhibited through interhemispheric projections coursing through the corpus callosum (CC), the biggest white matter tract of the brain. This mechanism makes it possible for motor commands originating from the primary motor cortex (M1) to reach the contralateral hand performing an action via the corticospinal tract (CST). It has been suggested that the premotor cortex (PMC) is an important component of the non-mirroring network since its interference with transcranial magnetic stimulation (TMS) enhances mirror activity in the inactive, mirror hand when a unilateral hand movement is performed. Indeed, modulation of parts of the non-mirroring network and interhemispheric projections can result in enhanced mirror movements (MM). It is not known whether specific interventions can *decrease* MM.

The clinical and methodological studies that compose the present thesis have two main objectives: (1) Determine whether transcranial direct-current stimulation (tDCS) can be used to assess non-mirroring network function and reduce MM intensity in healthy individuals; (2) Characterize brain function and anatomy in two clinical populations presenting specific genetic mutations that affect the development of structures involved in the lateralization of movement (the CC and CST).

Article 1 provides a theoretical basis for the present essay through a review of the literature pertaining to interhemispheric interactions in the production of unilateral movements.

Article 2 shows that tDCS can be used to study the non-mirroring network since a bilateral stimulation protocol significantly increased the intensity of physiological MM (pMM)

in healthy individuals. However, despite different stimulation protocols, it was not possible to reduce pMM.

In article 3, anatomical MRIs performed in individuals born without a CC revealed increases in cortical thickness in primary somatosensory (S1) and visual (V1) cortex, as well as in the hand representation of M1. Taken together, however, the data suggest that anatomical differences between acallosal patients and healthy participants are relatively subtle considering the size and function of the CC.

Article 4 showed that individuals presenting a mutation on the *DCC* gene display a phenotype similar to that of individuals presenting a mutation on the *RAD51* gene. *DCC* mutations affect the crossing of the CST at the pyramidal level, resulting in a CST that projects to both hands simultaneously, causing congenital mirror movements (CMM). This pathological condition is accompanied by neurophysiological anomalies that include reduced interhemispheric inhibition (IHI).

In summary, the studies comprised in the present thesis significantly increase our knowledge of the specific brain structures that enable the proper lateralization of movements. It also describes novel methods that can be used to investigate the non-mirroring network.

Keywords: mirror movements, congenital mirror movements, transcranial magnetic stimulation, transcranial direct-current stimulation, interhemispheric inhibition, corpus callosum, agenesis of the corpus callosum, premotor cortex, corticospinal tract, *DCC* gene.

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Liste des abréviations

VCS: Voie corticopsinale

M1: Cortex moteur primaire

MM : Mouvements miroirs

CC : Corps calleux

IIH : Inhibition interhémisphérique

CPM : Cortex prémoteur

CPMd : Cortex prémoteur dorsolatéral

AMS : Aire motrice supplémentaire

GB : Ganglions de la base

SMT: Stimulation magnétique transcrânienne

SMTr : Stimulation magnétique transcrânienne répétitive

AgCC : Agénésie du corps calleux

MMC : Mouvements miroirs congénitaux

DCC : *Deleted in colorectal cancer*

EMG : Électromyographie

PÉM : Potentiel évoqué moteur

SÉTcd : Stimulation électrique transcrânienne à courant direct

MMp : Mouvements miroirs physiologiques

PB : Potentiel bereitschaft

GABA : Acide gamma-aminobutyrique

CDK5RAP2 : *cyclin-dependent kinase 5 regulatory protein 2*

« If we knew what we were doing, it wouldn't be called research. »

Albert Einstein

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Chapitre 1

Introduction

1.1 Introduction générale

Tous les jours, nous utilisons nos mains de manière automatique afin de réaliser des actions diversifiées, allant d'un simple geste comme de ramasser notre crayon tombé au sol à un geste plus complexe, tel que boutonner une chemise ou lacer nos souliers. Derrière l'apparente simplicité avec laquelle nous parvenons à accomplir ces actions se cache une multitude d'interactions cérébrales permettant de diriger la biomécanique élaborée des mains et des doigts.

Ces mouvements requièrent des contractions musculaires indépendantes et précises des doigts qui ne se retrouvent que chez une infime partie du règne animal, principalement chez les primates. Parmi les espèces possédant cette capacité à manipuler des objets avec les mains, on constate une grande variabilité dans leur niveau de compétence, et ce même si elles possèdent une morphologie des mains très similaire entre elles du point de vue de la biomécanique (Heffner & Masterton, 1983). Cette manipulation de petits objets, de même que leur exploration tactile, requièrent des mouvements très précis de la main et des doigts. En effet, en plus de requérir la capacité de bouger chacun des doigts indépendamment les uns des autres, il est nécessaire de contrôler la force qui sera appliquée à l'objet (Heffner & Masterton, 1983; Johansson, 1998; Lawrence & Kuypers, 1968). Un exemple qui illustre bien le degré de sophistication requis dans la manipulation de petits objets est la cueillette d'une framboise : trop de force écrasera la framboise tandis que si la force n'est pas suffisante, la framboise glissera des doigts. Malgré le fait que les conditions biomécaniques nécessaires à la production de mouvements indépendants des doigts soient présentes chez de nombreux primates, la circuiterie neuronale sous-tendant ces mouvements n'est développée que chez un faible pourcentage d'entre eux (Nakajima, Maier, Kirkwood, & Lemon, 2000). À titre d'exemple, le singe *cebus capucinus* et le singe-écureuil ont tous les deux une morphologie de la main très similaire. Par contre, ils diffèrent significativement sur le plan de leur dextérité fine ; tandis que le *cebus capucinus* est en mesure d'exécuter des mouvements des doigts indépendants et d'utiliser une poignée de précision (pince pouce-index) lui permettant de manipuler de petits objets (Costello & Fragaszy, 1988; Westergaard & Fragaszy, 1985), le singe-écureuil est pour sa part incapable de bouger ses doigts de façon indépendante (Costello & Fragaszy, 1988;

Fragaszy, 1983), lui permettant uniquement d'utiliser une « poignée de puissance » (l'ensemble des doigts travaille en même temps pour ramasser un objet). L'une des caractéristiques neurophysiologiques pouvant expliquer cette différence sur le plan de la dextérité repose sur la densité de la voie neuronale descendante reliant le cerveau aux muscles de la main (Heffner & Masterton, 1983). Cette connexion entre le cerveau et la main se fait par l'entremise de la voie corticospinale (VCS). Cette voie est composée d'axones à conduction rapide prenant naissance dans le cortex moteur primaire (M1). Elle se dirige verticalement vers le tronc cérébral, croise la ligne médiane et traverse la moelle épinière jusqu'aux motoneurones innervant les différents muscles du corps. Ainsi, plus cette voie est importante, plus le cortex est en mesure d'exploiter une multitude d'interactions musculaires afin de maximiser la précision du mouvement (Heffner & Masterton, 1983). Il n'est donc pas surprenant de constater une forte corrélation entre le degré de dextérité manuelle d'une espèce et la densité des projections monosynaptiques provenant du cortex et innervant les motoneurones des muscles de la main et des doigts (Bortoff & Strick, 1993; Heffner & Masterton, 1983).

Chez les espèces animales ayant une grande dextérité, comme l'humain, il existe une tendance naturelle vers une contraction symétrique des muscles homologues, communément appelée mouvements miroirs (MM) volontaires. Ces mouvements symétriques demanderaient moins d'activation corticale que des mouvements bilatéraux non symétriques ou des mouvements unilatéraux (Cincotta et al., 2004; Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008). En effet, lorsque l'on demande à des sujets de faire des mouvements bilatéraux avec les membres supérieurs, il y a une forte tendance vers la synchronisation de la séquence motrice (Swinnen & Walter, 1991). Pour exécuter un mouvement purement unilatéral ou non synchronisé, le cerveau doit donc contrer cette tendance naturelle par l'entremise d'interactions interhémisphériques complexes sous-tendues par un large réseau d'aires corticales. Ces interactions permettent à l'hémisphère qui contrôle la main active d'inhiber l'hémisphère controlatéral qui innerve la main devant demeurer inactive. Cette inhibition transite par le corps calleux (CC), la plus grande commissure du cerveau reliant les deux hémisphères, et se nomme inhibition interhémisphérique (IIH). Plusieurs régions cérébrales sont impliquées dans la restriction de l'activité cérébrale dans l'hémisphère actif, dont M1, le

cortex prémoteur (CPM), l'aire motrice supplémentaire (AMS) et les ganglions de la base (GB) (Cincotta & Ziemann, 2008). L'ensemble des aires cérébrales impliquées dans la restriction de l'activité cérébrale à un seul hémisphère lors d'un mouvement unilatéral est communément appelé *réseau de transformation non-miroir*, puisqu'il supprime la tendance naturelle vers un mouvement bilatéral symétrique ou MM (Cincotta & Ziemann, 2008). Ainsi, toute dysfonction dans le réseau complexe qui sous-tend la production de mouvements unilatéraux, lequel repose en partie sur les interactions interhémisphériques inhibitrices entre les deux hémisphères et la VCS, peut contribuer à la présence de MM.

Le but de la présente thèse est d'approfondir les connaissances actuelles quant aux corrélats neuronaux sous-tendant l'exécution de mouvements unilatéraux chez l'humain. Elle peut se diviser en quatre objectifs distincts:

1) *Réaliser une recension des écrits portant sur les relations interhémisphériques permettant l'exécution d'un mouvement unilatéral*. Cette revue critique de la littérature permettra de bien définir le réseau neuronal sous-tendant la production de mouvements unilatéraux et servira d'assise théorique aux articles expérimentaux composant la thèse.

2) *Déterminer le rôle du cortex prémoteur dorsal dans le mouvement unilatéral chez l'individu en santé.* Plusieurs études en imagerie cérébrale fonctionnelle rapportent la présence d'activations soutenues du CPMd lors de mouvements unilatéraux des mains (Sadato, Yonekura, Waki, Yamada, & Ishii, 1997). La contribution du CPMd au réseau de transformation non-miroir a aussi été suggérée par des études en stimulation magnétique transcrânienne (SMT), lesquelles montrent que l'inhibition du CPMd est associée à une augmentation de l'activité miroir dans la main inactive lors d'un mouvement unilatéral (Cincotta et al., 2004; Giovannelli et al., 2006). Le second objectif de la thèse vise à mieux définir le rôle du CPMd dans le contrôle du mouvement unilatéral et à déterminer s'il est possible de *diminuer* l'activité miroir chez l'individu en santé à l'aide d'une technique non invasive de stimulation cérébrale. Cet objectif revêt une dimension clinique importante puisque les MM sont présents dans plusieurs pathologiques comme la maladie de Parkinson (Giovannelli et al., 2006).

3) *Déterminer le rôle du corps calleux dans le développement du réseau neuronal sous-tendant le mouvement unilatéral: agénésie du corps calleux.* Les interactions interhémisphériques motrices permettant d'inhiber l'hémisphère controlatéral à l'hémisphère actif et ainsi restreindre l'activité motrice au niveau de l'hémisphère duquel le mouvement est initié transite par le CC (Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000; Liepert, Dettmers, Terborg, & Weiller, 2001). Afin de déterminer le rôle du CC dans le contrôle du mouvement, plusieurs études ont été réalisées chez des patients nés sans CC, une condition appelée *agénésie du corps calleux* (AgCC). De manière surprenante, malgré l'absence du CC, ces patients présentent des déficits moteurs moins sévères que ceux auxquels on pourrait s'attendre et demeurent en mesure d'exécuter des mouvements unilatéraux (Lassonde, Sauerwein, Chicoine, & Geoffroy, 1991). Le troisième objectif de la thèse est d'utiliser le modèle de l'AgCC pour déterminer si le cerveau privé de CC à la naissance se réorganise d'une manière à permettre un développement moteur fonctionnel.

4) *Décrire les interactions entre la communication interhémisphérique et la voie corticospinale dans la production de mouvements unilatéraux: mouvements miroirs pathologiques.* Le mouvement unilatéral volontaire implique le réseau de transformation non-miroir, lequel restreint la commande motrice à l'hémisphère actif via les interactions interhémisphériques. Suite à ce processus, la commande motrice est acheminée aux muscles de la main controlatérale à travers la VCS. Le lien complexe entre les interactions interhémisphériques et la VCS dans le mouvement unilatéral peut être étudié chez une population de patients présentant des mouvements miroirs congénitaux (MCC; Gallea et al., 2013). En effet, une mutation au gène *deleted in colorectal cancer (DCC)* empêche le croisement optimal de la VCS au niveau de la décussation pyramidale, résultant en une VCS ipsilaterale aberrante innervant les motoneurones de la main dite "miroir" (Depienne et al., 2011). Ainsi, ces patients sont incapables de produire des mouvements unilatéraux puisque les deux mains se trouvent innervées par le même cortex moteur. Le quatrième objectif de la présente thèse a pour but de décrire les interactions interhémisphériques motrices associées à la présence de MMC chez des patients porteurs d'une mutation sur le gène DCC.

1.2 Le système moteur et les interactions interhémisphériques

1.2.1 Mesures de l'intégrité du système moteur

1.2.1.1 La stimulation magnétique transcrânienne (SMT)

La SMT est une méthode de stimulation non invasive qui utilise un champ magnétique pour stimuler les neurones situés à la surface du cortex cérébral (Barker, Jalinous, & Freeston, 1985). Le champ magnétique permet ainsi de dépolariser les neurones présents dans le rayon d'action du champ magnétique. La SMT est utilisée dans de nombreuses études pour investiguer le cortex moteur puisqu'il est facile d'observer ses effets et de les quantifier. En effet, lorsqu'un stimulateur magnétique est placé au-dessus du M1, la décharge magnétique dépolarise les neurones et active la VCS, ce qui provoque une contraction involontaire des muscles associés à la région stimulée. On peut mesurer l'intensité de cette contraction musculaire en utilisant l'électromyographie (EMG), qui enregistre le potentiel évoqué moteur (PÉM) du muscle cible controlatéral à la stimulation (Rothwell, Thompson, Day, Boyd, & Marsden, 1991). Lorsque les paramètres de stimulation sont modifiés, au niveau de l'intensité de la stimulation ou de sa fréquence, il est possible de mettre en évidence différents processus intrahémisphériques et interhémisphériques présents dans le cortex moteur.

1.2.1.2 Mesurer l'inhibition interhémisphérique

La SMT permet, grâce à un protocole élaboré par Ferbert et collaborateurs (Ferbert et al., 1992), de mesurer l'influence d'un M1 sur son homologue controlatéral. Ainsi, l'effet d'une stimulation de M1 (stimulus test) sur la taille d'un PÉM peut être modulé par une stimulation de l'hémisphère controlatéral survenant de 6 à 30 ms plus tôt ; la première stimulation (stimulus conditionnel) aura comme effet net la diminution de la taille du PÉM provoqué par le stimulus test. Cette inhibition interhémisphérique transite par le CC et est sous-tendue par des mécanismes GABAergiques (Ferbert et al., 1992).

1.2.1.3 Évaluer le rôle fonctionnel d'une région cérébrale

Un autre protocole utilisant la SMT permet d'interférer avec l'activité d'une région cérébrale pour en évaluer la fonction. Pour ce faire, la stimulation doit être appliquée de

manière répétée (SMT répétitive; SMTr) à la région cible, et ce à haute fréquence ou à basse fréquence. La stimulation répétée modifie temporairement, et pour une période qui excède la fin de la stimulation, l'activité neuronale de la région cérébrale stimulée (Anninos, Kotini, Tamiolakis, & Tsagas, 2006; Pascual-Leone, Walsh, & Rothwell, 2000). Une stimulation à fréquence élevée, de l'ordre de 5-20 Hz (Hz : nombre d'événements par seconde), augmente généralement l'excitabilité corticospinale (Berardelli et al., 1998; Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994). Lorsque la fréquence de stimulation est basse (environ 1 Hz), l'excitabilité corticospinale est habituellement réduite (Kobayashi & Pascual-Leone, 2003). Par exemple, l'effet d'une stimulation répétée sur le cortex moteur peut mener à une modulation de la taille des PÉM allant jusqu'à 20 minutes après l'arrêt de la stimulation. Conséquemment, la SMTr peut inhiber ou faciliter l'activité d'une région cible pour établir un lien causal entre celle-ci et un comportement.

1.2.1.4 La stimulation électrique transcrânienne à courant direct (SÉTcd)

Une autre technique permettant de moduler l'activité corticale d'une région cible est la stimulation électrique transcrânienne à courant direct (SÉTcd). De nombreuses études animales et humaines ont démontré qu'une stimulation à courant direct sous le seuil de réponse des neurones (1-2 mA) pouvait modifier l'excitabilité d'une région en modulant le potentiel membranaire des neurones se trouvant sous le site de stimulation. Ainsi, en modifiant certains paramètres de stimulation, il est possible d'augmenter ou de diminuer la probabilité de décharge d'un neurone, ce qui provoque, comme dans le cas de la SMTr, une inhibition ou une facilitation de l'activité neuronale (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). Cette technique offre une alternative intéressante à la SMT puisqu'elle est facile à utiliser, moins dispendieuse, sécuritaire et, selon certaines études, elle permettrait des effets à plus long terme que ceux produits par la SMTr (Nitsche et al., 2009).

1.2.2. La tendance naturelle du cortex moteur vers un mouvement symétrique bilatéral

Lorsque l'on exécute des mouvements avec les deux mains, la tendance naturelle du cerveau est de le faire de façon symétrique. En effet, il a été démontré que les mouvements

symétriques, lorsque les muscles homologues se contractent de façon simultanée (MM volontaire), sont plus stables que les mouvements asymétriques ou alternés. Cette différence est moins prononcée lorsque le mouvement est exécuté à faible fréquence, mais lorsque la fréquence des mouvements asymétriques augmente cela en réduit la stabilité ce qui mène à une transition involontaire vers un mouvement symétrique (Swinnen, 2002; Swinnen & Wenderoth, 2004). Par exemple, il est facile de produire des cercles ou des lignes avec les deux mains simultanément, mais lorsque l'on demande à un participant de produire une ligne avec une main et un cercle avec l'autre, ces derniers finissent par produire des ovales avec leur deux mains (Franz, Eliassen, Ivry, & Gazzaniga, 1996; Swinnen et al., 1998). Afin de contrer la tendance vers des mouvements symétriques ou miroirs, les mouvements unilatéraux ou bilatéraux asymétriques nécessitent le recrutement d'un vaste réseau cérébral, nommé *réseau de transformation non-miroir*, qui permet d'inhiber la tendance naturelle vers les mouvements symétriques à travers l'IIH.

Malgré l'efficacité de ce réseau, il est possible d'observer un « débordement » moteur subtil au niveau de la main qui doit demeurer inactive lorsqu'un un mouvement volontaire unilatéral est exécuté. Ce débordement moteur est appelé mouvement miroir physiologique (MMp) et est présent chez l'adulte en santé lorsqu'une tâche requiert le maintien d'une contraction musculaire unilatérale de grande intensité, lorsqu'un individu est fatigué ou lorsque la tâche est complexe (Armatas, Summers, & Bradshaw, 1994; Baliz et al., 2005; Bodwell, Mahurin, Waddle, Price, & Cramer, 2003). Dans ces conditions, l'hémisphère actif recrute son homologue controlatéral pour augmenter ses ressources et réaliser la tâche active de manière efficace. Cette activité bi-hémisphérique permet une meilleure exécution au niveau de la main active, mais provoque aussi une augmentation des MMp. (Banich, 1998; van der Knaap & van der Ham, 2011; Welcome & Chiarello, 2008). Un protocole élaboré par Mayston et collaborateurs (1999) permet de quantifier les MMp chez des individus en santé. Pour ce faire, le participant doit maintenir une contraction tonique constante avec son pouce et son index de la main « miroir » tandis que la main « volontaire» exécute des contractions phasiques, rapides et de courte durée. On peut alors observer, à l'aide de l'EMG conventionnelle, une augmentation de l'activité dans la main miroir dans les 100ms suivant la contraction phasique de la main volontaire (Mayston, Harrison, & Stephens, 1999).

1.2.3. L'inhibition interhémisphérique

L'IIH permet à un hémisphère cérébral de moduler le niveau d'activité de son homologue controlatéral grâce à des signaux acheminés via le CC. L'IIH est une composante importante de la production de mouvements unilatéraux. En effet, à l'approche d'un mouvement volontaire unilatéral, l'IIH est modulée en fonction de l'hémisphère qui se prépare à effectuer le mouvement : l'IIH provenant de l'hémisphère inactif vers l'hémisphère actif est graduellement diminuée pour se transformer en facilitation quelques millisecondes avant le mouvement. Pendant ce temps, l'IIH qui provient de l'hémisphère actif vers l'hémisphère inactif demeure constante et importante. Ce mécanisme bi-hémisphérique permet à l'hémisphère actif de s'accaparer la majorité des ressources cérébrales (R. Chen, Corwell, Yaseen, Hallett, & Cohen, 1998; Duque et al., 2005; Duque et al., 2007). La modulation de l'IIH favorisant le cortex qui est sur le point d'exécuter un mouvement unilatéral est associée à un contrôle de la main controlatérale qui est plus précis et efficace, tout en diminuant les MMp dans la main inactive (Hubers, Orekhov, & Ziemann, 2008; Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-Leone, 2004). À l'opposé, si l'IIH du cortex actif vers le cortex inactif est plus faible, l'activité corticale de l'hémisphère inactif est plus grande, causant une diminution de la performance avec la main controlatérale (Cabeza, 2002) et une augmentation des MMp (Hubers et al., 2008).

1.3. Réseau neuronal sous-tendant les mouvements unilatéraux

1.3.1 Origine du mouvement unilatéral

L'exécution d'un mouvement unilatéral de la main, et plus spécifiquement des doigts, prend son origine dans le M1 controlatéral à la main active. La grande majorité des projections du M1 qui passent par la VCS sont responsables du mouvement des muscles des doigts et du poignet. Il a été suggéré que le M1 serait essentiel et suffisant pour expliquer la dextérité

humaine. Toutefois, bien que M1 soit nécessaire au mouvement de la main, plusieurs études ont montré qu'un grand nombre de régions corticales et sous-corticales étaient également impliquées dans la préparation, l'exécution et la latéralisation des mouvements (Ehrsson et al., 2000; Forssberg, Eliasson, Redon-Zouitenn, Mercuri, & Dubowitz, 1999). Ces observations suggèrent que la programmation précise et le contrôle de la main dépendent également de plusieurs autres structures cérébrales spécialisées (Duque et al., 2003). Ces structures interagissent entre elles pour restreindre l'activité motrice au niveau de l'hémisphère qui s'apprête à exécuter le mouvement et ainsi maximiser la performance. On regroupe sous le terme de *réseau de transformation non-miroir* l'ensemble de ces activations, puisqu'elles permettent d'inhiber la tendance naturelle vers un mouvement symétrique miroir et favorisent l'exécution d'un mouvement purement unilatéral. La compréhension des mécanismes impliqués dans l'acheminement de l'output moteur exclusivement à la main controlatérale commence à émerger. En effet, des données provenant d'études chez le singe et l'humain suggèrent que ce réseau comprend l'AMS, le M1 ipsilatéral, les GB et le CPMd (Cincotta et al., 2004).

1.3.2 L'aire motrice supplémentaire

L'AMS a été décrite pour la première fois par Penfield et Welch en 1951 qui l'ont décrite comme étant une aire possédant l'ensemble de la représentation du corps (Penfield & Welch, 1951). Son organisation somatotopique contiendrait les jambes dans sa portion postérieure et le visage dans sa portion antérieure. Au plan anatomique, l'AMS possèderait des projections bilatérales rejoignant les deux M1 en plus de l'AMS controlatéral (Pandya & Vignolo, 1971), ce qui pourrait expliquer pourquoi la stimulation de plusieurs sites de l'AMS provoque des mouvements bilatéraux et parfois même des mouvements des quatre membres (Luppino, Matelli, Camarda, Gallese, & Rizzolatti, 1991; Macpherson, Marangoz, Miles, & Wiesendanger, 1982). Il existe plusieurs hypothèses quant au rôle précis de l'AMS, dont un rôle dans le contrôle de la stabilité posturale lors de la marche (Penfield & Welch, 1951), dans la coordination temporelle des séquences d'action (Gerloff, Corwell, Chen, Hallett, & Cohen, 1997; Lee & Quessy, 2003) et dans la coordination bilatérale (Brinkman, 1981; Serrien, Strens, Oliviero, & Brown, 2002). Chez l'humain, son activité serait plus spécifiquement liée à

la génération du potentiel bereitschaft (PB) qui est une activité cérébrale qui précède le mouvement volontaire (Deecke & Kornhuber, 1978). En effet, le PB serait localisé au niveau des AMS bilatéralement et précèderait d'environ 0.35 seconde les mouvements volontaires (Ikeda, Luders, Burgess, & Shibasaki, 1992). Ainsi, considérant que l'activation de l'AMS précède les mouvements et qu'elle possède des connexions bilatérales avec les M1, il a été suggéré qu'elle serait impliquée dans la préparation et la coordination bilatérale et unilatérale des mouvements (Cunnington, Iansek, Bradshaw, & Phillips, 1996). On note d'ailleurs une augmentation de son activité lors d'une tâche bilatérale non symétrique ou unilatérale (Grefkes et al., 2008; Sadato et al., 1997). L'ablation unilatérale de l'AMS chez le singe cause l'apparition de maladresse et une coordination bilatérale déficitaire. Par exemple, lorsque ces singes réalisent une tâche bilatérale, les deux mains ont tendance à se comporter de la même manière (en miroir), plutôt que de partager la tâche à exécuter entre elles (Brinkman, 1984). Chez l'humain, plusieurs études ont montré qu'un accident vasculaire cérébrale au niveau de l'AMS peut entrainer l'apparition de MM lorsque les patients exécutent une tâche unilatérale (Chan & Ross, 1988; Laplane, Talairach, Meininger, Bancaud, & Orgogozo, 1977).

1.3.3 Le cortex prémoteur dorsolateral

Le CPM est une région faisant partie du cortex moteur, situé antérieurement au M1. Il peut se diviser en sous-sections, dont chacune possède des propriétés différentes, ce qui confère au CPM un rôle dans des fonctions variées (Matelli, Luppino, & Rizzolatti, 1985; Preuss, Stepniewska, & Kaas, 1996). Premièrement, le CPM se divise en une portion dorsale (CPMd) et une portion ventrale (Swinnen & Wenderoth, 2004). Puis deuxièmement, ces portions peuvent se sous-diviser en section en rostrale et caudale. Certaines régions du CPM projettent directement à la VCS, ce qui suggère un rôle direct dans le contrôle moteur. Pour sa part, le CPMd est présumé jouer un rôle dans l'intégration des mouvements des deux mains en une séquence de contractions musculaires spécifiques et de prendre part à la suppression des MM au niveau de la main inactive (Cincotta et al., 2004; Giovannelli et al., 2006; Swinnen & Wenderoth, 2004). En effet, l'activité du CPMd est plus importante lorsqu'un individu exécute un mouvement bilatéral non synchronisé comparativement à un mouvement bilatéral synchronisé (Sadato et al., 1997). De plus, si on inactive le CPMd droit à l'aide de la SMTr

chez des participants en santé, on note une augmentation des MMp au niveau de la main droite (Cincotta et al., 2004; Giovannelli et al., 2006). Il a donc été suggéré que le CPMd contribue à restreindre l'activité motrice au niveau du M1 actif lors d'une tâche unilatérale.

1.3.4 Les ganglions de la base

Les GB regroupent une multitude de noyaux sous-corticaux comprenant le striatum, le pallidum, le noyau sous-thalamique et la substance noire (Lao et al., 2017). Les structures formant les GB sont fortement interconnectées avec le cortex cérébral et le thalamus. L'influence des GB à l'endroit du cortex est principalement inhibitrice et implique l'acide gamma-aminobutyrique (GABA). Les GB sont impliqués dans une variété de fonctions, dont l'apprentissage procédural, les comportements routiniers, le mouvements des yeux, la cognition, les émotions ainsi que dans le contrôle des mouvements moteurs volontaires (Nelson & Kreitzer, 2014; Stocco, Lebiere, & Anderson, 2010a). La contribution des GB dans le mouvement volontaire passe par la régulation de l'activité du M1, du CPM et de l'AMS afin que les mouvements volontaires puissent être exécutés adéquatement (Hoover & Strick, 1993; Jueptner & Weiller, 1998; Stocco, Lebiere, & Anderson, 2010b). L'importance des GB dans le fonctionnement global du cerveau est sans équivoque, compte tenu de l'ampleur des troubles neurologiques (Allison, Meador, Loring, Figueroa, & Wright, 2000) qui sont associés à un dysfonctionnement de ces structures. Par ailleurs, plusieurs de ces pathologies ont des composantes motrices. La plus connue est la maladie du Parkinson, mais on y retrouve également l'athétose (mouvements involontaires, incontrôlables, lents et sinueux), le bruxisme (grincement des dents), la paralysie cérébrale, la dystonie (trouble du tonus musculaire), la maladie de Fahr (lenteur des mouvements, rigidité, tremblement au repos), la maladie de Hungtington (mouvements incontrôlables de type chorée), etc. (Chesselet & Delfs, 1996; Oueslati, Khiari, Bchir, & Abdallah, 2016; Tan, Chan, & Chang, 2004). Dans la maladie de Parkinson, les études suggèrent un dysfonctionnement des GB au niveau de la substance noire entrainant une dégénérescence des cellules qui produisent la dopamine, ce qui affecterait le fonctionnement des GB. Les GB seraient alors moins en mesure de moduler les différentes régions cérébrales impliquées dans le contrôle des mouvements. Ceci se traduit par une diminution de l'activité de l'AMS (Playford, Jenkins, Passingham, Frackowiak, & Brooks,

1993) ainsi qu'une activation bilatérale des M1 (Cincotta et al., 2006) lorsque ces patients doivent exécuter une tâche motrice unilatérale. On note d'ailleurs une augmentation des MMp au niveau de la main inactive chez les patients Parkinsoniens (Cincotta et al., 2006).

1.3.5. État actuel des connaissances et avenues à explorer

En résumé, les données actuelles suggèrent qu'une altération de l'une des régions du *réseau de transformation non-miroir* affecte la capacité d'un individu à produire un mouvement strictement unilatéral. En effet, une telle altération engendre une augmentation des MMp au niveau de la main inactive. Les études en SMTr suggèrent qu'il est possible d'augmenter la présence de MMp en diminuant l'activité de l'une des composantes du *réseau de transformation non-miroir*. Toutefois, il n'existe aucune étude démontrant qu'une *augmentation* de l'activité de ce réseau aurait comme conséquence directe de réduire le niveau de MMp. En raison des nombreuses pathologies neurologiques associées à la présence de MM, une telle démonstration revêtirait une importance clinique certaine. Or, il est possible de moduler à la hausse l'excitabilité corticale d'une région cible à l'aide de la SÉTcd, rendant plausible une réduction des MMp à l'aide d'une intervention non invasive, peu coûteuse et facile d'utilisation.

1.4 Le rôle du corps calleux dans les mouvements unilatéraux

1.4.1 Le corps calleux et la communication interhémisphérique

Le CC est la commissure la plus importante du cerveau, servant de lien entre les deux hémisphères cérébraux grâce à plus de 190 millions d'axones (Tomasch, 1954). Ces fibres axonales sont présentes à la naissance (Luders, Thompson, & Toga, 2010), mais la maturation du CC continue bien après celle-ci et un CC mature et pleinement myélinisé est observé chez l'enfants à partir de l'âge de 10 ans (Armatas et al., 1994; Giedd et al., 1999; Mayston et al., 1999). La myélinisation du CC permet la transmission rapide des influx nerveux, d'isoler les axones et de les prémunir contre des sources d'interférence, résultant en une communication interhémisphérique rapide et efficace (Mayston et al., 1999).

Le CC est une structure importante dans le contrôle volontaire des mouvements unilatéraux en permettant au cortex actif de transmettre un signal inhibiteur au cortex qui doit demeurer inactif. Il permet ainsi une meilleure latéralisation du mouvement et une réduction de l'activité involontaire miroir dans la main qui doit demeurer inactive. Bien que subtils chez l'adulte, des MM visibles au niveau des doigts sont observables chez l'enfant de moins de 10 ans. Contrairement aux adultes, il est possible d'enregistrer une activité corticale bilatérale lorsque ceux-ci exécutent une tâche unilatérale (Mayston et al., 1999). Le niveau d'IIH entre les deux hémisphères cérébraux est fortement corrélé au degré de myélinisation du CC (Koerte et al., 2009). Ainsi, la maturation du CC est associée à une diminution proportionnelle des MMp chez l'enfant (Armatas et al., 1994; Mayston et al., 1999). La capacité à exécuter une tâche motrice unilatérale repose donc sur une maturation complète du système d'inhibition transitant par le CC. Chez l'adulte, il existe une relation linaire entre l'intégrité des fibres qui composent le CC et l'IIH (Wahl et al., 2007) . En effet, plus celles-ci sont efficaces, plus l'IIH est forte. Par ailleurs, les changements morphologiques associés au vieillissement n'épargnent pas le CC, lequel subit une atrophie progressive avec l'âge (Mattay et al., 2002). On peut par exemple observer une diminution de la taille et de la myélinisation des fibres du CC chez les personnes âgées. De façon concomitante, on note une diminution de l'IIH et une augmentation de l'activation de l'hémisphère inactif lors d'un mouvement unilatéral dans cette population. Cette activation bilatérale affecte la capacité à exécuter des mouvements de façon strictement unilatérale des personnes âgées et on note une réapparition des MM similaire à ce qui est rapporté chez l'enfant de moins de 10 ans (Bodwell et al., 2003).

En résumé, le CC est une structure importante dans le contrôle des mouvements unilatéraux et dans la restriction du mouvement au niveau de la main active. S'il n'est pas mature ou que son intégrité est diminuée, on observe une diminution de l'IIH causant une augmentation des MMp, voire l'apparition de MM.

1.4.2 L'agénésie du corps calleux et son impact fonctionnel

1.4.2.1 Description et prévalence

Les individus nés sans CC (agénésie du corps calleux; AgCC) offrent une façon complémentaire d'évaluer le rôle du CC dans le mouvement unilatéral. Cette malformation congénitale est relativement fréquente et se situe sur un continuum allant de l'absence complète de CC jusqu'à l'hypogénésie (absence partielle) des fibres du CC (Paul et al., 2007). Cette condition se retrouve chez 1:4000 individus, ce qui en fait l'une des malformations cérébrales les plus communes (Glass, Shaw, Ma, & Sherr, 2008). L'étiologie de l'AgCC est identifiable dans environ 25% des cas rapportés (Paul et al., 2007) et est souvent liée à une autre condition neurologique, telle que l'hydrocéphalie (Schoner et al., 2013), la microcéphalie (Paciorkowski et al., 2013) ou l'alcoolisme foetal (Paul, 2011). Puisque l'AgCC est une condition neurologique très hétérogène, les symptômes varient grandement entre les personnes atteintes, allant d'une absence relative de symptômes jusqu'à des difficultés sévères nécessitant l'éducation spécialisée (Paul, Schieffer, & Brown, 2004; Siffredi, Anderson, Leventer, & Spencer-Smith, 2013). Nonobstant un potentiel intellectuel plus faible qu'attendu étant donné l'historique familial, l'intelligence des individus atteints d'AgCC semble demeurer dans les limites de la normale (Chiarello, 1980). De plus, malgré l'absence d'IIH (Lepage et al., 2012), les individus atteints d'AgCC présentent des dysfonctions de communication interhémisphérique relativement légères et ils ne présentent généralement pas de syndrome de déconnexion (Lassonde et al., 1991). Ces résultats contrastent nettement avec ce qui est observé chez les patients "split brain", chez qui le corps calleux est sectionné chirurgicalement (Duquette, Rainville, Alary, Lassonde, & Lepore, 2008; Lassonde et al., 1991; Sauerwein & Lassonde, 1997). Ceci suggère que le cerveau des individus atteints d'AgCC est plus efficace pour compenser et minimiser l'impact délétère associé à l'absence de la commissure la plus importante du cerveau.

1.4.2.2 Gènes impliqués dans l'agénésie du corps calleux

Des études récentes ont mis en lumière une contribution de certains éléments génétiques spécifiques dans l'AgCC, et ce indépendamment d'autres conditions cérébrales. Parmi celles-ci, notons le gène "disrupted-in-schizophrenia1" (*DISC1*), nommé ainsi en raison de son rôle possible dans la schizophrénie (Millar, Christie, Semple, & Porteous, 2000). En effet, ce gène est exprimé fortement lors du développement du CC des souris embryonnaires. Une mutation sur ce gène a d'ailleurs été identifiée chez 144 patients AgCC, renforçant sa

potentielle contribution dans l'étiologie de l'AgCC (Osbun et al., 2011; Paul et al., 2007). Récemment, le séquençage complet des gènes d'une famille canadienne-française, dont tous les membres sont atteints d'AgCC, a permis d'identifier un mutation sur le gène « cyclin-dependant kinase 5 regulatory protein 2 » (*CDK5RAP2)* comme candidat dans l'AgCC isolée (Jouan et al., 2016). Ces résultats suggèrent que la combinaison de deux mutations hétérozygotes "missense", qui affecteraient les deux allèles du gène *CDK5RAP2,* pourraient être asscié à un phénotype anormal et causer l'AgCC. En effet, une mutation délétère sur ce gène est connue pour causer la microcéphalie autosomale récessive primaire, une déficience intellectuelle ainsi que des anomalies dans le développement du CC (Bond et al., 2005; Lizarraga et al., 2010). Une étude réalisée dans nos laboratoires a tenté de déterminer le rôle du gène *CDK5RAP2* dans l'AgCC en étudiant deux membres d'une même fratrie, dont la mère est agénésique et membre de la famille canadienne-française porteuse de la mutation. L'un d'eux présentait une microcéphalie, une déficience intellectuelle de même qu'une agénésie partielle du CC, soit le phénotype attendu à la suite d'une mutation sur le gène *CDK5RAP2*. Étonnamment, aucune mutation délétère sur le gène *CDK5RAP2* n'a été identifiée comme pouvant expliquer le phénotype du progatoniste (Beaulé et al. 2016; voir Annexe 2). Ces résultats suggèrent que le phénotype rapporté est probablement causé par une mutation sur un second gène ayant également un rôle dans le développement du CC, et que cette mutation est héritée du côté paternel. Ces résultats additionnés aux autres études portant sur l'AgCC suggèrent que plusieurs gènes et d'interactions de gènes sont impliqués dans le bon développement du CC.

1.4.2.3 La plasticité cérébrale dans l'AgCC

Les mécanismes compensatoires chez les individus atteints d'AgCC ont été associés à une augmentation de la plasticité cérébrale au cours de l'enfance. Le cerveau dépourvu de CC recrute alors des structures neuronales alternatives afin de faciliter la communication interhémisphérique (Lassonde et al., 1991). En effet, d'autres projections axonales présentes naturellement et qui connectent également les deux hémisphères pourraient sous-tendre une partie de la communication interhémisphérique en augmentant leur densité en l'absence du CC. La commissure postérieure et la commissure antérieure sont deux exemples de route interhémisphérique alternative qui ont été suggérées dans l'AgCC (Lassonde et al., 1991). Il

existe également des études animales suggérant que les fibres nerveuses peuvent former des synapses avec des classes cellulaires atypiques lorsque leurs cibles conventionnelles ne sont pas développées adéquatement (Mariani, 1983; Wilson, Sotelo, & Caviness, 1981). Ainsi, il a été suggéré que l'absence précoce du CC pourrait être associée à la présence de projections axonales qui ne se seraient pas développées dans un contexte de développement « normal » (Lassonde et al., 1991). Ces hypothèses sont basées sur le fait qu'il semble y avoir une plus grande communication interhémisphérique chez les patients AgCC que chez les patients « split brain ».

Des études menées chez l'animal tendent à démontrer que l'absence précoce du CC modifie certaines caractéristiques morphologiques du cerveau. Une réduction de l'épaisseur néocorticale de souris AgCC génétiquement modifiées a été démontrée dans les régions cérébrales recevant normalement des connexions afférentes du CC (Abreu-Villaca, Silva, Manhaes, & Schmidt, 2002). Il a été suggéré que les neurones qui reçoivent normalement des inputs importants du CC « mourraient » à la suite de la perte de leurs afférences au cours de la période critique d'ontogenèse et de synaptogénèse (Abreu-Villaca et al., 2002). Chez l'humain, la maturation du CC coïncide avec une période de plasticité importante au cours de laquelle l'enfant développe ses capacités motrices bilatérales, apprend à nommer des stimuli présents dans leurs deux mains et présente une meilleure précision dans le transfert du locus du toucher entre leurs mains (Galin, Johnstone, Nakell, & Herron, 1979). Au même moment, il semble y avoir un développement cortical marqué dans le cerveau, résultant en des réductions et des augmentations de l'épaisseur corticale (Shaw et al., 2006). Ainsi, les individus atteints d'AgCC offrent une occasion unique d'approfondir nos connaissances quant au lien présent entre le développement des voies du CC et la maturation du cortex.

1.4.3 État actuel des connaissances et avenues à explorer

En résumé, malgré l'importance du CC dans la communication interhémisphérique et le rôle de cette dernière dans les mouvements unilatéraux, les individus qui naissent sans CC présentent moins de déficits au plan moteur que ce à quoi on pourrait s'attendre. Certains modèles animaux suggèrent une réorganisation du cortex dans l'AgCC qui pourrait en partie

expliquer ces résultats. Toutefois, aucune étude n'a démontré cette réorganisation cérébrale chez l'humain.

1.5 La voie corticopsinale

1.5.1 Maturation et développement

Lors du développement embryonnaire du tronc cérébral, la majorité des voies axonales doivent préserver une relation stricte avec la ligne médiane afin de former des voies de communication précises. Plusieurs de ces voies doivent traverser la ligne médiane, sans la retraverser, à un moment précis du développement afin de pouvoir rejoindre leurs cibles du côté controlatéral du corps. C'est le cas de la VCS, une voie axonale reliant le cortex aux motoneurones de la moelle épinière associée au contrôle du mouvement des membres et du tronc (Kolb & Whishaw, 2009). Cette voie axonale est plus développée chez l'humain et le primate, permettant une meilleure dextérité manuelle que les autres espèces (Rathelot & Strick, 2009). La migration adéquate de cette voie axonale majeure dépend d'indices spécifiques qui sont présents le long de sa trajectoire. Ces indices axonaux, présents dans l'environnement extracellulaire, peuvent attirer ou repousser les axones en croissances, selon les récepteurs qui sont présents à sa surface. Les protéines *netrines* (attraction) et *slits* (répulsion) sont deux exemples d'indices de guidage axonal qui sont exprimés dans la ligne médiane ventrale afin de guider la VCS (Brose et al., 1999; Harris, Sabatelli, & Seeger, 1996; Kennedy, Serafini, de la Torre, & Tessier-Lavigne, 1994). Leur effet est dépendant des récepteurs présents sur le cône axonal en croissance, avec le récepteur DCC liant la protéine netrine pour attirer la VCS vers la ligne médiane (Deiner et al., 1997; Fazeli et al., 1997; Kennedy et al., 1994; Serafini et al., 1994) et le récepteur Robo liant la protéine slit pour repousser la VSC de la ligne médiane (Bagri et al., 2002; Brose et al., 1999; Long et al., 2004). Ainsi, afin de permettre à la VSC grandissante de migrer normalement et ipsilatéralement de son point d'origine, soit du cortex vers la médulla, la VCS est guidée par un équilibre entre l'attraction netrin/DCC et la répulsion slit/Robo (Kim et al., 2015). Une fois rendue à la médulla, cette voie axonale module son équilibre attraction/répulsion en exprimant

une protéine venant interférer avec le site de fixation de la protéine répulsive slit à son récepteur Robo (Chen, Gore, Long, Ma, & Tessier-Lavigne, 2008; Sabatier et al., 2004). L'interférence ainsi créée permet à la protéine attractive netrin et à son récepteur DCC d'attirer la majorité de la VCS vers la ligne médiane pour la faire croiser du côté controlatéral afin qu'elle puisse rejoindre ses cibles situées de l'autre côté de la ligne médiane. Un faible pourcentage (8-10%) de la VCS demeure ipsilatérale pour innerver d'autres motoneurones (Rosenzweig et al., 2009). Lorsque la VCS traverse la ligne médiane, la protéine interférente cesse d'être exprimée, ce qui permet à la protéine répulsive *slit* de lier de nouveau son récepteur Robo, repoussant une fois de plus la VCS de la ligne médiane pour s'assurer qu'elle ne la recroise pas (Chen et al., 2008; Sabatier et al., 2004).

1.5.2 Erreur dans le guidage de la VCS : les mouvements miroirs congénitaux

Même si le guidage adéquat des voies axonales est dépendant d'interactions complexes impliquant plusieurs gènes, protéines et autres molécules, il existe peu de pathologies connues associées à des erreurs de guidage axonal (Nugent, Kolpak, & Engle, 2012). Une des rares manifestations d'une erreur de guidage de la VCS se présente chez les personnes atteintes de mouvements miroirs congénitaux (MMC), une condition dans laquelle la VCS ne traverse pas complètement la ligne médiane, ayant pour conséquence la présence d'une VCS ipsilaterale. Ainsi, ces patients ont une VCS qui innerve les motoneurones des deux côtés de la ligne médiane, soit la main controlatérale et la main miroir ipsilaterale. Ces patients souffrent de mouvements involontaires du côté ipsilateral qui ont lieu au même moment que le mouvement volontaire controlatéral, mais généralement avec une ampleur moindre (Meneret, Trouillard, Depienne, & Roze, 1993). En effet, chacun des cortex moteurs projette ses connexions des deux côtés du corps. Habituellement, les MMC affectent les extrémités distales du haut du corps, comme les doigts, les mains et les avant-bras (Nugent et al., 2012).

Les MMC ont été décrits pour la première fois par Drinkwater en 1914, mais l'arrivée du terme MM remonte aux travaux de Bauman en 1932. Les MMC peuvent varier en sévérité, mais la majorité des individus ont des MM d'amplitude moindre que le mouvement volontaire

(Meneret et al., 1993). Les MMC persistent habituellement toute la vie sans détérioration ou amélioration et ne s'accompagnent pas d'autre manifestation neurologique (Meneret et al., 1993). Les MMC sont très rares, avec une prévalence de moins de 1 : 1 000 000 (Meneret et al., 1993). Les personnes présentant des MMC souffrent de difficultés modérées dans les activités de la vie quotidienne, touchant particulièrement le mouvement unilatéral et les tâches demandant une coordination bilatérale importante, tandis qu'une douleur au niveau des membres supérieurs lors d'activités manuelles soutenues peut aussi être présente (Gallea et al., 2011; Meneret, Welniarz, Trouillard, & Roze, 2015). Tel que décrit précédemment, les MM peuvent survenir de façon isolée (MMC), mais ils peuvent également accompagner un syndrome neurologique complexe. Les caractéristiques cliniques des MM qui accompagnent ces syndromes ressemblent à ceux étudiés chez les patients atteints de MMC. Ainsi, on retrouve des MM visibles dans le syndrome de Kallmann, le syndrome de Klippel Feil, l'hémiparésie congénitale, le syndrome de Joubert, le syndrome de Moebius, le syndrome de Seckel et le syndrome de Wilderyanck (Meneret et al., 1993). L'étiologie des MM dans ces troubles est diverse. Dans certain cas, la maladie affecte le bon développement de la VCS qui ne croise pas complètement la ligne médiane, tel que démontré dans le syndrome de Klippel Feil (Gunderson & Solitare, 1968), ou elle peut être associée à une projection strictement ipsilatérale du cortex moteur à la main miroir, comme ce qui est observé dans certain cas d'hémiparésie congénitale (Norton, Thompson, Chan, Wilman, & Stein, 2008).

1.5.3 Les gènes impliqués dans les MMC

1.5.3.1 Le gène RAD51

La relation précise entre une déficience au niveau du gène *RAD51* et les MMC demeure incertaine et surprenante puisque ce gène a initialement été décrit comme jouant un rôle dans la réparation de l'ADN et dans le maintien de l'intégrité génomique (Costanzo, 2011; Park et al., 2008). La première hypothèse visant à expliquer le rôle du gène *RAD51* dans les MMC était que les patients présentaient des MMC en raison d'une diminution des niveaux de RAD51 au niveau de la VCS en développement, causant une diminution de la stabilité génomique et une augmentation de l'apoptose lors de la migration de la VCS (Arata et al., 2009; Costanzo, 2011; Park et al., 2008). Cependant, il a été découvert par la suite que *RAD51*

était également exprimé au niveau des cellules corticales des souris lors de la maturation du cerveau. RAD51 a alors été détecté dans une sous-population d'axones de la VCS en développement au niveau de la décussation pyramidale, suggérant un rôle dans le guidage axonal (Depienne et al., 2012). Cette nouvelle hypothèse expliquerait la présence d'une VCS ispilatérale pathologique causant des MMC chez les personnes porteuses de la mutation. Une étude neurophysiologique de patients porteurs d'une mutation au niveau du gène *RAD51* et présentant des MMC a rapporté des anomalies au niveau du système moteur et des interactions interhémisphériques (Gallea et al., 2013). Ainsi, les individus atteints présentaient une décussation anormale de la VCS, une IIH réduite, une activation bilatérale des M1 lors de mouvements unilatéraux et une activation atypique de l'AMS lors de mouvements unilatéraux et bilatéraux. Ces données suggèrent que la latéralisation adéquate d'une commande motrice requière des interactions précises entre la communication interhémisphérique et le branchement corticospinal (Gallea et al., 2013).

1.5.3.2 Le gène DCC

Le gène *DCC* a été identifié originalement comme étant un suppresseur tumoral, puisqu'une absence ou une réduction significative de la protéine DCC a été rapportée dans la majorité des cancers du côlon en phase terminale (Fearon et al., 1990; Hedrick et al., 1994). Toutefois, une étude récente de Srour et collaborateurs (2010) menée avec notre laboratoire suggère qu'une mutation sur le gène *DCC* pourrait être responsable des MMC (Srour et al., 2010). En effet, dans une famille Québécoise dont plusieurs membres présentent des MMC, une mutation sur le gène *DCC* a été identifiée (Srour et al., 2009). Il est connu que le gène *DCC* code pour la protéine netrin-1, qui est un récepteur jouant un rôle dans le guidage axonal, principalement lors du croisement axonal au niveau de la ligne médiane (Depienne et al., 2011; Srour et al., 2010). Il semble exister une hétérogénéité génétique pouvant causer les MMC puisque trois mutations différentes sur le gène *DCC* ont été identifiées comme étant responsables des MMC, et ce dans trois familles différentes (Depienne et al., 2011). Le rôle du gène *DCC* dans les MMC a été confirmé grâce à une étude utilisant une technique d'invalidation génétique (knock-out) permettant d'inactiver totalement le gène *DCC* chez la souris. Les données comportementales montrent que les souris dépourvues du gène *DCC* se déplacent en sautant à la façon d'un kangourou (Finger et al., 2002). Au même titre qu'une

personne présentant des MMC, chaque mouvement de la souris est symétrique, la souris ayant perdu la capacité d'exécuter des mouvements strictement unilatéraux. Srour et collaborateurs (2010) suggèrent qu'une mutation du gène *DCC* rend la protéine résultante moins efficace. La conséquence en serait une projection aberrante de la VCS ipsilatérale lorsque cette dernière traverse la ligne médiane.

1.5.4 État actuel des connaissances et avenues à explorer

En résumé, les MMC causé par une mutation sur les gènes *RAD51* et *DCC* semblent affecter le croisement normal de la VCS. Ce branchement anormal serait responsable des MMC, puisque chacun des cortex moteurs innerve les deux mains simultanément. Ainsi, ces personnes perdent la capacité à exécuter des mouvements purement unilatéraux. Alors que les processus neurophysiologiques ont été bien décrits chez les patients atteints d'une mutation sur *RAD51*, très peu d'informations sont disponibles quant aux interactions interhémisphériques et les processus neurophysiologiques accompagnant une mutation sur le gène *DCC*.

1.6 Objectifs expérimentaux et hypothèses

1.6.1 Article 1 : Revue de la littérature sur les interactions interhémisphériques dans le contrôle du mouvement unilatéral

L'objectif général de cette thèse est d'étudier le rôle des interactions interhémisphériques permettant de restreindre l'activité motrice au cortex actif et permettre l'exécution de mouvements strictement unilatéraux. L'objectif principal du premier article composant cette thèse est de faire une recension des écrits sur le sujet afin de présenter une assise théorique aux articles subséquents.

1.6.2 Article 2 : Modulation des mouvements miroirs physiologiques à l'aide de la stimulation transcrânienne à courant direct sur le cortex prémoteur dorsolatéral

L'objectif principal de l'article 2 est double: en premier lieu, nous utiliserons la SÉTcd pour diminuer l'excitabilité corticale du CPMd et augmenter les MMP, répliquant ainsi les résultats antérieurs obtenus avec la SMTr. En second lieu, nous tenterons d'augmenter l'excitabilité corticale du CPMd de manière à réduire les MMP. Nous émettons les hypothèses suivantes :

1) L'inhibition du CPMd à l'aide de la SÉTcd cathodale provoquera une hausse de l'activité physiologique miroir;

2) L'augmentation de l'excitabilité du CPMd à l'aide de la SÉTcd anodale provoquera une diminution de l'activité physiologique miroir.

1.6.3 Article 3 : Étude de l'épaisseur corticale chez des adultes atteints d'agénésie du corps calleux

L'objectif principal de l'article 3 est d'évaluer la plasticité corticale présente chez des personnes atteintes d'AgCC. Pour ce faire, l'épaisseur corticale sera mesurée chez des individus présentant une AgCC et comparée à celle d'individus en santé. Nous émettons l'hypothèse suivante :

1) Les personnes atteintes d'AgCC vont présenter une organisation corticale différente des participants contrôles, notamment au niveau des structures motrices.

1.6.4 Article 4 : Investigation neurophysiologique des mouvements miroirs congénitaux chez les membres d'une famille porteuse d'une mutation sur le gène DCC

L'objectif principal de l'article 4 est de mesurer l'activité neurophysiologique intrahémisphérique et interhémisphérique chez les membres d'une famille dont certains sont porteurs d'une mutation sur le gène *DCC* et présentent des MMC. Nous émettons les hypothèses suivantes :

1. La SMT provoquera un PÉM au niveau de la main miroir chez tous les sujets atteints de MMC ;

2. Les sujets ayant une mutation du gène *DCC* et des MMC présenteront une IIH moindre que les sujets n'ayant pas de MMC ;

3. Les sujets porteurs de la mutation sur le gène *DCC* mais qui ne rapportent pas de MMC présenteront un système moteur similaire aux sujets n'ayant pas la mutation et aux sujets contrôles.

Chapitre 2

Article 1 : Interhemispheric control of unilateral movement

Interhemispheric control of unilateral movement

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2.1 Abstract

To perform strictly unilateral movements, the brain relies on a large cortical and subcortical network. This network enables healthy adults to perform complex unimanual motor tasks without activation of contralateral muscles. However, mirror movements (involuntary movements in ipsilateral muscles that can accompany intended movement) can be seen in healthy individuals if a task is complex or fatiguing, in childhood and with increasing age. Lateralization of movement depends on complex interhemispheric communication between cortical (i.e. dorsal premotor cortex, suppmemntary motor area) and subcortical (i.e. basal ganglia) areas, probably coursing through the corpus callosum (CC). Here, we will focus on transcallosal interhemispheric inhibition (IHI), which facilitates complex unilateral movements and appears to play an important role in handedness, pathological conditions such as Parkinson's disease, and stroke recovery.

2.2 Introduction

Humans have a natural tendency towards symmetrical contraction of homologous muscles (also called voluntary mirror movements), which are known to require less cortical activation than alternated bimanual movements or unilateral movements [1, 2]. For example, it has been shown that if bimanual movements are executed with the upper-limbs, there is a strong tendency towards synchronization of motor patterns [3]. This is why the execution of strictly unilateral motor movement requires complex interhemispheric interactions between a wide range of cortical areas. These interactions are needed to restrict motor output to the contralateral primary motor cortex (M1) that controls the intended hand movement, which belong to the "non-mirroring" transformation network [4]. Experimental and clinical data suggest a relevant role of the corpus callosum (CC) in this network. For example children, who have an immature CC, have a higher incidence of mirror movements (MM), as do some patients with agenesis of the CC [5]. This network enables healthy adults to perform strictly unilateral tasks, although some subtle MM can be observed in the unused hand if the task is complex or fatiguing [6].

Any dysfunction in the complex network that underlies unilateral movement, which relies in part on inhibitory interhemispheric interactions, can contribute to the presence of MM. In the present article, we will review specific aspects of the non-mirroring transformation network to higlight its role in lateralization of voluntary movements. Current data regarding physiological mirroring seen in healthy adults and the role of IHI in the lateralization of movements will also be discussed. Finally, the neuroanatomical substrates of the non-mirroring network and the effects of aging on the reappearance of MM will be presented.

2.3 Mirror movements

2.3.1 MM in children

MM are movements that are observed in the contralateral hand that are the mirror reversals of the intended movement of the active hand. MM observed in children are explained by an under-myelinated nervous system [5, 7] that does not permit the interhemispheric communication necessary for the restriction of motor output to the M1 contralateral to the intended movement. The corpus callosum (CC) is the biggest white matter bundle of the brain and its function is to connect both hemispheres [8, 9], and it appears that its incomplete myelinisation could partly explain MM in healthy children [5]. However, it is important to note that immaturity of other parts of the distributed "non-mirroring" network may also play an important role in MM seen in children. MM are seen in healthy children and decrease with increasing age until the age of 10 years [5, 10, 11]. There seems to be a substantial decrease in MM, particularly from 5 to 8 years of age, which has lead some authors to suggest that it may serve as a developmental cue [12, 13]. The overt MM seen in healthy children disappear with maturation of the central nervous system and myelinisation of the CC [5, 14, 15] and there is a significant relationship between chronological age and size of the CC [16]. As the myelinisation of the CC occurs, there is a concomitant increase in IHI between the two motor cortices, which could also be used as a marker of motor development [17]. Therefore, the ability to execute unilateral motor tasks seems to rely on the correct maturation of this transcallosal inhibitory system since impaired inhibition is associated with MM [7, 18]. Notwithstanding theses observations, MM have been only sporadically reported in patients with agenesis of the CC, whereas most acallosal patients display no overt MM, suggesting a relative role played by the CC in MM. Because of the reduced IHI seen in children, the ipsilateral M1 controlling the mirror hand has a higher level of excitation if the voluntary hand is active. Consequently, bilateral cortical activity can be recorded in healthy children when performing a unilateral task [5], which enhances the probability of MM. In healthy adults, transcallosal IHI presumably suppresses activity in the ipsilateral M1 resulting in strictly unilateral movements. MM seen in healthy children thus seem to be the result of the bilateral activity of both M1 when performing a unilateral task. These observations provide strong evidence that a mature central nervous system capable of transcallosal IHI is a key factor in controlling unwanted MM when performing a unimanual task.

2.3.2 The role of interhemispheric inhibition in unilateral movements

To perform strictly unilateral movements there is a "non-mirroring" process that restricts the motor output in the contralateral hemisphere and supresses motor activation of the mirror hand [19, 20]. When an individual is preparing to execute a finger movement, it is followed by a temporary inhibition of the homologous M1 controlling the mirror finger in the passive hand [19]. TMS-induced MEPs are progressively facilitated in the 80-120 ms preceding EMG onset in healthy adults [21-23]. This shift in facilitation of the contralateral M1 and inhibition of the ipsilateral M1 following intended movements could be linked to interhemispheric interactions of the two M1. If a participant is asked to prepare a hand movement in a reaction time paradigm and a conditioning TMS pulse is applied over the ipsilateral M1 followed by a test pulse over the contralateral M1, IHI will be stronger immediately after the go signal. But as the voluntary movement onset nears, IHI is released, leading to increased excitability [24-26]. By comparison, if the conditioning pulse is delivered to the contralateral M1, which will then inhibit the ipsilateral M1, the inhibition remains deep from the beginning through the end of movement preparation [24-26].

It has been suggested that the ability to perform unilateral finger movements without MM depends on the appropriate modulation of IHI between the contralateral and ipsilateral M1 that occurs during movement preparation [19, 25, 27]. This hypothesis, that the transcallosal increase in IHI originating from the active M1 to the mirror M1 is responsible for the inhibition of undesired MM, was tested during a bimanual motor task by Hüber and colleagues [28]. In that study, participants had to maintain a tonic isometric contraction of the mirror hand while the active hand was executing short-duration contractions. It was found that IHI was inversely correlated with motor overflow in the mirror hand. That is, the more the M1 contralateral to the active hand executing short contractions (M1-active) was able to inhibit the ipsilateral M1 (M1-mirror), the less mirror activity was seen in the mirror hand performing a tonic isometric contraction. This phenomenon was further tested using low frequency rTMS to interfere with the M1-active to determine whether releasing inhibition from the M1-active would enhance mirror activity in the hand maintaining the tonic contraction. In line with the hypothesis, less IHI from the active M1 to the mirror M1 was found, resulting in increased

mirroring [28]. This further suggests that the active M1 is partly responsible for the inhibition of MM through IHI to the mirror M1. Similarly, Kobayashi and colleagues [29] reported that low frequency rTMS over M1 resulted in enhanced motor performance (finger-tapping task) of the ipsilateral hand. Notably, the incrase in performance was associated with increased excitability of the unstimulated M1, which was possibly obtained by suppressing inhibition from the stimulated M1 to the contralateral M1. It was later shown that the same protocol could improve the learning of a simple motor task in the ipsilateral hand while disturbing learning in the contralateral hand [30]. These two studies suggest that when a unilateral hand movement is executed, activation of the active M1 has an influence on the contralateral M1, acting as a "brake" that, when withdrawn, can disinhibit the contralateral M1 and lead to behavioral improvement [31]. Therefore, it seems that IHI modulation is crucial for restricting the motor output to the contralateral M1 and inhibiting the mirror M1 for an accurate, strictly unilateral movement of the hand.

Additional evidence for the presence of mutual inhibition between motor cortices comes from stroke patients, where IHI towards the affected M1, which controls the paretic hand, is increased [24]. Moreover, it appears that stronger IHI towards the affected hemisphere is negatively correlated with motor function recovery, suggesting a direct relationship between increased IHI from the intact hemisphere to the lesioned hemisphere and poor recuperation of motor function in chronic stroke patients [24]. Following on this, it is not surprising applying low-frequency rTMS over the non-affected M1 to reduce its excitability can improve motor function in the paretic hand of stroke patients through a mechanism by which transcallosal inhibition from the non affected hemisphere is released, leading to increased excitability and function of the affected M1 [32].

IHI between the motor cortices can also be tested by the brief interruption or attenuation of voluntary EMG activity produced by focal single-pulse TMS of the ipsilateral M1, the so-called ipsilateral silent period (iSP) [33]. Similarly to IHI [34], the iSP is mediated by a transcallosal pathway [35, 36], but the two measures appear to rely on different neural substrates [37]. There is evidence that the iSP reflects a key phenomenon that helps restrict motor output in the contralateral M1. Indeed, it seems that activation of the M1 performing a

voluntary movement with the contralateral hand increases interhemispheric inhibition as measeured by the iPS. This evidence points to a pivotal role for the mechanism underlying the iPS in suppressing unwanted MM and controlling unilateral movement [33].

Numerous factors have been reported to modulate interhemispheric interactions. For example, in a force generation task, it was shown that when a participant is maintaining a contraction at 70% maximal force, IHI has a disinhibitory effect on the M1 ipsilateral to the voluntary contraction, as reflected by reduced short intracortical inhibition (SICI). This suggests a change in IHI depending on task features [38]. Along the same line, it has been shown that IHI differs depending on which arm muscle is tested. Indeed, IHI from different arm representations does not strictly follow a "proximal-to-distal" gradient but instead may depend on the role that each muscle plays in functional movement synergies [39]. Finally, it has also been reported that training can modulate IHI. This was pointed out in a study testing professional musicians, who require enhanced coordination. It was found that IHI is lower in musicians as compared to controls, suggesting a modulatory effect of training on IHI [40].

2.3.3 Physiological mirroring in healthy adults

It is known that the amount of mirror EMG activity seen in healthy subjects increases if the task is demanding, if fatigue is induced, if there are cognitive distractions or decreased attentional capacities, and if age increases [41-45]. A protocol has been developed to probe physiological mirroring in healthy adults, following the observation that facilitation of the motor response can be achieved by simultaneous contraction of ipsilateral and contralateral hand muscles [46, 47]. This lead Mayston and collaborators [5] to report that involuntary mirror EMG activity of the right first dorsal interosseous (FDI) muscle can be induced in healthy adults if they maintain a background isometric muscle contraction with the mirror FDI (right) while performing intended unilateral brief phasic contractions with the left homologous muscle, resulting in motor overflow to the right hand. This protocol has been used in numerous studies where it has been repeatedly shown that mirror activity can occur in healthy participants [5, 48, 49], which is assumed to result from the transfer of activation from the task-M1 to the mirror-M1 through the CC [48].

Since physiological mirroring in healthy individuals cannot be explained by an ipsilateral projection originating from the M1 contralateral to the intended movement, alternate mechanisms must be proposed. There is growing evidence suggesting that physiological mirroring depends on the activation of the ipsilateral M1, which normally has a crossed CS tract connecting to the mirror hand [50-52]. This transfer of activation is though to occur trough a transcallosal pathway [1, 20, 34]. Therefore, the CC seems to play an important role in restricting motor overflow since, through callosal fibers, each M1 can have an interhemispheric influence over the other. This influence can either be a direct excitatory effect or an indirect inhibitory effect by excitating inhibitory interneurons [44, 53]. Evidence for a transcallosal role in IHI comes in part from studies showing that patients with agenesis of the CC display no IHI [35, 54] and that children have no IHI and an immature CC [5]. With this in mind, some authors have suggested that an intact and fully myelinated CC is necessary for effective IHI, which is also important to supress activity in the contralateral M1 [28].

The relationship between a functional CC and IHI was investigated in a study that combined TMS and diffusion tensor imaging (DTI). A direct correlation was found between fractional anisotropy (FA) of the CC, which represents the coherence of diffusion of water molecules along the WM tract, and the strength of IHI evaluated by Ferbert's paired-pulse TMS protocol [55]. Other studies have investigated the link between IHI and measures of FA in the CC in healthy humans [56] and patients with WM dysfunction [57], and suggest that WM tract integrity can be used as a predictor of IHI in healthy and diseased individuals [55, 58]. These results confirm that proper myelination of the CC is important since it enables rapid conduction of nerve impulses and, at the same time, isolates axons to prevent unwanted interference to enhance quality of interhemispheric communication coursing through the CC [5].

The CC appears to play an important role in the control of unilateral movements and in preventing mirroring by facilitating interactions to keep motor outputs contralateral to intended movements [35, 53]. This is in line with studies in monkeys, where species that do not display bimanual skills do not possess direct transcallosal M1-M1 connections [59]

whereas in macaques, in whom M1-M1 connections are found, skilled coordination abilities are seen [60]. Similarly in humans, studies with patients with an abnormal CC have shown that it is crucial for fast and complex unilateral and bilateral coordination, as well as for the ability to learn new bimanual skills [61-63]. Other evidence for a crucial role of the CC as part of the non-mirroring transformations network comes from patients with schizophrenia. There is growing evidence that the development of the CC is abnormal in schizophrenia, leading to impaired transcallosal connectivity of the two hemispheres [64]. This was confirmed using DTI and MRI, in which structural abnormalities and reduced volume of the CC was observed [65] for first-episode patients as well as high-risk individuals [66]. It was suggested that CC abnormalities could result in neurological soft signs (NSSs) [67]. NSSs have a high prevalence in schizophrenia, with 50-65% of patients being affected [68]. Individuals with schizophrenia display higher levels of motor overflow in the non-active hand compared to controls [67]. The higher incidence of mirroring activity in the non-active hand of schizophrenia patients was later associated with deficient intracortical inhibition originating from the M1 ipsilateral to the active hand [69], which in turn could be associated with reduced IHI between the active and non-active M1. With low IHI, each M1 shows a higher degree of excitation expressed by lower intracortical inhibition, thus enhancing the possibility that overflow occurs in the non-active hand [29, 69].

2.3.4 MM in adults

If MM persist after the age of 10, they are considered pathological. There are different genetic aetiologies that can explain the persistent presence of MM. They can be seen in adults that do not have other motor abnormalities and are then called congenital mirror movements (CMM) [54, 70-73]. They can also be found in genetic syndromes like Kalmann's syndrome [74-76], Klippel Field syndrome [77, 78], congenital hemiparesis [79, 80] and schizophrenia [67, 81, 82]. MM can also reappear later in life in acquired conditions like in Parkinson's disease (PD) [49, 83], stroke [84, 85] and can be present in normal aging [43, 44, 86].

The neurophysiological hallmark of CMM is the presence of an ipsilateral, fast-conducting corticospinal tract connecting the contralateral M1 to the ipsilateral hand. Evidence

for this aberrant ipsilateral connection comes in part from transcranial magnetic stimulation (TMS) studies where it has been repeatedly shown that in individuals with CMM, the ipsilateral motor evoked potential (MEP) elicited while at rest by a single TMS pulse over M1 has the exact same latency as the contralateral MEP [72]. This rules out the possibility that the involuntary mirror electromyographic (EMG) response is the result of a transcallosal transfer of excitability from the contralateral M1 to the ipsilateral M1 since such a transfer is expected to take about 8-9 ms [87]. Along the same lines, Lepage and collaborator [54] reported the case of a patient with agenesis of the corpus callosum (CC) showing ipsilateral and contralateral MEPs of the same latency.

Some evidence suggests that a gene, the Deleted in Colorectal Carcinoma (DCC), may be responsible for CMM [88-90]. The DCC gene stands for Deleted in Colorectal Cancer and is a receptor for netrin-1, which is a protein necessary for axon guidance across the body's midline [89-91]. It seems that there is a genetic heterogeneity that causes CMM since three different mutations on the DCC gene have been reported to cause CMM in three different families [90]. The role of the DCC gene has been confirmed by the fact that "knocking out" the DCC gene or the ephrin gene in a mouse results in movements being synchronized in a mirror-like fashion [91, 92]. This suggests a possible misdirected ipsilateral corticospinal projection occurring when the CS tract crosses the midline, possibly explaining the presence of MM in this population [89]. However, in several other familial cases of CMM no DCC mutations have been identified, which led to the discovery of a novel gene responsible for CMM [93]. It was found that a mutation on the RAD51 gene could also lead to CMM. The RAD51 gene is mostly present in the mouse cortex at a developmental stage critical for the correct establishment of the corticospinal tract (CST) [93]. These finding strongly suggest that CMM reported in otherwise healthy adults are the result of specific mutations that affect either the DCC or RAD51genes culminating in an aberrant ispilateral CST.

2.3.5 MM in pathological conditions

MM are also seen in specific conditions. Kalmann's syndrome (KS) is mainly characterized by hypogonadotrophia, hypogonadism and anosmia [75]. However, only the X-

linked form of KS is associated with MM [74]. Mayston and collaborators [75] suggested an abnormally developed ipsilateral tract as an explanation for MM in KS, as MM exhibited by KS patients had the exact same latency as the contralateral voluntary response. Also, it was reported that mirror responses decreased in size at the same time as the contralateral response if the TMS coil was moved away from the maximum response region, suggesting that the ipsilateral and contralateral corticospinal (CS) axons projecting to both hands are connected to the same M1 in both hemispheres. The pathological ipsilateral tract in XKS is suggested to innervate bilateral motoneurons of the distal upper limb muscles with a variable size effect as measured by MM [76]. MM are also found in Klippel Field syndrome (KFS), which is characterized by a short neck, impaired cervical mobility and low airline [77] and is commonly associated with MM [78]. In these patients, the MM are mainly observed in the distal upper limb muscle [77]. An autopsy of a deceased patient with KFS revealed the absence of pyramidal decussation of the CS tract [94]. The bilateral motor responses exhibited in KFS patients show comparable properties to contralateral responses seen in healthy controls [77]. In patients with MM in KFS [77] and XKS [75], if they are performing unimanual voluntary movements, it is possible to observe a short duration central peak in the cross-correlograms obtained from multiunit EMG activity recorded simultaneously from both homologous muscles. This activity contrasts with control subjects who only display a contralateral response, thus adding weight to a possible abnormal corticospinal branching of their motor cortex projection. MM may also occur in patients with severe congenital hemiparesis [79, 80]. In this pathological condition, the unaffected motor cortex has abnormal ipsilateral corticospinal fibers branching to the paretic hand, thus resulting in MM. Interestingly these patients are, to some extent, capable of lateralized motor activity [79]. This was reported in an experiment where mirror hand activity was recorded with EMG, showing that it was less activated than the hand performing the intended contraction. It was thus suggested that a reorganization of the CST in these patients results in separate pathways connecting the unaffected motor cortex to both hands. It was shown that an intended contraction of the paretic hand is followed by an inhibition of the crossed CST to the good hand, as seen with reduced MEPs in the mirror hand compared with a rest condition [79]. This suggests that in patients with hemiparesis, the unaffected motor cortex is able to inhibit homologous motor representations [79].

2.3.6 The case of right handedness

There is growing evidence suggesting that manual preference in the use of one hand could be explained by an asymmetry in IHI [26]. For example, IHI from the dominant M1 towards the non-dominant M1 was compared with IHI from the non-dominant M1 towards the dominant M1, where it was found that the former was deeper [95]. This was also shown by Duque and colleagues [26], who reported that modulation of IHI with movements of the right and left hands in right-handed healthy subjects was asymetrical. In the preparation of movement, the balance in IHI was profound in both hemispheres, which could help restrict MM during unilateral motor tasks. However, as movement onset approached, an asymmetry began to appear, revealing increased disinhibition of the contralateral M1 during right hand movement compared with left hand movement. The shift in IHI leading to higher excitation was only seen when the right hand was performing the task whereas IHI towards the non-dominant M1 remained deep. In the non-dominant M1, when the left hand was performing the task, there was an almost constant IHI balance towards each hemisphere [26]. This asymmetrical modulation of IHI with regards to right and left hand movement could play an important role in fine motor coordination of the dominant hand. The release of inhibition from the non dominant hemisphere to the dominant hemisphere executing a task with the contralateral hand leads to enhanced excitation of the dominant hemisphere while at the same time maintaining a deep inhibition of the non-dominant mirror hemisphere, which restrains the occurrence of MM [96]. This important excitatory gain could allow more refined movements by the dominant hand through effective intracortical excitatory connections of the dominant hemisphere with better control over antagonistic and irrelevant representations [97].

It has been suggested that in order to counteract higher IHI towards the non-dominant M1 controlling the left hand in right-handed subjects, the non-dominant M1 has to recruit more corticospinal neurons to accomplish comparable performance to that of the right hand [98]. This has lead to the hypothesis that the increased mobilization of corticospinal neurons required by the non-dominant hand could express itself in the form of interhemispheric

facilitation towards the ipsilateral, dominant M1 [26]. It could also be an adaptive mechanism aimed at counteracting the higher levels of inhibition targeting the right hemisphere. Since the right M1 inhibits the left M1 at lesser levels, through IHI, when the right M1 is active in a task, the left M1, which is not fully inhibited, could maintain slight IHI towards the right M1 forcing the right M1 to recruit more CS neurons to perform as well as the right hand. There is evidence for this asymetry, as it was found that the ipsilateral dominant cortex is more active during left hand movement than the ipsilateral non-dominant cortex during right hand movements [6, 19]. It is thus possible that the left M1 activity that is seen during left hand movement results in persistent IHI towards the non-dominant active M1, leading to poorer performance with the non-dominant hand [26]. Along the same lines, increased MM in the right hand of right-handed subjects might be a consequence of the left M1contribution during hand movements performed with the non-dominant hand [99]. Taken together, these data may partly explain why the protocol used by Mayston and collaborators [5] can induce mirror movements in healthy participants more easily when the right hand maintains the tonic, isometric contraction while the left hand performs brief movements. The tonic contraction of the dominant right hand keeps the left M1 activated, which then leads to greater IHI towards the right M1. This higher inhibition in the right M1 could then result in even lower IHI towards the dominant M1, which has greater excitability, as shown by reduced intracortical inhibition [100]. This higher excitation level in the dominant M1 makes it more vulnerable to the excitation that is produced by bimanual movement, which has to be inhibited [35]. However, since the dominant M1 is overexcited, it results in slight motor overflow. This is more easily achieved with the right hand because if the left hand is tonically contracted, the right M1 produces less IHI towards the left M1, which is then able to restrict motor overflow, without expanding it to the contralateral hemisphere. At the same time, IHI of the dominant M1 is also stronger, lowering the activation of the contralateral M1, thus producing lower motor overflow in the non-dominant left hand [48]. However, it should be noted that MM in the non-dominant hand using the Mayston protocol have also been reported [48]. It should be mentionned that IHI from the dominant to the non-dominant M1 is but one of the mechanisms that have been proposed to explain hand dominance. For example, there is evidence that enhanced efficiency of motor neurone synchronization may be present in the arm preferentially used by an individual [101]. It has also been suggested that that a release of

inhibitory input to the contralateral M1 from a more strongly activated right M1 may facilitate better *bimanual* coordination [102].

2.4 Neuroanatomical substrates

To perform unilateral movements the brain relies on a largely distributed network of motor cortical and subcortical areas, which is called the non-mirroring network. The understanding of this network and the mechanism involved in restricting motor output to the contralateral muscle, which requires the transformation of a default bilateral MM to a lateralize unilateral movement, is starting to emerge. Data from healthy humans, patients and lesioned monkeys support the view that this network relies on the supplementary motor area (SMA) [103], the dorsal premotor cortex (dPMC) [1], the ipsilteral M1 [26, 28] and the basal ganglia [83].

2.4.1 Dorsal premotor cortex

Studies using positron emission tomography have shown that right dorsal premotor cortex activation is more important during out-of-phase bimanual movements compared to in-phase movements, also known as voluntary MM [104]. This points to a role for the dPMC in the non-mirroring process since it is recruited more prominently when asymmetrical movements are required compared to voluntary mirroring. The functional importance of the dPMC in the non-mirroring process was confirmed by an rTMS study where stimulation was applied over the right dMPC of healthy participants while performing a unilateral contraction of the left hand. It was shown that disruption of the right dPMC increased excitability of the CS projections from the left M1 to the right mirror hand. This was seen only if the left hand was performing a voluntary contraction [1]. This suggests that the right dPMC plays a role in the non-mirroring network responsible to the restriction of motor output in the right M1 when the left hand is performing a unilateral manual task. This idea was further supported by Giovannelli and colleagues [49] where they showed that low-frequency rTMS of the right dPMC enhances physiological mirroring in healthy adults. It should be noted that in both these

studies, stimulation of dPMC resulted in no overt MM although slight motor overflow was present in the mirror hand. This suggests that the dPMC is part of a network of areas underlying non-mirroring transformations [1] that contribute in restricting the motor output to the hemisphere contralateral to the intended movement [1, 49].

2.4.2 Supplementary motor area

There is evidence suggesting a role for the supplementary motor area (SMA) in the non-mirroring cortical network since unilateral ablation of the SMA in monkeys produces long-lasting decreases in bimanual coordination, with greater effect if the lesion is located in SMA contralateral to the non-dominant hand [105]. Additional lesion evidence comes from the report of a man who suffered an infarct to the right SMA and in which mirror movements were seen when writing and performing bimanual coordination tasks [103]. This suggested that the SMA was part of the non-mirroring transformation of motor programs which originated in the left hemisphere prior to execution by the right M1 of left hand movement [103]. Similarly impaired motor control was seen in three patients with unilateral ablation of the SMA to help control epilepsy, in which alternating movements were impaired in the hand needing reciprocal coordination [106]. Neuroimaging in healthy humans has also revealed greater activation of the SMA when bilateral, asymmetric movements are performed compared with symetric movements, similarly to what is observed in dPMC [2, 104]. SMA involvement in non-mirroring transformations can also be seen anatomically since it projects bilaterally to M1 via the CC and reaches the PMC and the contralateral SMA [107]. In fact, M1 receives its major ipsilateral projection from the SMA [108]. The role of the SMA in motor control seems crucial since disturbances in bimanual coordination that include MM may be present in patients with SMA damage [103].

The idea that the non-mirroring program of motor control relies on a large neural network involving the dPMC and SMA is supported by studies using scalp movement-related cortical potentials (MRCP). It seems that both unilateral and bilateral voluntary movements are preceded by a pre-movement EEG potential called the Bereitschaftspotential (BP), which is a slow negativity that is bilaterally distributed over extensive areas of the scalp and that

occurs approximatively two seconds before movement onset [109, 110]. With regards to hand movements, the main source of this "early" BP is believed be located in the bilateral SMA and lateral precentral gyrus [110], although some studies have reported higher amplitudes over the contralateral SMA [111]. This pre-movement activity suggests a role for the SMA in the preparation of upcoming movement and its bilateral presence, in addition to its connection to ipsilateral and contralateral M1 [108], makes the SMA a perfect candidate for an integrative role in coordinating bimanual movements [112]. Following the early BP, there is an increase in its gradient approximatively 400ms before movement onset, which exhibits a markedly different scalp distribution and is called Negative Slope (NS0) [113]. The NS0 originates in M1 and PMC, shows precise somatotopy [110, 111], and if it is bilaterally distributed during unilateral hand movements, rather than being predominantly contralateral, bilateral activation of M1 is present and may result in MM, probably through the lack of transcallosal inhibition [110]. Following contralateral NS0 is the motor potential (MP), which peaks concurrently with movement onset. The MP is localized in a restricted area of the contralateral scalp and is though to reflect the activity of pyramidal tract neurons taking place in the contralateral M1 [110]. These finding are in agreement with the SMA playing a major role in the preparation of movement, since it is activated early during motor preparation and is bilaterally distributed. This bilateral activation is followed by restricted contralateral activations in PMC and M1, which in turn will give rise to strictly unilateral movements.

2.4.3 Basal ganglia

It has also been suggested that the basal ganglia could play a substantial role in sequential movements, in the timing movements, in selecting the muscles required for a motor task as well as for the execution of overlearned motor programs [114]. With this in mind, it is not surprising that the SMA receives strong indirect projections from the basal ganglia (GPi) via the thalamus [115]. In PD, evidence points out to impaired basal ganglia function through depleted substantia nigra dopaminergic cells, leading to reduced motor control [116]. Interestingly, MM are one of the symtpoms that can be present in PD [83]. There is neurophysiological evidence that MM in PD are the result of M1 activation ipsilaterally to the intended movement rather than resulting from the presence of an ipsilateral CS pathway [83].

Hence, it has been hypothesized that MM in PD are the result of a deficiency of the basal ganglia to support the cortical network that is believed to underlie non-mirroring transformations necessary for unilateral movements [49, 83]. Dysfunctional basal ganglia should have a consequence on its output towards the SMA, which is what is seen in PD, where cerebral blood flow in SMA is reduced compared to healthy individuals [117]. Further evidence that the SMA is impaired in PD comes from the fact that the early BP is reduced [118]. An alternative explanation for the presence of MM in PD is that abnormalities of the basal ganglia can lead to a loss of cortical inhibition, which may produce excessive activation in superfluous muscles when performing voluntary movement [119]. Indeed, intracotrical inhibition has been shown to be reduced in untreated PD patients, reflecting abnormal excitability of the motor pathway [120].

To perform lateralize unilateral movements the brain relies on a distributed network which seem to imply the dPMC, the SMA and the basal ganglia. The disruption of any part of this network enhances the natural tendency towards symmetrical bimanual movement. But only modest effects are seen when disrupting parts of this network suggesting that none of these brains regions are solely responsible for the non-mirroring process.

2.5 MM and aging

MM are seen in healthy children up to the age of 10 years and probably reflect the fact that a fully matured CC is associated with greater IHI, underlying the ability to perform complex unilateral motor tasks [5]. As was seen earlier, if MM continue after that age they are considered abnormal and are usually the consequence of the presence of an ispilateral fast-conducting CS tract originating from both M1 [4]. However, even in the absence of an aberrant ipsilateral projection, an intact CC is needed to restrict motor output in the hemisphere contralateral to an intended movement. As such, if the CC is dysfunctional, for instance in schizophrenia [65], motor abnormalities such as increased motor overflow can be seen [67]. Even in healthy subjects with an intact CC, physiological mirroring can be present, especially when performing complex and fatiguing motor tasks [35].

With increasing age, motor overflow also appears to increase [43]. This could be linked to the fact that normal aging is associated with numerous morphological changes within the brain, include atrophy of grey and white matter [121]. Neuroimaging studies have shown that in addition to quantitative decreases in white matter, the quality of the remaining WM is compromised in older adults [122]. In otherwise healthy older individuals, there is a decrease in the size and myelination of CC fibres, which is believed to lead to abnormal transcallosal communication. In turn, this would result in increased motor overflow to the hemisphere ipsilateral to the intended movement and ultimately MM. However, recent findings suggest that the naturally occurring reduction of transcallosal pathways is related to a surprising shift in the link between callosal integrity and IHI. Indeed, it was found that older adults with greater callosal tract integrity also displayed a reduction in IHI and significantly greater interhemispheric facilitation [123]. This is consistent with the HAROLD model proposed by Cabeza [124] in which it is suggested that age-related increases in bilateral activation may be a compensatory mechanism to maintain good functioning. There is evidence that the HAROLD model may generalize to motor function [125]. This would be consistent with the reported age-related amplification of motor overflow in more demanding tasks in the elderly since increasing the attentional demands of a given task is believed to favor recruitment of bilateral areas. This in turn would mean increased activity in the contralateral hemisphere resulting in mirror activity in the ipsilateral, non-active hand [44]. It is therefore not surprising that normally occurring recruitment of bilateral brain areas in a more demanding task, and the consequent motor overflow observed in healthy adults, seems to be enhanced with increasing age. Furthermore, since transcallosal integrity in older adults is associated with lower levels of IHI and a shift towards interhemispheric facilitation, it could partly explain the higher bilateral brain recruitment that is needed for the elderly to maintain good functioning in demanding tasks, but also as a consequence creating increased motor overflow. Taken together, these data suggest that healthy older adults benefit from interhemispheric cooperation between specific brain areas, which is reflected in higher interhemispheric facilitation, lower IHI and greater overflow to the contralateral motor cortex [123]. This also suggests an adaptive mechanism since greater motor overflow in older adults is associated with increased dexterity [43].

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Chapitre 3

Article 2 : Modulation of physiological mirror activity with transcranial direct current stimulation over dorsal premotor cortex

Modulation of physiological mirror activity with transcranial direct current stimulation over dorsal premotor cortex

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3.1 Abstract

Humans have a natural tendency towards symmetrical movements, which rely on a distributed cortical network that allows for complex unimanual movements. Studies on healthy humans using rTMS have shown that disruption of this network, and particularly the dorsal premotor cortex (dPMC), can result in increased mirror movements. The aim of the present set of experiments was to further investigate the role of dPMC in restricting motor output to the contralateral hand and determine whether physiological mirror movements (pMM) could be decreased in healthy individuals. Physiological mirror movements were assessed before and after transcranial direct current stimulation (tDCS) over right and left dPMC in three conditions: bilateral, unilateral left and unilateral right stimulation. Mirror EMG activity was assessed immediately before, 0, 10 and 20 minutes after tDCS. Results show that physiological mirroring increased significantly in the hand ipsilateral to cathodal stimulation during bilateral stimulation of the dPMC, 10 and 20 minutes after stimulation compared to baseline. There was no significant modulation of physiological mirroring in the hand ipsilateral to anodal stimulation in the bilateral condition or following unilateral anodal or unilateral cathodal stimulation. The present data further implicate the dPMC in the control of unimanual hand movements and show that physiological mirroring can be increased but not decreased with dPMC tDCS.

3.2 Introduction

In humans, symmetrical movement using homologous muscles has been shown to require less cortical activation when compared to asymmetrical bimanual movements or unilateral movements (Cincotta *et al.*, 2004; Grefkes *et al.*, 2008), which suggest that the brain has a natural tendency towards symmetrical movements (also referred as voluntary mirror movements). To overcome this natural tendency and perform strictly unilateral movements, the human brain relies on complex intra- and interhemispheric interactions that include a large number of cortical areas. These activations circumscribe the motor output in the active motor cortex controlling the intended movement and are therefore referred to as the "non-mirroring transformation network" (Cincotta *et al.*, 2004). Although this network allows unimanual movements, subtle motor overflow can be recorded in the contralateral inactive motor cortex, especially if a complex motor task is being performed by the active hand (Mayston *et al.*, 1999; Grefkes *et al.*, 2008). The overflow in the inactive motor cortex can result in involuntary motor activity of the homologous muscle representation, known as physiological mirror movements (pMM). Visible MM can be seen in children under 10 years of age, probably due to an immature cortex and partial myelinisation of the non-mirroring transformation network. If MM persist beyond this age, they are considered pathological (congenital mirror movements; cMM) and are most probably caused by an aberrant ipsilateral corticospinal motor tract (Cohen *et al.*, 1991; Cincotta *et al.*, 1994; Cincotta *et al.*, 2003; Cincotta & Ziemann, 2008; Franz *et al.*, 2015). Although visible MM usually disappear in healthy individuals after 10 years of age, subtle pMM can be recorded in adults under specific conditions. A procedure first described by Mayston and collaborators (1999) has been used to elicit mirror activity in healthy individuals (Mayston *et al.*, 1999). In this protocol, involuntary mirror EMG activity (pMM) can be generated if a participant maintains an isometric contraction with the "mirror" hand while performing brief unilateral voluntary phasic contractions with the contralateral hand.

There is growing evidence suggesting that the dorsal premotor cortex (dPMC) plays a significant role in the non-mirroring network. For example, Sadato and colleagues (1997) using positron emission tomography showed that the dPMC is more activated in asymmetrical

bimanual movements when compared to symmetrical movements (Sadato *et al.*, 1997). This was further investigated by Cincotta and colleagues (2004) who tested the functional relevance of the dPMC via the application of repetitive transcranial magnetic stimulation (rTMS) to disrupt dPMC function and measure its impact on pMM. It was shown that disruption of the right dPMC caused an increase in the excitability of the motor projection from the left primary motor cortex (M1) to the right mirror hand when the left hand was performing a voluntary contraction (Cincotta *et al.*, 2004). This result was also supported by Giovannelli and colleagues (2006) who showed that low frequency rTMS over the right dPMC increases pMM recorded in the right hand of healthy adults (Giovannelli *et al.*, 2006). These findings suggest that the right dPMC is involved in the non-mirroring network restricting motor output to the right M1 while it is performing a unimanual motor task with the left hand.

Transcranial direct current stimulation (tDCS) is a technique that is known to safely modulate cortical excitability of the motor cortex in healthy humans (Nitsche & Paulus, 2000). Using this device, it is possible to produce low amplitude currents (1-2 mA) that will modulate brain excitability (Nitsche & Paulus, 2000). For example, Williams and colleagues (2010) have shown decreases in corticospinal excitability in the left hemisphere, reduced transcallosal inhibition from the left to the right hemisphere, and improvements in motor learning with the left hand following bilateral tDCS with cathodal stimulation over the dominant, left M1 and anodal stimulation over the non-dominant, right M1 (Williams *et al.*, 2010). Following on this, increasing dPMC activity with tDCS stimulation over a region that includes the dPMC (dPMC+) could hypothetically decrease pMM. This could have significant clinical relevance since MM are present in many pathological conditions such as Parkinson's disease (Espay *et al.*, 2005) and stroke (Kim *et al.*, 2003). The aim of the present study was thus to determine whether pMM could be reduced in healthy individuals through modulation of dPMC activity. Because of the uncertainty in the excitatory and inhibitory nature of various tDCS electrode montages and stimulation parameters (e.g. (Batsikadze *et al.*, 2013; Monte-Silva *et al.*, 2013; O'Shea *et al.*, 2014), two distinct tDCS protocols were applied: "bilateral" tDCS (both electrodes placed over homologous dPMC) and "unilateral" tDCS (one electrode placed over dPMC and the return electrode placed over the contralateral supraorbital region).

3.3 Material and Methods

3.3.1 Experiment 1: effects of bilateral tDCS over the dPMC on pMM

Eight healthy participants (4 men and 4 women; mean age = 22; SD = .78) were recruited through public advertisements. The following exclusion criteria were used: psychiatric or neurological history, traumatic brain injury, presence of a pacemaker, piece of metal implanted in the skull or history of fainting, seizures or substance abuse. All subjects were right-handed and gave their written informed consent. The study was approved by the *Comité d'Éthique à la Recherche de la Faculté des Arts et Sciences de l'Université de Montréal* . The study was conform to the Declaration of Helsinki. Subjects received a financial compensation of $40 CAN for their participation. The study consisted of two tDCS sessions each separated by at least 48 h. Each participant was subjected to the two following conditions in a pseudo-randomized order: 1) bilateral tDCS stimulation: left anodal and right cathodal (LA/RC) stimulation over the dPMC+; 2) bilateral tDCS stimulation: left cathodal and right anodal (LC/RA) stimulation over the dPMC+.

Transcranial magnetic stimulation. Prior to tDCS, two self-adhesive electrodes were placed over the first dorsal interosseous (FDI) muscle on both hands and a ground electrode was positioned over the right wrist. The electromyographic (EMG) signal was amplified and filtered (20-1000Hz) using a Powerlab 4/30 system (ADInstruments, Colorado Springs, Colorado, USA). TMS was delivered through an 8 cm figure-of-eight coil connected to a MagPro stimulator with a biphasic current waveform (Magventure, Atlanta, USA). The coil was positioned flat on the scalp of the participants with the handle pointing backwards at an angle of 45 degree away from the midline. Single TMS pulses were delivered to the hand area of M1 to identify the optimal position (hot spot), which was defined as the coil position that elicited motor evoked potentials of maximum amplitude in the contralateral FDI muscle. This procedure was done for both hemispheres. The dPMC position was estimated as 3 cm rostral to the individually determined M1 hot spot on each hemisphere (Cincotta *et al.*, 2004; Giovannelli *et al.*, 2006).

Transcranial direct current stimulation. tDCS was delivered using a Magstim DC Stimulator (Magstim Ltd, Wales, UK) through a pair of conductive rubber electrodes (small square electrodes, 25cm^2) inserted into saline-soaked sponges and placed over the dPMC+ region. The polarity of the electrical stimulation (anodal or cathodal) was dependent upon the polarity of the electrode positioned over the dPMC+ ipsilateral to the mirror hand. For both conditions, current was ramped up for 15 seconds, remained constant at 1 mA intensity for 20 minutes, and then ramped down for 15 seconds.

Physiological mirroring. Subjects were comfortably seated on a chair with their arms fully supported by their legs and their palms facing upward. They were instructed to maintain a tonic contraction with the ipsilateral (to anodal or cathodal stimulation) hand (FDI_{MIRROR}) with the minimum strength needed to hold a pencil without dropping it. While maintaining this tonic contraction, participants were instructed to respond to an auditory signal by performing a voluntary phasic pinch contraction with the contralateral index and thumb (FDI_{VOL}), during which EMG signal which was recorded. Twenty trials were performed with an interval of two seconds. This task was performed before (baseline), 0, 10 and 20 minutes after tDCS. Physiological mirroring was defined as a significant increase in the averaged 100 ms background EMG activity of the tonically contracting FDI muscle of the mirror hand, starting exactly at the beginning of the phasic contraction of the contralateral active hand, compared to 1000 ms of background EMG activity prior to the phasic contraction, following Mayston et al. (1999).

3.3.2 Experiment 2 effects of unilateral tDCS over the dPMC on pMM

Sixteen healthy participants were recruited through advertisements. Eight participants received unilateral tDCS over the left hemishpere (two sessions: cathodal, anodal), and 8 participants received unilateral tDCS over the right hemisphere (two sessions: cathodal, anodal). The same exclusion criteria as in Experiment 1 were used. All subjects were right-handed and gave written informed consent. The study was approved by the *Comité d'Éthique à la Recherche de la Faculté des Arts et Sciences de l'Université de Montréal*. The study was

conform to the Declaration of Helsinki. Subjects received a financial compensation of $40 CAN for their participation. The study protocol was identical to Experiment 1 in terms of stimulation parameters (duration, intensity, electrode size) except for electrode positioning. Eight participants (3 men and 5 women; mean age = 21.5, SD = 2.73) were randomly assigned to the following conditions: 1) unilateral anodal tDCS (anode over *left* dPMC (LA) and cathode over *right* supraorbital (RS) area); 2) unilateral cathodal tDCS (cathode over *left* dPMC (LC) and anode over *right* supraorbital area (RS)). Eight additional participants (3 men and 5 women; mean age = 22; SD = 3.00) were randomly assigned to the following conditions: 1) unilateral anodal tDCS (anode over *right* dPMC (RA) and cathode over *left* supraorbital (RS) area); 2) unilateral cathodal tDCS (cathode over *right* dPMC (RC) and anode over *left* supraorbital area (RS)).

3.3.3 Statistical analysis

All 20 EMG traces of the FDI_{MIRROR} in each condition were rectified and averaged off-line. These measures were entered in a 2X2 repeated measures ANOVA with HAND (tonically contracted mirror hand: left or right) and CONTRACTION PHASE (two phases in EMG measurement of the mirror hand: 1000 ms of EMG signal in the tonically contracted FDI while the contralateral FDI is at rest and 100 ms of EMG signal in the tonically contracted FDI starting at the beginning of the phasic contraction of the contralateral FDI) to confirm the increase in physiological EMG signal in the FDI_{MIRROR}.

For bilateral stimulation, a 2X2X4 repeated ANOVA with SIDE (mirror EMG activity in the hand contralateral or ipsilateral to the tDCS target hemisphere), POLARITY (cathodal, anodal) and TIME (baseline, 0, 10 and 20 minutes after tDCS) as within-subjects factors. For unilateral stimulation a 2X2X4 mixed ANOVA was performed with SIDE (stimulated hemisphere) as the between-subjects factor and POLARITY and TIME as the within-subjects factors.

To determine whether tDCS modulated activity in the phasically contracting FDI (in intensity and duration), leading to changes in pinch force, two 2X2X4 ANOVAs with

POLARITY (contralateral to the phasic contraction: anodal; cathodal), HAND (left or right hand performing the phasic contraction) and TIME (baseline, 0, 10 and 20 minutes after tDCS) were performed. For intensity, EMG signal during the 20 phasic contractions (root mean square), for every condition, was rectified and averaged offline for the entire duration of the phasic burst. Averaged duration of the EMG signal was measured by identifying the beginning and end of the phasic bursts for every condition.

3.4 Results

3.4.1 Physiological mirror movements

To confirm that the protocol generated pMM, the baseline level of pMM was computed for all participants for the 3 conditions. A 2X2 repeated measures ANOVA (HAND; CONTRACTION PHASE) was computed. A significant increase in EMG signal was found in the mirror hand during voluntary contraction of the contralateral hand ($F= 21.2$; $p<0.001$) while no effect of HAND (right vs left) was found ($F=0.63$; $p=0.44$). Of the 24 participants, 22 showed pMM, defined as an increase in EMG activity in the tonically contracted hand during contralateral phasic movements. Since no difference was found for the hand factor, all the pMM data were collapsed in the SIDE factor (target hemisphere).

3.4.2 Experiment 1

The effects of bilateral tDCS (i.e. LA/RC, LC/RA over both dPMC+) on pMM are presented in Figure 1. A 2X2X4 repeated measures ANOVA (side; polarity; time) was computed on the EMG data (averaged EMG signal in the tonically contracting hand beginning with the phasic contraction (100 ms) over the preceding EMG signal (1000 ms)) for each condition. No significant main effect was found for side ($F=1.96$; $p=0.21$), polarity ($F=.002$; $p=0.96$) or time ($F=1.07$; $p=0.38$). However, a significant interaction between polarity and time was found ($F=3.84$; $p=.025$). Post-hoc t-tests revealed a significant increase in pMM 10 minutes ($t=2.48$; $p=0.04$) and 20 minutes ($t= 4.39$; $p= .003$) following ipsilateral cathodal/contralateral anodal stimulation compared to baseline. For ipsilateral

anodal/contralateral cathodal stimulation, no significant difference was found between baseline pMM and post-stimulation pMM 0, 10 and 20 minutes after stimulation.

EMG activity in the phasically contracting FDI was assessed with two 2X2X4 repeated measures ANOVAs with POLARITY, HAND, and TIME as factors. For both intensity and duration, there was no significant main effect and no interaction between factors (all $p > 0.05$; Table 1).

3.4.3 Experiment 2

The effects of unilateral tDCS over dPMC+ (i.e. LA/RS, LC/RS over left dPMC+ and RA/LS, RC/LS over right dPMC+) on pMM are presented in Figure 3. A 2X2X4 mixed ANOVA (hemisphere; polarity; time) was computed (averaged EMG signal in the tonically contracting hand beginning with the phasic contraction (100 ms) over the preceding EMG signal (1000 ms)). No significant effect of hemisphere ($F=.039$; $p=0.54$), polarity ($F= 4.18$; $p=0.06$) or time ($F=2.42$; $p=0.08$) was found. There was no significant interaction between factors.

3.5 Discussion

The aim of the present study was to determine whether normally occurring pMM could be reduced in healthy participants using tDCS over a region that includes the dPMC (dPMC+). Bilateral stimulation of homologous dPMC+ resulted in increased pMM in the hand ipsilateral to the dPMC+ receiving cathodal stimulation. The increase in pMM was significant 10 and 20 minutes after stimulation for both left and right hands. When polarity was reversed in the bilateral stimulation condition, or following unilateral anodal and unilateral cathodal stimulation, pMM were not modulated at any time point. Thus, and contrary to the hypothesis, physiological mirroring could not be reduced with tDCS of the dPMC+.

The present findings show that pMM could be modulated when cathodal stimulation was

administered over ipsilateral dPMC+, but only when anodal stimulation was simultaneously applied over the contralateral dPMC+. Indeed, cathodal stimulation alone (with the anode over the contralateral supraorbital region) did not increase or decrease pMM. Bilateral tDCS over both primary motor cortices has generally been shown to increase corticospinal excitability under the anode and reduce corticospinal excitability under the cathode (Mordillo-Mateos *et al.*, 2012; Tazoe *et al.*, 2014); but see (O'Shea *et al.*, 2014)). If this pattern of effects holds for dPMC+ stimulation, the present findings would be consistent with rTMS data showing that 1 Hz rTMS over the right dPMC, which is believed to be inhibitory, increases physiological mirroring in the ipsilateral hand (Giovannelli *et al.*, 2006). However, the present results suggest that modulation of interactions between both dPMC+ may also contribute to the tDCS effects since additional contralateral anodal stimulation was required to modulate pMM. Indeed, in such a design, stimulation effects should not be limited to each individual dPMC+, but also to the inhibitory/excitatory balance between both regions. In that regard, bilateral stimulation of primary motor cortices has been shown to significantly alter interhemispheric inhibition (IHI), where left anodal/right anodal tDCS decreases *left to right* IHI while at the same time decreasing *right to left* IHI (Tazoe *et al.*, 2014). Taken together, these data suggest that a combination of cathodal tDCS over ipsilateral dPMC+ and anodal tDCS over contralateral dPMC+ has a stronger effect of pMM than dPMC+/supraorbital tDCS. It is worth noting that some clinical evidence (Vines *et al.*, 2008; Lindenberg *et al.*, 2013; Sehm *et al.*, 2013) supports the idea that "bilateral" tDCS may be more efficacious in certain conditions.

Interestingly, no significant difference was found between hemispheres, where both left and right cathodal stimulation over the ipsilateral dPMC+ resulted in increased pMM in the bilateral protocol. This is a novel finding since previous studies have targeted the right dPMC, highlighting its role in restricting MM in the right hand (Cincotta *et al.*, 2004; Giovannelli *et al.*, 2006). The present results suggest that the left dPMC may also contribute in restricting MM in the inactive left hand, therefore playing a part in the non-mirroring network sustaining unimanual movement of the dominant right hand. However, since stimulation is bilateral, increased pMM in the left hand could be the result of increased activity in the contralateral right dPMC+ rather than decreased activity in the left dPMC+, as well as the interaction between both homologous areas.

Further studies are needed to clearly disentangle the contribution of right and left dPMC in the non-mirroring network. One avenue could be to investigate specifically the role of the left dPMC in the non-mirroring network using rTMS over the left dPMC.

The involvement of dPMC+ in focalizing motor output to the contralateral M1 during voluntary movements is well-established (Cincotta *et al.*, 2004). However, the present data suggest that the role of ipsilateral dPMC in restricting motor output to the contralateral hand is limited, since pMM were only moderately enhanced and did not result in visible MM, similarly to what was previously reported with rTMS (Cincotta *et al.*, 2004; Giovannelli *et al.*, 2006). This suggests the involvement of other structures forming a distributed cortical network restricting motor output to the active hand. Conversely, tDCS may not provide enough focality to elicit visible MM. Indeed, tDCS applied with 25cm^2 electrodes undoubtedly reaches additional areas believed to be part of the non-mirroring network, such as SMA (Laplane *et al.*, 1977; Chan & Ross, 1988; Sadato *et al.*, 1997) and M1 (Duque *et al.*, 2007; Hubers *et al.*, 2008). As a result, tDCS may simultaneously modulate activity in areas that have differing roles in limiting mirror output, resulting in subtle effects that are the result of complex interactions between modulated areas. High-definition tDCS (Edwards et al., 2013), which provides focal electrical stimulation to the brain, may provide an oportunity to disentangle the respective contribution of specific cortical areas in restricting motor output to the contralateral hand.

Finally, the failure to decrease pMM has clinical implications for patients with mirror movements. Indeed, different stimulation protocols, sites of stimulation and polarities were chosen in the present study to maximize the possibility of decreasing pMM in healthy participants and ultimately reducing mirror movements in patient populations. Although the present approach was not successful, it has been repeatedly shown that slight changes in tDCS parameters can yield widely differing after-effects. For example, increasing stimulation intensity from 1mA to 2mA reverses the effects of cathodal stimulation (Batsikadze *et al.*, 2013) whereas increasing stimulation duration from 13 minutes to 26 minutes reverses the effects of anodal tDCS (Monte-Silva *et al.*, 2013). This suggests that a systematic evaluation of stimulation parameters such as stimulation intensity and duration as well as electrode size

may lead to the discovery of an optimal set of parameters that can significantly reduce pMM. Despite these results, the present findings offer significant insight into the neural underpinnings of the non-mirroring network that may ultimately provide greater understanding of the pathophysiology of mirror movements and lead to successful treatment approaches.

3.6 Acknowledgements

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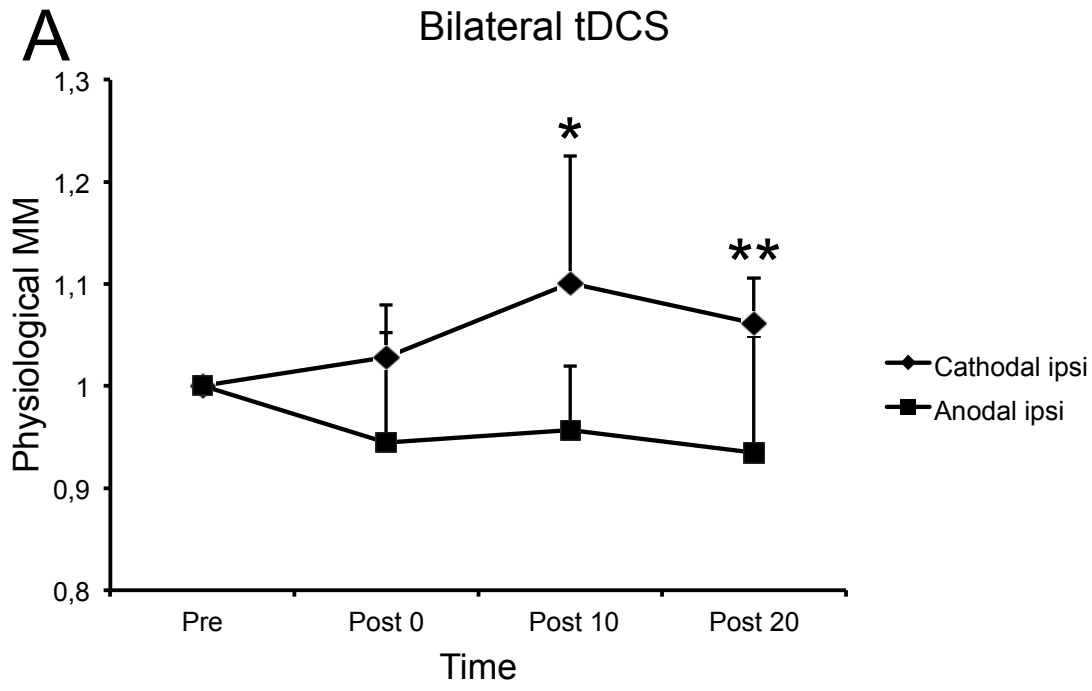
3.8 Figure

Figure 1: The effects of tDCS on physiological mirror movements

Legend : **(A)** FDI_{MIRROR} EMG activity before and after bilateral stimulation of dPMC+ (averaged EMG signal in the tonically contracting hand beginning with the phasic contraction (100 ms) over the preceding EMG signal (1000 ms)). *Cathodal ipsi* represents EMG activity in the mirror hand while the ipsilateral hemisphere is receiving cathodal stimulation and the contralateral hemisphere is receiving anodal stimulation. *Anodal ipsi* represents EMG activity in the mirror hand while the ipsilateral hemisphere is receiving anodal stimulation and the contralateral hemisphere is receiving cathodal stimulation. **(B)** FDI_{MIRROR} EMG activity before and after unilateral stimulation of dPMC+ (averaged EMG signal in the tonically contracting hand beginning with the phasic contraction (100 ms) over the preceding EMG signal (1000 ms)). *Cathodal* and *anodal* represent EMG activity in the mirror hand ipsilateral to stimulation while the return electrode is placed over the contralateral supraorbital area. Bilateral stimulation increases pMM compared to baseline 10 and 20 minutes after stimulation, when the cathode is placed ipsilaterally to the mirror hand and the anode contralaterally to the mirror hand. * : $p<0.05$; ** $p<0.01$.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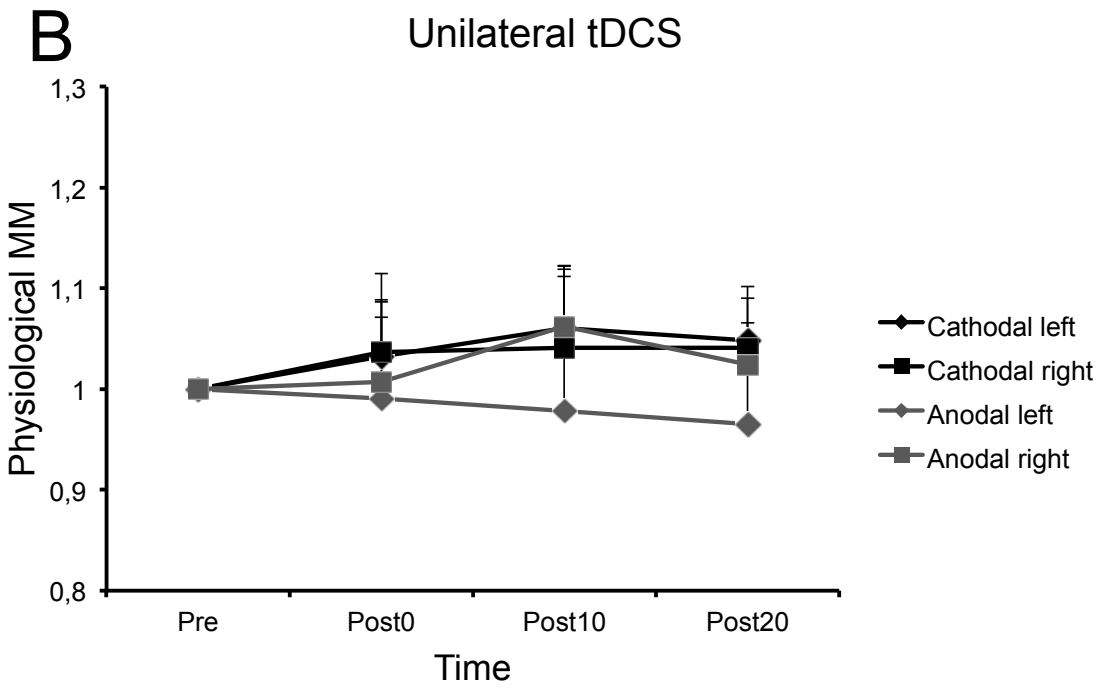
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Cathodal right
Anodal left
Anodal right

3.9 Table

Table 1. Intensity and duration of EMG activity in phasically contracting hand contralateral to stimulation polarity (data for right and left hemispheres are averaged)

Cathodal	Pre	Post0	Post10	Post20
Intensity	0.032	0.029	0.028	0.030
Duration	0.85	0.84	0.86	0.83

Anodal	Pre	Post0	Post10	Post20
Intensity	0.039	0.034	0.032	0.034
Duration	0.81	0.78	0.79	0.81

Chapitre 4

Article 3 : Cortical thickness in adults with agenesis of the corpus callosum

Cortical thickness in adults with agenesis of the corpus callosum

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4.1 Abstract

Agenesis of the corpus callosum (AgCC) is a congenital malformation that can occur in isolation or in association with other neurological conditions. Although the behavioral manifestations associated with AgCC have been widely studied, the effects of complete absence of the corpus callosum (CC) on cerebral cortex anatomy are still not completely understood. In this study, cortical thickness in adults with complete AgCC was compared to a group of healthy controls. Results showed highly variable patterns of cortical thickness in AgCC individuals, with few areas showing significant and consistent alterations including primary visual cortex, primary somatosensory cortex and primary motor cortex. These results suggest relatively limited effects of AgCC on cortical morphology, which are mostly restricted to primary sensory and motor areas.

4.2 Introduction

The corpus callosum (CC) is the principal commissure of the brain connecting the two hemispheres with over 190 million axons (Tomasch, 1954). The maturation of the CC continues well after birth, and a fully mature and myelinated CC is generally seen in children at around 10 years of age (Armatas, et al., 1994; Giedd, et al., 1999; Mayston, et al., 1999). The major role of this white matter bundle is to allow the transfer and integration of information between homologous regions of the cerebral hemispheres. Early disruption in the maturation of the CC can lead to a developmental condition known as agenesis of the corpus callosum (AgCC), a relatively frequent congenital malformation ranging from complete absence to hypogenesis (partial absence) of CC fibers (Paul, et al., 2007). This condition occurs in 1:4000 individuals, making it one of the most common human brain malformations (Glass, et al., 2008). The etiology of AgCC has an identifiable cause in about 25% of the cases (Paul, et al., 2007), and is usually related to other neurological conditions, such as hydrocephalus (Schoner, et al., 2013), microcephaly (Paciorkowski, et al., 2013), or foetal alcohol syndrome (Paul, 2011). Recent studies have highlighted the potential contribution of specific genetic elements in the occurrence of AgCC independently of other brain conditions. Among them, the Disrupted-in-Schizophrenia 1 (DISC1) gene, named because of its possible role in schizophrenia and related disorders (Millar, et al., 2000), was found to be highly expressed in the developing CC of embryonic mice. Osbun and colleagues (2011) also identified a variant form of the DISC1 gene, possibly pathogenic, in 144 AgCC patients, further suggesting an important role of this gene in the development of the CC and in the etiology of AgCC (Osbun, et al., 2011; Paul, et al., 2007).

Since AgCC is an heterogeneous condition, symptoms can vary greatly between affected individuals, ranging from relative absence to severe impairment requiring special education and assistance in every day living (Paul, et al., 2004; Siffredi, et al., 2013). Nonetheless, although full-scale IQ can be lower than what is expected considering family history, global intelligence generally remains within normal limits (Chiarello, 1980). Moreover, individuals with AgCC show relatively mild dysfunction in interhemispheric communication, as very few disconnection deficits are observed (Duquette, et al., 2008; Lassonde, et al., 1991; Sauerwein,

et al., 1981). This contrasts sharply with what is observed in split-brain patients, for whom it is generally agreed that interhemispheric dysfunction is more severe and often present in the form of a disconnection syndrome (Sperry, 1968). Indeed, it is well established that complete section of the CC in adults abrogates or greatly impairs interhemispheric transfer of sensory information (Reuter-Lorenz, et al., 1995). Patients with surgical section of the CC are unable to compare sensory information when it is sent separately to each hemisphere (Gazzaniga, et al., 1965). In this population, although there seems to be a partial recovery of some of their deficits, most of these impairments are long-lasting (Goldstein, et al., 1975; Sauerwein and Lassonde, 1997; Serrien, et al., 2001). This suggests that the brain of individuals with AgCC is more efficient in its capacity to compensate and minimize the detrimental effects associated with the lack of its principal commissure, probably through neuroplastic adaptations during development.

Compensatory mechanisms in AgCC individuals have been associated with enhanced cerebral plasticity during childhood (Lassonde, et al., 1991), possibly allowing the recruitment of alternative neural structures to enable interhemispheric communication. Indeed, other naturally occurring pathways could assume increased interhemispheric communication during ontogenesis in the absence of callosal fibers, such as the anterior and posterior commissures (Lassonde, et al., 1991). There is also evidence from animal studies suggesting that nerve fibres can form synapses with atypical classes of cells when their conventional targets have unsuccessfully developed (Mariani, 1983; Wilson, et al., 1981). Lassonde and colleagues (1991) have suggested that early absence of callosal connections can induce pathways that would not have been formed under normal circumstances, accounting for the greater interhemispheric communication that is observed in AgCC subjects compared to split-brain patients. In that regard, different alternative pathways have been suggested to play a role in this compensatory mechanism, namely the anterior commissure, the intercollicular or posterior commissures and/or the reinforcement of existing ipsilateral connections (Lassonde, et al., 1991). Although these alternative pathways allow the maintenance of interhemispheric communication and possibly contribute to the superior performance of individuals with AgCC in comparison to split-brain patients, these compensatory mechanisms have their limits (Sauerwein and Lassonde, 1983). Indeed, in visual or sensorimotor tasks, when speed of

response and error ratios are taken into account instead of accuracy, AgCC patients are impaired comparatively to healthy controls (Lassonde, et al., 1988; Sauerwein and Lassonde, 1983). AgCC patients also have persistent deficits in bimanual coordination, characterized by slower performance and clumsiness (Chiarello, 1980; de Guise, et al., 1999; Mueller, et al., 2009). Other studies have reported that the congenital absence of the CC affects binaural listening performance (Hausmann, et al., 2005; Lessard, et al., 2002). A possible explanation for these results is that when the brain matures with total absence of the CC, it results in a lower level of cortical recruitment (Lassonde, et al., 1988). Thus, changes in cortical pathways accounting for the lack of callosal connections could alter the responsiveness of each hemisphere (Duquette, et al., 2008).

Animal research indicates that absence of the CC early in development can modify morphological characteristics of the brain. For example, Abreu-Villa et al. (2002) found evidence of a reduction in neocortical thickness in genetically modified AgCC mice (BALB/cCF strain) in regions usually characterized by rich callosal afferent connections (Abreu-Villaca, et al., 2002). These authors hypothesized that neurons that are normally intended to receive extensive callosal input die as a result of the loss of their afferents during the critical periods of cortical ontogenesis and synaptogenesis. This hypothesis is consistent with the well-established idea that neuronal survival relies upon activity-dependent processes during synapotogenesis (Jevtovic-Todorovic, et al., 2003; Mennerick and Zorumski, 2000). Indeed, callosal projections are known to have excitatory influences over the contralateral hemisphere (Bloom and Hynd, 2005), and callosal deafferention in the developing brain of AgCC mice may decrease the activity pattern of the neurons usually receiving strong callosal afferents, resulting in neuronal death (Ribeiro-Carvalho, et al., 2006). In humans, maturation of the CC coincides with a period of plasticity in which children improve intermanual matching, are able to name tactile stimuli in either hand and show better accuracy in transferring the locus of touch between hands (Galin, et al., 1979). At the same time, there seems to be great cortical development of the brain leading to the thinning of some cortical regions and thickening of others (Shaw, et al., 2006). Thus, individuals with AgCC present a unique opportunity to gain insight on the relationship between the development of callosal pathways and the maturation of the cortex. In the present study, cortical thickness was

measured in five individuals with complete AgCC and compared to a group of eleven healthy controls. Based on animal research, we hypothesize that the absence of CC would be associated with cortical thinning in numerous brain regions, predominantly located in primary sensorimotor areas.

4.3 Material and methods

4.3.1 Participants

Two groups of participants were recruited: 1) an experimental group comprising five participants with AgCC, and 2) a control group of eleven neurologically intact participants. The study was approved by the local ethics committee and all participants provided written informed consent prior to testing. The AgCC group had a mean age of 37.6 years (range 22-42) and an average IQ of 76. The control group had a mean age of 33.8 years (range 23-51) and consisted of six men and five women, three of which were left-handed. The average IQ of the control group was 111 based on the revised Wechsler Adult Intelligence Scale. The patients are described individually below.

M.G.

Case M.G. is a 34 year-old, left-handed man and the youngest child of a French Canadian family of four children, three of which have AgCC. He experienced respiratory difficulties at birth. At the age of 4, he had prolonged enuresis, impoverished motor coordination and delayed speech acquisition that lead him to be referred to a neurologist; agenesis of the CC was then detected with pneumoencephalography. At age 8, a complete agenesis of the corpus callosum was confirmed with CT and MRI scans with preservation of the anterior commissure. M.G global IQ was 77 based on the Ottawa-Wechsler Intelligence Scale; he finished high school and is unemployed.

L.G.

Case L.G. is a 41 year-old, right-handed woman and is the third child from the family of M.G. She was born prematurely in the 7th month of gestation following a laborious breach birth.

When she was 3.5 years, she suffered a light cranial trauma caused by a fall on the head, which required hospitalisation. An EEG was then performed revealing a slow dysrhythmia without epileptic foci. She was re-hospitalized at 6 years for elective mutism and ataxia. No neuropsychological deficits were observed, but pneumoencephalography revealed agenesis of the corpus callosum, which was later confirmed by CT and MRI when she was 17 years old. The scans revealed a normal anterior commissure. As a child, she had to attend special classes for children with learning disabilities. Mutism and ataxia vanished, and she seemed socially well adjusted. L.G.'s full scale IQ is 78 based on the Ottawa-Wechsler Intelligence Scale.

S.G.

Case S.G. is a 42 years-old, right-handed woman. She is the oldest sister of M.G. and L.G. Like her siblings, she was born following a breach delivery. She was asymptomatic with the exception of a slow acquisition of walking related to motor incoordination usually noticed in callosal agenesis during development. Her milestones were otherwise considered normal. She volunteered with her parents to have a CT scan to investigate the presence of the congenital abnormality in her family. It was then discovered that she had complete callosal agenesis and an intact anterior commissure. S.G has a global IQ of 84 based on the WAIS-R, graduated from high-school and is employed in a home for the elderly.

S.P.

Case S.P. is a 35 years-old, left-handed man. S.P reports that he suffered several concussions as a child, but these events were not registered in his medical file. He quit school when he was in sixth grade and started working when he was 13 years old. When he was 23 years old, he suffered ventriculoperitoneal derivation for hydrocephaly, which provoked absence seizures. The MRI showed complete absence of the corpus callosum with an intact anterior commissure. S.P.'s global IQ is 75 based on the WAIS-R.

J.P.L.

Case J.P.L. is a 22 years-old, right-handed man. When he was born he had an abnormal cardiac rhythm and suffered from anoxia. J.P.L. was diagnosed with a complete callosal

agenesis and colpocephaly. At the time of the scan he was living with both his parents and had a part-time job. He has finished high school and his global IQ is 65 based on the WAIS-R.

4.3.2 MRI acquisition and analysis

Magnetic resonance images were acquired on a Siemens 3T Magnetom TIM TRIO scanner with a 12-channel head coil (Siemens, Erlangen, Germany) with the following acquisition parameters: three-dimensional high-resolution T_1-weighted images of the brain, sagittal MP-RAGE sequence (number of slices: 176; 1 mm^3 resolution; repetition time: 2300 ms; echo time: 2,91 ms).

Cortical thickness analysis

High-resolution T_1-weighted images were preprocessed using the CIVET pipeline (McConnell Brain Imaging Center, McGill University, Canada). Preprocessing included non-uniformity corrections, brain extraction, segmentation of grey/white matter tissues, and computation of white and grey matter surfaces using 81,920-polygon meshes. Cortical thickness was computed from the distance between corresponding nodes in the grey and white matter surface meshes. After registration to a standard MNI space, patients/controls comparisons were carried out using the SurfStat toolbox (www.math.mcgill.ca/keith/surfstat/) running on Matlab©.

Analysis of cortical thickness was conducted using three methods. First, individual patient differences with the control group were assessed following the method of Boes et al. (2012)(Boes, et al., 2012). This comparison was performed by computing a 95% confidence interval around the mean thickness of the control group for every node, and testing the null hypothesis that each corresponding node in individual patients is included within this confidence interval ($P < .05$, uncorrected). Following this, the consistency of cortical thickness patterns among the AgCC group was evaluated by conducting a conjunction analysis, where nodes that were statistically different in every patient and displayed the same direction of change (i.e. patient < controls, or patient > controls) were labeled and visualized on an average surface map to identify common differences in cortical thickness among patients. Secondly,

between-group differences were assessed using a general linear model with group contrasts (i.e. patients – controls) at each node, corrected for multiple comparisons using false discovery rate (Storey, 2002). Thirdly, variations in cortical thickness were assessed in regions of interest (ROI) consisting of the main primary cortices (primary motor cortex (M1), hand region of M1, primary somatosensory cortex (S1), primary auditory cortex (A1), and primary visual cortex (V1)), defined using the AAL atlas (Tzourio-Mazoyer, et al., 2002). The selection of these ROIs was based on studies suggesting behavioral effects of AgCC associated with primary sensorimotor areas (Moes, et al., 2009; Schilmoeller and Schilmoeller, 2000). Independent sample t-tests were used for ROI analysis (alpha level $P < .05$, uncorrected).

4.4 Results

The total absence of a corpus callosum was confirmed in all 5 AgCC participants using anatomical MRI (Figure 1). At the individual level, each AgCC patient showed numerous, albeit heterogeneous, areas of cortical thickness abnormalities compared to the normative group (Figure 2 & Table 1). To establish the presence of consistent morphological differences amongst the AgCC group in comparison to controls, a conjunction analysis was performed, revealing cortical areas that were either consistently thicker or thinner in all of the AgCC patients (Figure 3). This analysis revealed the presence of very small areas of consistent thickness abnormalities in the anterior cingulate cortex bilaterally, left primary somato-sensory cortex, left primary visual cortex and left orbitofrontal cortex, all of which were thicker. Between-group whole-brain analysis showed small areas of significant cortical thickening located in the medial part of the brain, namely in the posterior cingulate, the anterior portions of the cingulate cortex bilaterally, and the left calcarine sulcus (Figure 4). Finally, an analysis was performed on regions of interest (ROIs) defined *a priori*. No significant difference in cortical thickness was observed in primary motor cortex and primary auditory cortex. Significant areas of cortical thickening were found in the M1 hand area ($F = 4.92_{(1.14)}$, $p = 0.044$), primary somatosensory cortex ($F= 4.83_{(1.14)}$, $p = 0.045$) and primary visual cortex ($F=5.22_{(1.14)}$, $p = 0.039$).

4.5 Discussion

The primary aim of the present study was to determine whether congenital absence of the corpus callosum is associated with aberrant cortical morphology in adults. This was achieved by individually comparing cortical thickness of subjects with AgCC to a group of healthy controls, investigating between-group differences at the whole-brain level and, based on previous behavioral evidence (Moes, et al., 2009; Schilmoeller and Schilmoeller, 2000), and comparing cortical thickness in predefined ROIs. In general, results showed very few and limited effects of AgCC on cortical structure. Whole-brain analysis yielded subtle differences between groups, mostly located on the medial portion of the brain, while conjunction analysis revealed the presence of cortical thickening in spatially restricted areas that included somatosensory and visual regions. Finally, the ROI approach revealed cortical thickening in S1, V1 and the hand region of M1 in AgCC patients.

The presence of cortical thickening in human AgCC is at odds with animal studies that reported cortical *thinning* associated with congenital absence callosal fibers in regions normally richly innervated by the CC (Abreu-Villaca, et al., 2002; Ribeiro-Carvalho, et al., 2006). Reductions in cortical thickness in these acallosal animal models may not be directly comparable to what is observed in human subjects, however. For example, Ribeiro-Carvalho and collaborators (2006) reported reduced thickness in layers V (area 6) and II+III (border of area 17/18a) of mice in which the corpus callosum was surgically sectioned on postnatal day 1, leading to probable axotomy-related cell death. More closely related to the present data, Ribeiro-Carvalho et al. (2006) found similar cortical thickness decreases in BALB/cCF mice, where 7% of the animals are born with complete AgCC. In this case, the BALB/cCF genetic mutation itself may have had an effect on cortical thickness. Nevertheless, the presence of increased cortical thickness in human AgCC is intriguing. It has been suggested that increased cortical thickness in congenital disorders may be related to groups of neurons missing their migrating targets in the cortex forming nodules of neurons lining the brain or ventricular surface, thus increasing cortical thickness (Guerrini and Marini, 2006; Guerrini, et al., 2003;

Hyde, et al., 2007). Another possible explanation for increased cortical thickness is that aberrant neuronal migration can lead to faulty cortical organization, such as polymicrogyria (excessive number of small and prominent convulsion gap by enlarged sulci) (Guerrini and Marini, 2006; Hyde, et al., 2007). These aberrant cortical formations can manifest as epilepsy (Guerrini, et al., 2003) or be associated with dyslexia (Chang, et al., 2005) and are suggested to occur in congenital amusia (Hyde, et al., 2007). These hypotheses are coherent with AgCC since many neuronal targets during neuronal migration are sequestered into one hemisphere and could thus die during ontogenesis (as is suggested in mice) or form aberrant neuronal structures and artificially inflate cortical thickness.

Although patients with AgCC are surprisingly functional in everyday living, sensory and visual deficits can still be observed. For example, Schiavetto et al. (1993) found that AgCC patients have a higher threshold in a two-point discrimination task performed over the trunk (Schiavetto, et al., 1993). Other studies have found higher pain tolerance in AgCC (Doherty, et al., 2006; Moes, et al., 2009). It was also reported that AgCC patients have difficulties in depth perception, distance perception, color perception and binocular vision (Corballis and Finlay, 2000; Lassonde, et al., 1988; Moes, et al., 2009; Saint-Amour, et al., 2004). This is coherent with a study that found that 60% of their AgCC patient showed visual problems (Schell-Apacik, et al., 2008). Moreover, according to Schilmoeller and Schilmoeller (2000), visual problems are the second most frequent clinical feature in patients with AgCC (prevalence of 33%), after mental retardation. Other studies suggest also that AgCC patients display impaired visuomotor learning in a bihemispheric condition (de Guise, et al., 1999). Functional MRI data have also shown significant reorganization of visual cortical areas in individuals with AgCC (Bittar, et al., 2000). Taken together, these studies suggest a possible link between the pattern of abnormal cortical thickness in visual areas of the brain reported here and specific dysfunctions related to the processing of sensory information.

In addition to dysfunctions in sensory cortices, individuals with AgCC showed abnormal cortical thickness in the hand knob of the primary motor cortex. This is in line with behavioral data where motor impairments have been reported in individuals with AgCC. Indeed, it has been shown that children with AgCC acquire gross and fine motor function later

than healthy controls (Moes, et al., 2009). Transferring motor information between hands is also reported to be more difficult in individuals with AgCC (Chicoine, et al., 2000). Furthermore, de Guise and colleagues (de Guise, et al., 1999) reported motor coordination deficits in AgCC patients that were more pronounced in tasks requiring rapid motor execution. Along the same lines, studies have shown speed deficits in AgCC individuals when a motor component is required (Franz and Fahey, 2007; Mueller, et al., 2009; Silver and Jeeves, 1994). Interestingly, neurophysiological impairments have also been reported in the motor system of patients with AgCC. Using transcranial magnetic stimulation, Fecteau and colleagues (Fecteau, et al., 2006) found increased intracortical inhibition in the primary motor cortex of individuals with AgCC. Similarly to what was found for sensory areas, motor impairments in AgCC may be related to the abnormal pattern of cortical thickness found in primary motor cortex.

Although individuals with AgCC in the present study show significant abnormalities in cortical thickness in primary brain areas compared to healthy subjects, these differences are relatively mild when one considers the anatomical importance of callosal fibers. This is, however, in line with results from a recent study where the major white matter bundles of children with corpus callosum dysgenesis were found to be very similar to those of healthy controls in terms of morphology, fiber number and microstructure (Benezit, et al., 2015). Interestingly, very similar patterns of white matter interhemispheric asymmetry were also found between controls and children with corpus callosum dysgenesis. For example, a right bias in the corticospinal tract and the superior longitudinal fasciculus was found for both healthy and dysgenetic children (Benezit, et al., 2015). Along the same lines, Tyszka and collaborators (2011) have reported that patients with complete AgCC have, compared to healthy controls, nearly identical resting-state functional networks. Most notably, homotopic areas of the AgCC brain are highly correlated in terms of functional connectivity, suggesting the presence of interhemispheric interactions despite congenital absence of the corpus callosum (Tyszka, et al., 2011). This should not be taken to imply, however, that the brain of patients with congenital AgCC follows identical anatomical developmental patterns to that of healthy individuals. For example, axons that do not cross the midline during development to

become callosal fibers can form anterior-posterior tracts of white matter known as "Probst bundles" (Paul, et al., 2007). Additionally, a recent connectomic study found reduced global connectivity, increased local connectivity, and greater variability of intrahemispheric connectivity in individuals with AgCC compared to healthy controls (Owen, et al., 2013). It is important to note that in that same study, changes in the connectome were greater in AgCC individuals than what was predicted by a "virtual lesion" approach whereby the effects of removing callosal fibers are derived onto the normal connectome (Owen, et al., 2013). This suggests that the core dysfunction leading to AgCC may also impact non-callosal areas and that plastic reorganization probably compensates for the absence of callosal fibers (Owen, et al., 2013).

Further studies are needed to better characterize brain development and function in the absence of its principal commissure. For example, the conjunction analysis revealed a consistent thicknening in the anterior cingulate and the orbitofrontal cortex of AgCC patients. Although these regions did not appear as significantly different in whole brain analysis, it is interesting to note that these areas are involved in social behavior and introspection, two areas of known difficulties in AgCC patients (Paul et al., 2007). It should be noted, however, that the purported link between areas of abnormal cortical thickness and specific behavioral deficits in the present sample remains speculative in the absence of behavioral data. Future studies using larger sample sizes are necessary to clarify the link between structural abnormalities and motor, cognitive and social difficulties in AgCC patients.

4.6 Conclusion

Taken together, the present results suggest that the brain of AgCC individuals is characterized by distinct patterns of cortical abnormalities that may underlie the behavioral heterogeneity of the condition. Consistent differences in cortical thickness between individuals with AgCC and healthy controls were found to be relatively limited, however. Nevertheless, common areas of cortical abnormalities were present in primary motor, somatosensory and visual areas, paralleling some of the common behavioral deficits observed in AgCC. The

mechanism underlying the possible vulnerability of primary areas to the loss of callosal fibers remains to be determined. The presence of large, fast-conducting fibers in the specific parts of the CC that connect motor, somatosensory and visual areas, as opposed to smaller slow-conducting fibers connecting higher-order association areas (Doron and Gazzaniga, 2008; Fabri, et al., 2014), may offer some insight.

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4.8 References

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4.9 Figures

Figure 1. MRI of the five participants with AgCC in midsagital view showing total absence of the corpus callosum.

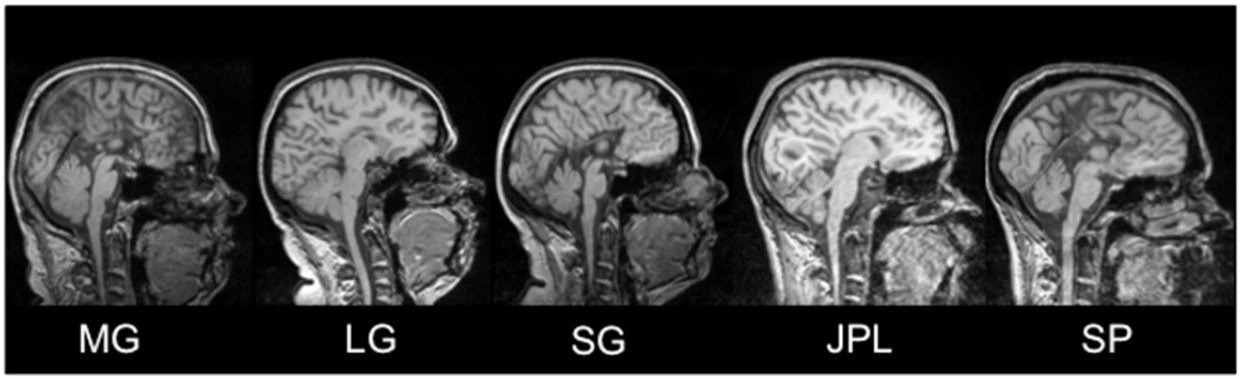


Figure 2. Cortical thickness results for the five AgCC patients, compared to healthy controls

Legend: Results are presented on the cortical surface of an average brain. Colors represent the magnitude of cortical thickness differences in millimeters for each AgCC participant.

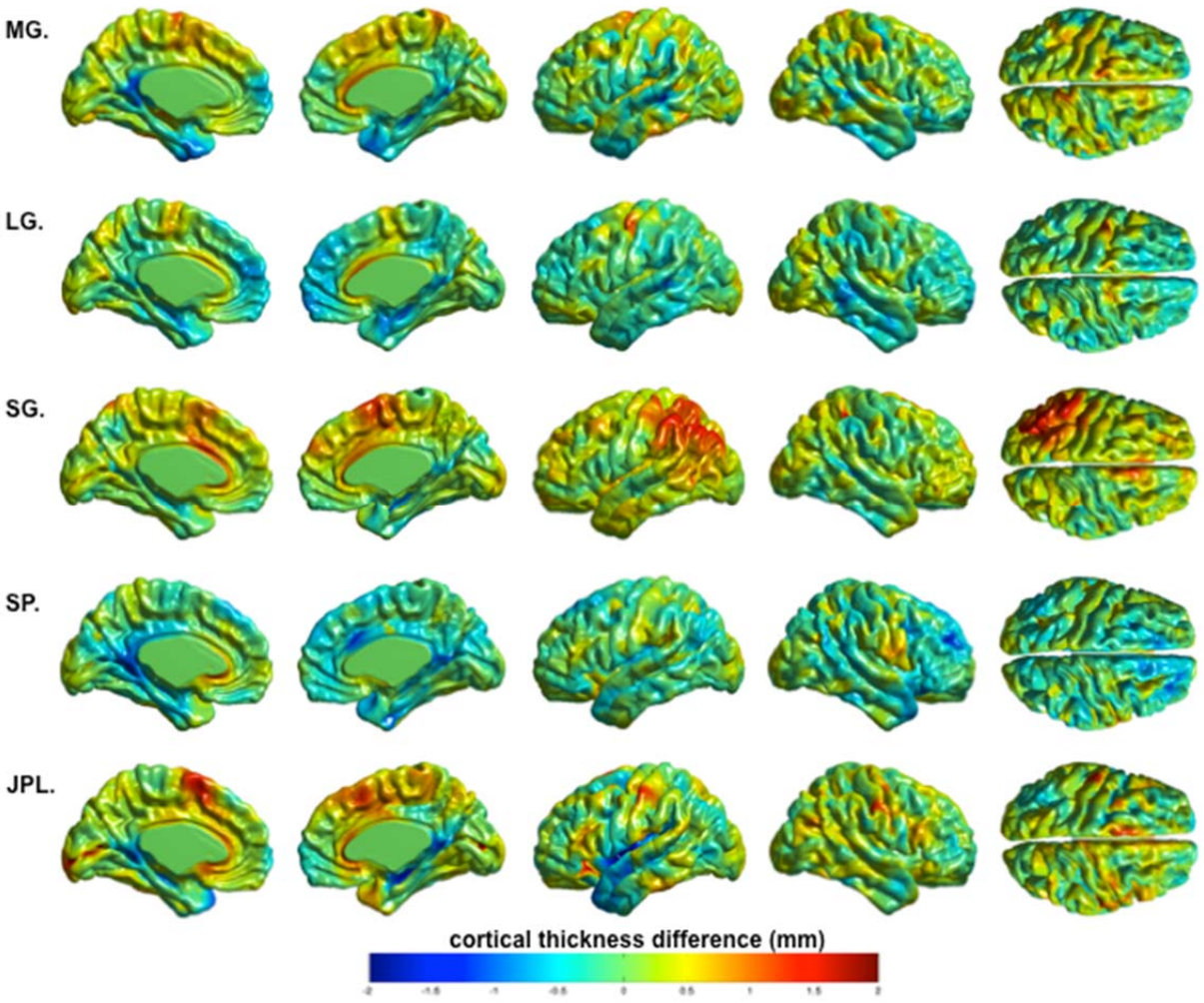


Figure 3. Conjunction analysis showing thickening or thinning of brain areas present in all subjects, compared to controls

Legend: Each color identifies a specific cluster, held constant in the different views.

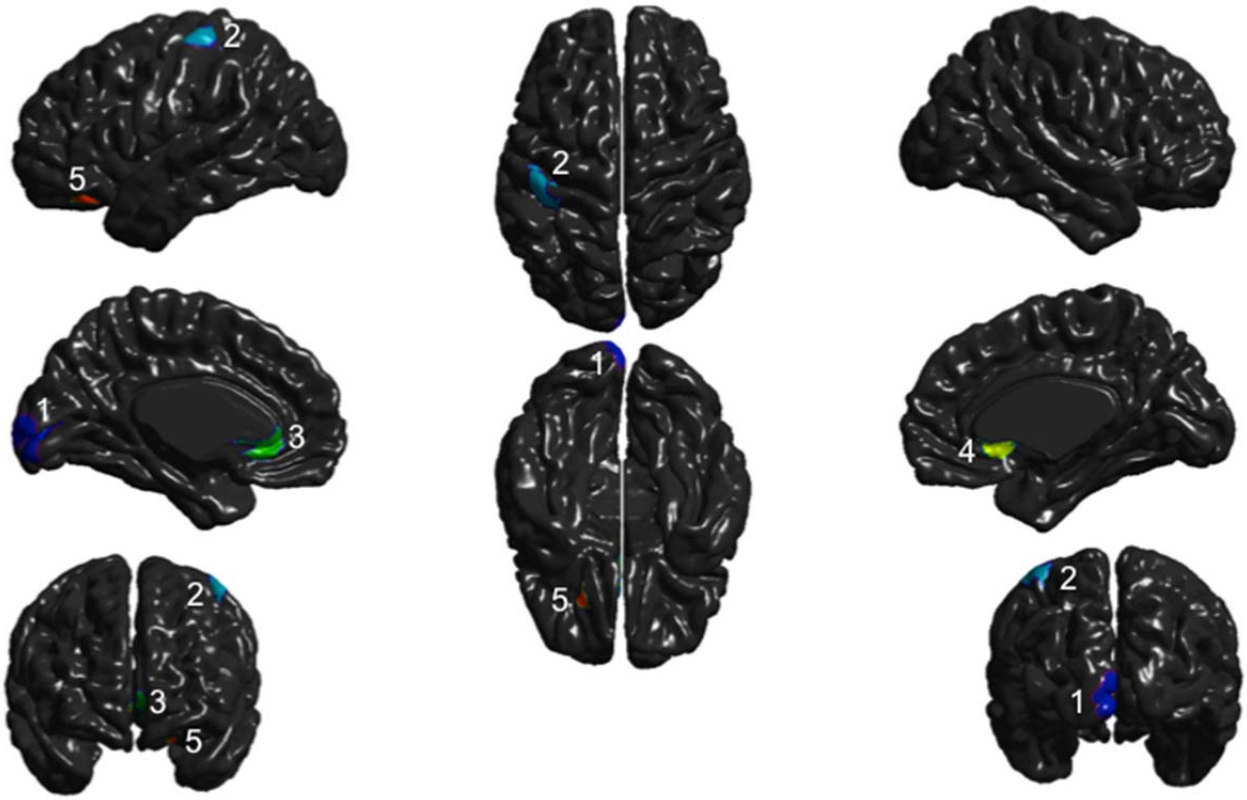
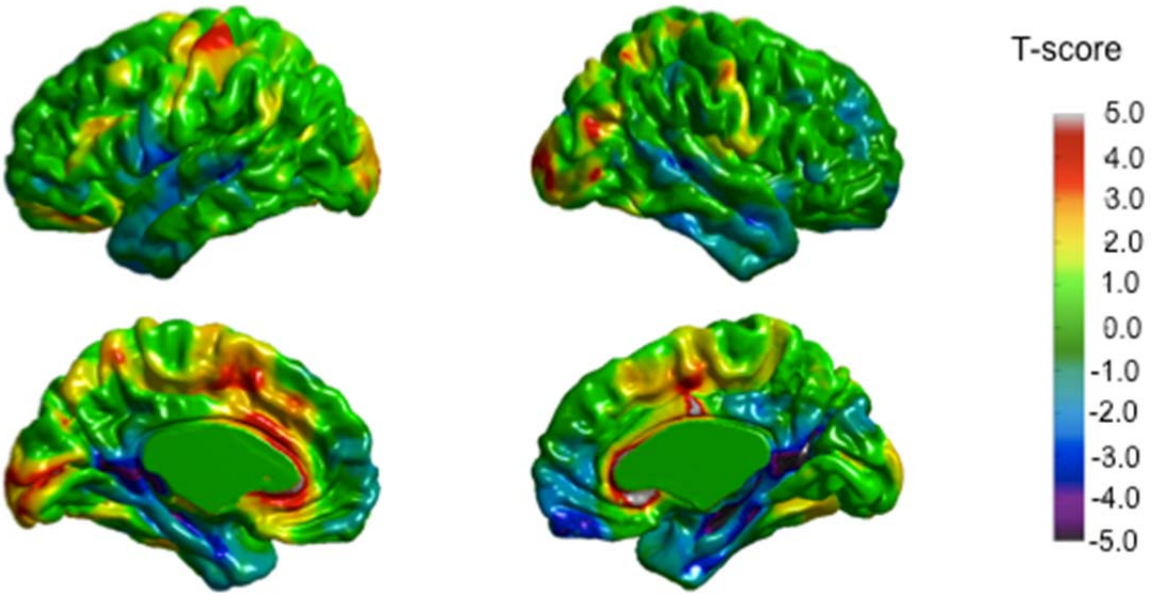


Figure 4. Whole brain analysis (t-values) of the combined AgCC patients compared to the control group



5.10 Table

Table 1. Areas of significant cortical thickness difference

Analysis	Cluster ID	*x*	*y*	*z*	*P*-value
Conjunction	1: V1 L	0.3	−99.2	4.4	
	2: S1 L	−46.1	−24.8	66.1	
	3: Ant-cingulate L	−4.6	29.7	−3.4	
	4: Ant-cingulate R	2.1	20.3	−6.1	
	5: Orbitofrontal L	−21.9	33.2	−21.7	
Whole-brain	Post-cingulate	2.35	−4.4	37.0	0.022
	Ant-cingulate R	1.9	21.7	−5.8	0.0001
	Ant-cingulate L	−3.2	30.5	−1.1	0.032
	Calcarine L	−0.4	−81.1	7.5	0.019
ROI	M1 Hand L	−34.8	−16.6	70.7	0.044

Chapitre 5

Article 4 : Neurophysiological investigation of congenital mirror movements in DCC mutation carriers

Neurophysiological investigation of congenital mirror movements in *DCC* mutation carriers

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Keywords: Mirror movements; DCC mutation; Neurophysiological investigation; TMS

5.1 Abstract

Congenital mirror movements (CMM) is a pathological motor condition in which normal voluntary movements of one side of the body are accompanied by involuntary movements of the homologous muscles on the opposite side. CMM usually affect upper limbs and have been linked to a mutation on the *DCC* or *RAD51* gene. While the role of *RAD51* in CMM is still unclear, *DCC* encodes the receptor for netrin-1 protein, which is involved in axonal guidance towards the midline. Here, transcranial magnetic stimulation, electromyography and behavioural tasks were used to assess motor function in individuals with a *DCC* mutation. Thirty-one members of a four-generation French Canadian family with CMM were recruited, 12 of whom had CMM and a *DCC* mutation. CMM+ and CMM- participants were compared to 14 unrelated healthy controls. Results show that CMM+ participants have an abnormal ipsilateral corticospinal tract causing CMM of various intensity. Only the CMM+ group displayed CMM, which were less pronounced than voluntary movements, except in one CMM+ participant. CMM+ participants also displayed weaker interhemispheric inhibition between primary motor cortices compared to CMM- and controls. The present study shows that CMM+ individuals have an abnormal motor pathway and suggests that individuals with a *DCC* mutation without CMM have a motor system very similar to that of healthy controls. Thus, although the *DCC* mutation is inherited in an autosomal dominant fashion, its penetrance is incomplete.

5.2 Introduction

In the embryonic brainstem of humans and other mammals, many major axon tracts preserve rigorous relationships with the midline to form precise pathways. Many of these tracts have to cross the midline, without recrossing it, to reach their target sites in the contralateral side of the body. This is the case of the corticospinal tract (CST), an axon tract connecting contralateral motor neurons that is more developed in humans and primates, allowing better manual dexterity than other species [1]. The correct migration of this major axon tract depends on specific cues that are present along its trajectory. These axon guidance cues present in the extracellular environment will either attract or repel the growing axon, depending on the receptors that are present at its surface. In humans and other mammals, netrins (attractive) and slits (repulsive) are two examples of guidance axon cues that are expressed by the ventral midline to guide the CST [2-4]. Their effect is highly dependent on receptors present in the growing axon cone, with deleted in colorectal cancer (DCC) receptors binding netrins to attract the CST towards the midline [2, 5-7] and Robo receptors binding slits to repulse the CST away from the midline [4, 8-11]. To allow the growing axons of the CST to migrate normally and ipsilaterally from their initial growing point in the cortex to the medulla, the growing CST is guided through a balance of netrin/DCC attraction and slit/Robo repulsion [12]. At the medulla, the growing axons modulate the attraction/repulsion balance by expressing a protein that will interfere with the binding of slit-repulsive cues to their Robo receptors [13, 14]. This allows the netrin/DCC receptors to attract most axons of the CST towards the midline and decussate contralaterally to continue down the spinal cord. A small percentage (8-10%) of the growing CST will remain ipsilateral, as they do not innervate the same motor neurons [15]. After crossing the midline, the interference protein is no longer expressed, allowing the slits to bind their repulsive Robo receptors, repelling once more the CST to ensure that it will not re-cross the midline [13, 14].

Although the correct guidance of axon tracts relies on complex interactions involving numerous genes, proteins and other molecules, there are relatively few known human disorders associated with axon guidance errors [16]. One manifestation of a CST-misguiding disorder is pathological mirror movements (PMM), a condition where the CST of the patient

does not completely cross the midline, resulting in an aberrant CST projecting to the ispilateral (mirror) hand. Thus, patients with PMM suffer involuntary movements of one side of their body that occur simultaneously with the intentional movement of the contralateral homologous muscle, but usually to a lesser extent [17]. Indeed, in PMM each motor cortex is connected to both sides of the body. PMM typically affect the distal upper extremities like fingers, hands and forearms of patients and persist throughout life [16]. Pathological mirror movements can be distinguished from physiological mirror movements (pMM), which can be seen in healthy young children and usually disappear around the age of 10, a period known for maturation of the cortex and myelination of the corpus callosum allowing efficient interhemispheric inhibition [18]. Physiological mirror movements can be investigated by applying transcranial magnetic stimulation (TMS) over the motor cortex of children, which elicits a motor evoked potential (MEP) in the contralateral hand as well as a delayed ipsilateral MEP, probably resulting from the transfer of the motor output across the corpus callosum (CC) towards the mirror motor cortex [19, 20]. When MM persist beyond 10 year of age, they are considered pathological and are then referred to as congenital mirror movements (CMM). Although similar at sight, pMM and CMM do not share the same neurophysiological underpinnings. When applying TMS over one motor cortex, children with CMM show two distinct mirror MEPs. The first MEP is temporally synchronized with the contralateral MEP, suggesting a pathological ispilateral corticospinal tract connecting the mirror hand. The second mirror MEP is delayed and probably results from transcallosal activation of the mirror M1, corresponding to normally occurring pMM seen in healthy children [19].

Three nonexclusive hypotheses have been proposed to explain CMM in adults [21-23]. A first hypothesis suggests that MM result from the transcallosal overflow of activity from the active motor cortex to the mirror motor cortex, eliciting involuntary mirror responses. Since motor signals need to cross the midline through the CC, the mirror response is usually seen 10 ms after the voluntary movement. These MM are supposed to generate pMM and are usually seen in children and older adults, due to reduced interhemispheric inhibition [18]. A second hypothesis proposes that MM are the result of an exclusively ipsilateral, pathological, fast conducting corticospinal tract connecting the ipsilateral hand. This tract exists normally in humans at birth and withdraws around the 15th postnatal month [24]. A possible explanation

for CMM would be that this naturally occurring ipsilateral projection persists due to genetic factors, which would prevent its normal withdrawal. Finally, the third hypothesis states that the CST does not completely cross the midline, resulting in a pathological ipsilateral projection that originates from the normally decussating contralateral CST [25, 26]. In this view, MM result from of a lack of decussation at the midline resulting in a pathological, not fully decussating, ipsilateral tract.

Mirror movements in CMM patients have been extensively documented [for reviews: 17, 21, 22, 27]. However, the identification of genetic mutations causing CMM in the absence of other neurological conditions remains elusive. To date, two genes have been identified as possibly causative in CMM: *DCC* [26] and *RAD51* [28], which account for 35% of affected individuals [17]. DCC plays a role in the guidance and decussation of axons at the midline [29, 30] whereas RAD51 is strongly expressed in the developing motor system and could play an important part in the decussation of the developing CST [28]. It was found that mutations in both of these genes are inherited in an autosomal dominant way, which means that an affected individual has a 50% chance of passing the mutation to an offspring. However, a child that inherits a *DCC* or *RAD51* pathogenic variant may never manifest CMM because of reduced penetrance of these mutations [17]. Indeed, depending on the type of mutation, the penetrance is not the same in affected individuals. For example, truncate variants (the mutation induces a premature termination during translation resulting in a shortened, usually non-functional protein) of the *DCC* or *RAD51* genes are associated with a penetrance of 50% [25, 26, 28] whereas missense variants (the mutation causes a different amino acid to be part of the protein, changing its final form and usually affecting its effectiveness) is associated with lower penetrance [25].

The precise relationship between *RAD51* deficiency and *CMM* is unclear and unexpected since it was first identified as playing a role in DNA repair by homologous recombination and maintenance of genomic integrity [31-33]. This led to the hypothesis that *RAD51* patients could have MM since lower *RAD51* levels in the developing CST would induce reduced genomic stability and increased apoptosis, which could then result in specific neurological defects causing MM [32, 33]. However, it was later found that *RAD51* is

expressed in cortical cells of mice during brain maturation. *RAD51* was detected in a subpopulation of the developing CST axons at the level of the pyramidal decussation, suggesting a role in axonal guidance [28]. This could explain why *RAD51* deficiency causes a pathological ipsilateral CST causing MM in this population. A neurophysiological investigation of patients with a *RAD51* mutation recently showed the following motor system abnormalities [34]: *1)* abnormal decussation of the CST; *2)* reduced interhemispheric inhibition (IHI) and bilateral activation of the primary motor areas (M1) during intended unilateral movements; and *3)* abnormal SMA activation for both unilateral and bilateral movements. These data suggest that the correct lateralization of motor commands requires a precise interaction between interhemispheric communication and corticospinal wiring.

The DCC gene was first thought to encode a tumor suppressor, where its absence or reduced expression was found in most late-stage human colon tumors [35, 36]. More recently, *DCC* was shown to be an axon guidance receptor, binding with netrins [37]. Mutations on the *DCC* gene were recently identified as causing CMM without other neurological abnormalities [26]. To date, 3 distant families with CMM and *DCC* mutations have been identified, two of which were caused by a truncate *DCC* protein lacking the netrin binding domain as well as the trans-membrane and cytoplasmic domains [16]. As expected, in vitro data corroborate that at least one *DCC* mutation significantly reduces netrin binding [26]. Thus, these mutations seem to result in *DCC* haploinsufficiency in humans causing a similar phenotype in all mutants (CMM) [22]. The relevance of both *DCC* and netrin in the correct migration of growing axon tracts has been highlighted in animal studies where a genetically modified DCC mutant allele was introduced in the genetic background of mice. Homozygotes for this mutant allele, called DCC-/- mice, were found to have complete *DCC* expression loss. These mice died shortly after birth and further analysis revealed complete agenesis of the corpus callosum and total absence of the hippocampal commissure. The axons forming these commissures were present but did not cross the midline, remaining ipsilateral and forming aberrant probst bundles. [7]. This confirmed a role for *DCC* in axon guidance in critical developmental stages, when axons need to cross the midline. Meanwhile, a less severe mutation, where the *DCC* gene results in a truncated *DCC* protein, like what is seen in CMM patients, resulted in viable mice. The mutation was called DCC_{Kanga}. Homozygote $DCC_{Kanga/Kanga}$ mice also displayed axon guidance

errors within the CC. Importantly, the CST failed to decussate at the midline, resulting in uncrossed ispilateral CST projections [38]. The phenotype of $DCC_{Kanga/Kanga}$ mice was found to mimic that of human CMM patients, as these animals could alternate the movement of their hindlimbs resulting in hopping movements, much like those of a kangaroo [38]. Taken together, these studies suggest a major role for *DCC* in the normal maturation of axon tracts and a link between *DCC* mutations and congenital mirror movements.

In the present study, motor function and physiology was systematically assessed in members of a large French Canadian family with a history of congenital mirror movements and *DCC* mutation [26]. More specifically, the neurophysiology of corticospinal projections and interhemispheric interactions was evaluated using single- and double-coil transcranial magnetic stimulation over primary motor cortex.

5.3 Material and Methods

5.3.1 Participants

Thirty-one members of a four-generation French Canadian family were recruited for this study. Twelve family members displayed visible CMM and a *DCC* mutation (DCC+/MM+; left-handed = 1, mean age = 44.18 (range: 20-63), males/females ratio = 5:2). Seven family members had a confirmed *DCC* mutation but did not display CMM (DCC+/MM-; left handed = 4, mean age = 49.71 (range: 27-72), males/females ratio = 2:5). The remaining 12 family members had no CMM and no DCC mutation (DCC-/MM-; left-handed = 2, mean age = 37,92 (range: 22-63), males/females ratio = 4:8). Fourteen unrelated healthy controls with normal neurological status, matched for age, gender and handedness (left-handed =1, mean age = 42.89 (range: 19-60), males/females ratio = 7:7) were recruited. All participants gave their written informed consent and the protocol was approved by the local ethics committee.

5.3.2 Genetics

Participants who have not been genotyped previously (Srour et al 2010) were characterized for *DCC* variants. Coding exons and the exon-intron boundaries of *DCC* were screened for mutations based on sequence (NM_005215) (UCSC March 2006 Assembly HG 18). Primers were taken from a previously published article (Srour et al 2010). PCR products were sequenced on the ABI 3700 sequencer at the Genome Quebec Centre for Innovation according to the manufacturer's recommended protocol (Applied Biosystems). Sequences were aligned and analyzed using SeqMan 4.03 (DNAStar, WI, USA) and Mutation Surveyor v.3.1 (SoftGenetics, PA, USA)."

5.3.3 Mirror movements

Prior to testing, two self-adhesive electrodes were placed on the first dorsal interosseous (FDI) muscle bilaterally and a ground electrode was positioned on the right wrist. The electromyographic (EMG) signal was amplified using a Powerlab 4/30 system (ADInstruments, Colorado Springs, Colorado, USA), filtered with a band pass of 20-1000Hz and digitized at a sampling rate of 4KHz. Mirror movements were investigated using two electrophysiological protocols. First, while participants were comfortably seated on a chair, they were asked to relax their arms with their palm facing upward while being fully supported by their legs. They were instructed to respond to an auditory signal by pressing, then releasing, a small stress ball three times with one hand while the other hand was at rest. This protocol was performed for both hands and repeated five times. A protocol known to generate pMM in healthy subjects was then performed [18]. In this task, participants were instructed to maintain a tonic contraction with one hand (FDI_{MIRROR}) using the minimal strength needed to hold a pencil without dropping it. Meanwhile, participants were required to respond to an auditory signal with their other hand by performing a voluntary phasic pinch contraction (FDI_{VOL}). This was performed twenty times for both hands. Physiological MM were defined as a significant increase in the background EMG activity of the hand maintaining the tonic contraction, starting at the moment of the phasic contraction of the FDI_{VOL} and lasting 100ms, compared to 1000ms of background activity prior to the phasic contraction.

5.3.4 Single pulse TMS

TMS was delivered through an 8 cm figure-of-eight coil connected to a Magstim 200 stimulator with a monophasic current waveform (Magstim, Whitland, UK). The coil was positioned flat on the scalp at an angle of 45 degree from the midline. Single pulse stimulation was performed over the hand area of M1 at the optimal position (hot spot) eliciting MEPs of maximal amplitude in the contralateral FDI muscle. Stimulation intensity was adjusted to elicit contralateral MEPs of 1mV amplitude. MEPs were recorded using Scope v4.0 software (ADInstruments). This procedure was performed ten times for each hemisphere and MEPs were recorded bilaterally in the FDI muscle to confirm the presence or absence of mirror MEPs in all subjects. Peak-to-peak amplitudes of contralateral and ipsilateral MEP were measured and averaged off-line.

5.3.5 Double-coil TMS

Interhemispheric inhibition (IHI) was measured using a protocol described by Ferbert and collaborators (1992) using two 50mm custom-made coils connected to two Magstim 200 stimulators (Magstim, Whitland, UK)[39]. Each coil was placed over their respective M1 hot spot in the right and left hemispheres. The intensity of each TMS pulse was adjusted to elicit MEPs of approximately 1 mV contralaterally. A test stimulus was preceded by a conditioning stimulus applied 40ms earlier. IHI was measured for left-to-right and right-to-left directions of inhibition.

5.3.6 Serial reaction time task (SRTT)

A modified version of the SRTT [40], running on Superlab (version 4.0; Cedrus, San Pedro, CA), was performed by all participants. The task consisted of the presentation of three dots and an asterisk displayed horizontally in alternating positions. The participant had to press, as fast and accurately as possible, a key corresponding to the location of the asterisk. In the first segment of the task, participants had to perform a total of 13 blocs using their right hand. Each of the blocks consisted of 10 repetitions of the same 12 items sequence. The two initial blocks were random-ordered sequence blocks, dissimilar from the subsequent repeating sequences. After the last block of the repeating sequence (S10), a third random block was

presented (R3). Sequence-specific learning was defined as the difference in RT between R3 and S10. After completing the first segment of the task, participants had to perform three additional blocks using their left hand. Again, the first two blocks were randomly ordered (R4, R5) and were followed by a block of the sequence presented previously in the first segment, but in a mirror image position (S/L). Transfer of the motor skill was defined as the difference between R5 and S/L.

5.3.7 Statistical analysis

As a first step, the DCC+/MM- and DCC-/MM- groups were compared on all measures to determine if the sole presence of a DCC mutation, without mirror movements, was associated with a different pattern of motor activity. As all statistical tests were non significant, the DCC+/MM- and DCC-/MM- groups were collapsed into a single group (MM-) for all statistical analyses. Statistical analysis was conducted with mixed ANOVAs using group (DCC+/MM+, MM-, controls) as the between-subjects factor. When required, post-hoc tests were conducted with a Bonferroni correction.

5.4 Results

5.4.1 Mirror movements

A DCC mutation was observed in 19 of the 31 family members. Of these 19 individuals, 12 presented mirror movements. The presence of mirror movements was systematically associated with TMS-induced MEPs in the ipsilateral hand. Ipsilateral MEPs could be induced by single-pulse TMS for all patients with MM, in every trial. In controls, DCC+/MM-, and DCC-/MM- patients, no ipsilateral MEPs could be evoked when stimulating at an intensity of up to 80% of maximum stimulator output. Whereas the amplitude of ipsilateral MEPs was smaller than contralateral MEPs in 7 patients with MM, a reverse pattern was observed in the remaining 5 patients (Figure 1A).

Amplitudes of ipsilateral and contralateral MEPs were compared between groups (Figure 1B). A mixed ANOVA was performed with raw MEP data with stimulated hemisphere (dominant, non-dominant), side (ipsilateral, contralateral) and group (DCC+/MM+, MM-, controls) as factors. There were significant main effects of side ($f=19.6$; $p<0.001$) and group ($f=11.1$; $p<0.001$). The interactions between side and group ($f=6.4$; $p=0.004$) and the interaction between hemisphere, side and group ($f=6.0$; $p=0.005$) were also significant. Decomposition of the three way interaction revealed that whereas contralateral MEPs were always of greater amplitude than ipsilateral MEPs in the MM- and control groups, they were of equal size in the DCC+/MM+ group when the dominant ($t=0.9$; $p=0.41$) or non-dominant ($t=0.6$; 0.66) hemisphere was stimulated. To determine whether ipsilateral MEPs were the result of a fact-conducting, ipsilateral corticospinal projection, ipsilateral and contralateral MEP latencies were compared in the DCC+/MM+ group. A repeated measure ANOVA with hemisphere (dominant, non-dominant) and side (ipsilateral, contralateral) was performed on MEP latency data. There was a significant main effect of side ($f=1.9$; $p=0.027$), where MEPs elicited from stimulation of the dominant hemisphere had a shorter latency. There was no difference in latency between ipsilateral and contralateral MEPs. Finally, to determine whether ipsilateral projections were similar for both hemispheres, ipsilateral MEP coefficients were computed with raw amplitude data (ipsilateral MEPs/contralateral MEPs) and correlated between the dominant and non-dominant hemispheres (Figure 1C). A significant correlation was found ($r=0.89$; $p<0.001$).

To validate the presence of MMs exclusively in the DCC+/MM+ patient group, a two-way mixed ANOVA was performed on the EMG data (mirror hand) collected during the ball squeezing procedure with stimulated hemisphere (dominant, non-dominant) and group (DCC+/MM+, MM-, controls) as factors. There was a main effect of group ($f=32.2$; $p<0.001$), which was explained by greater ipsilateral FDI activity in the DCC+/MM+ group compared to both the MM- ($p<0.001$) and control ($p<0.001$) groups (Figure 2A).

The presence of physiological mirror movements was also compared between groups with a two-way mixed ANOVA with stimulated hemisphere (dominant, non-dominant) and group (DCC+/MM+, MM-, controls) as factors. There was a significant main effect of group

(f=31.1; p<0.001), which was explained by greater pMM in the DCC+/MM+ group compared to both the MM- (p<0.001) and control (p<0.001) groups (Figure 2B).

5.4.2 Interhemispheric inhibition

Interhemispheric inhibition was measured from the dominant to the non-dominant hemisphere and from the non-dominant to the dominant hemisphere. A mixed ANOVA with direction (dom⇒non-dom, non-dom ⇒dom) and group (DCC+/MM+, MM-, controls) as factors revealed a main effect of group (f=12.9;p<0.001), which was explained by reduced IHI in the DCC+/MM+ group compared to both the MM- (p<0.001) and control (p<0.001) groups (Figure 3A).

5.4.3 Serial reaction time task

To determine whether groups performed differently on sequence-specific learning, a mixed ANOVA with block (A10, R3) and group (DCC+/MM+, MM-, controls) as factors was performed. There was a significant main effect of block (f=27.3; p<0.001). This shows that all three groups learned the sequence equally. To determine whether groups transferred the newly learned sequence to the left hand equally, a mixed ANOVA with block (R5, S/L) and group (DCC+/MM+, MM-, controls) as factors was performed. There was a significant main effect of block (f=4.8; p=0.035). This shows that all three groups transferred the sequence equally to the left hand.

To determine whether learning a new motor task had an effect on interhemispheric interactions, physiological mirror movements were assessed immediately after the SRTT and compared to pMM before the SRTT. A coefficient of change (pMM pre-SRTT/pMM post-SRTT) was computed and entered in a repeated measures ANOVA with hemisphere (dominant, non dominant) and group (DCC+/MM+, MM-, controls) as factors. There was a significant main effect of group (f=17.4; p<0.001), where pMM significantly increased in the DCC+/MM+ group compared both the MM- (p<0.001) and control (p<0.001) groups (Figure 3B).

5.5 Discussion

In this study, the neurophysiology of the motor pathway was assessed in a large family in which some members present a DCC gene mutation and congenital mirror movements. The study revealed that: *1)* Patients with a DCC mutation but no CMM have neurophysiological motor responses similar to those of family members without a DCC mutation and to those of healthy controls; *2)* In patients with a DCC mutation and CMM, TMS-induced ipsilateral MEPs are present in 100% of the trials when contralateral MEPs have an amplitude of approximately 1mv; *3)* Latency data suggest that CMM in DCC+ individuals are the result of a fast-conducting, ipsilateral projection; *4)* Mirror responses elicited from the dominant and non-dominant hemispheres are undistinguishable; *5)* Patients with CMM show reduced interhemispheric inhibition originating from both the dominant and non-dominant hemispheres; *6)* Patients with CMM show normal motor learning and interhemispheric transfer of a newly acquired motor skill; *7)* In patients with CMM, learning a motor skill is associated with increased physiological mirror movements.

Individuals with a DCC mutation but no visible CMM were identical to healthy controls and family members with no DCC mutation, on all measures. Interestingly, Franz and collaborators [41] reported that three individuals carrying either a *DCC* or *RAD51* mutation with no visually discernable MM showed subtle but unequivocal CMM detected by accelerometer-equipped gloves. It is also well documented that patients with CMM can learn to suppress parts of unintended movements with increased attentional focus. Thus, it may be that some of the DCC+/MM- patients in the present study did have motor abnormalities similar to those identified in patients with *RAD51* mutations or DCC+/MM+ patients, albeit at a much lower intensity. However, the complete lack of ipsilateral MEPs and absence of increased physiological mirror movements in DCC+/MM- patients strongly argues against this hypothesis. This is coherent with the incomplete penetrance associated with DCC mutation in humans [17]. Penetrance refers to the percentage of individuals carrying a specific mutation who also manifest the clinical phenotype linked to the mutation [42]. In the present case,

affected family members carry a mutation causing a truncate variant of DCC, which has an estimated penetrance of 50% [25, 26, 28]. Thus, although the *DCC* mutation is autosomal dominant [17], individual heterozygotes for the mutation may never manifest any effect of the mutation and remain identical to DCC-/MM- and healthy controls. Indeed, each individual has two copies of every gene and the level to which the mutant allele contributes to the clinical profile is unique and influences penetrance [43]. In line with a unique contribution of the mutated allele, family members in the present study displaying the CMM phenotype had MM that widely differed in intensity (Figure 1A). Thus, carrying the DCC mutation is not sufficient to generate the CMM phenotype, where the penetrance and expressivity of the gene are influenced by a combination of numerous factors like gene-gene and gene-environment interactions [44].

In the present study, mirror MEPs elicited by single-pulse TMS were present in 100% of stimulation trials for both the dominant and non-dominant hands, in line with previous studies of DCC patients [23, 45, 46]. In contrast, it has been reported that mirror MEPs could only be elicited in 33% of TMS trials for the non-dominant hand and 12% of TMS trials for the dominant hand in patients with *RAD51* mutations [34]. This points to a major difference between DCC and RAD51 mutation carriers, where the ispilateral corticospinal tract seems more readily excitable in DCC patients. Despite this difference, MEP latency data strongly suggest the presence of a pathological ispilateral motor tract connecting the mirror hand in patients carrying both mutations. Indeed, in DCC+/MM+ patients, mirror MEPs elicited by TMS had the same latencies as the contralateral MEP, a result that was also reported in *RAD51* patients with CMM [34]. However, it may also be that the CST innervates both hands through spinal branching. Tractography of patients with a *RAD51* mutation revealed a higher proportion of fibers in the uncrossed CST compared to the crossed CST at the level of the pyramidal decussation [41]. Since *RAD51* and *DCC* mutations share similar pathophysiology and that DCC haploinsufficiency has a strong impact on CST decussation, spinal branching is unlikely. Two major hypotheses for CMM in *DCC* patients could thus be proposed: 1) CMM are the result of a pathological ipsilateral CST independent from the normal occurring contralateral tract; 2) CMM arise from a branched CST that does not fully decussate at the medullary pyramids, which connects both the contralateral and ipsilateral hands. Since it is

known that the *DCC* gene codes a receptor present on developing axon tracts that binds the netrin guiding cue present at the midline, the second hypothesis is more likely to explain CMM in *DCC* patients. Additionally, an independent ispilateral tract from a distinct origin in the primary motor cortex should be associated with deficiencies on proteins acting on the withdrawal of CST axons rather than a guiding receptor. Indeed, although an ipsilateral, independent CST is known to exist in newborns only to withdraw some time after birth, DCC is not involved in withdrawal mechanisms. Animal studies also support an axonal guiding role for DCC, since mutant mice lacking the *DCC* gene show severe abnormalities in the commissural development of axons [7]. For example, the corpus callosum is absent in these mutant these mice despite the presence of its fibers, which fail to cross the midline, forming an aberrant bundle of white matter [7]. Kanga mice, which have a less severe mutation of the *DCC* gene resulting in a less functional truncate DCC protein, similar to what is seen in *DCC* patients, move in mirror like fashion that mimics CMM in *DCC* patients.

Mouse models where a DCC mutation leads to CMM-like deficits are similar to those with a mutation on the gene coding for the *netrin* protein [47]. However, the impact on developing axons tract is more severe in mice carrying a mutation affecting the netrin protein (the guiding axon cue binding *DCC* receptors) compared to *DCC* mutant mice [47]. As a result, loss of the *netrin* protein is associated with a more severe phenotype than loss of the *DCC* receptor itself, suggesting that *DCC* receptors are not the only receptor responsible for CST guidance through *netrin* binding [47]. This could explain why *DCC* deficiency in MM+ patients leads to partial uncrossing of the CST, highlighting the ability of *netrin* to attract the CST through other binding receptors. Taken together, these results suggest that *DCC* deficiency could cause diminished midline guidance attraction of the growing CST leading to a faulty decussation at the level of the pyramids. This would result in parts of the CST not decussating at the midline and reaching targets in the mirror hand. However, remaining *DCC* activity would still allow parts of the CST to reach contralateral targets. The present results suggests that the balance of ipsilateral/contralateral patterns of connection can vary dramatically between individuals, as ipsilateral MEPs can be much smaller or much larger than their contralateral counterparts.

Family members with a DCC mutation and mirror movements showed reduced interhemispheric inhibition (IHI) compared to healthy controls and family members with no mirror movements. Reduced IHI has also been reported in patients carrying a *RAD51* mutation [34]. In healthy individuals, IHI limits interhemispheric cooperation when bimanual movements are executed [48] but is essential for purely unimanual movements [49, 50]. Reduced IHI could be a compensatory mechanism in CMM patients since normal inhibitory projections could theoretically reduce ipsilateral mirror activation branching to the contralateral hand, resulting in loss of motor control. A DCC mutation could also affect maturation of the corpus callosum, leading to abnormal interhemispheric signal transfer. Indeed, mice with a complete absence of DCC receptors show total agenesis of the corpus callosum [7] and patients with RAD51 mutations show subtle CC abnormalities [34]. For example, fractional anisotropy of transcallosal fibers connecting the primary motor cortices was higher in patients with RAD 51 mutations compared to healthy controls. This was specific for the hand motor cortex, as fractional anisotropy was similar between groups for fibers connecting the face area. Increased transcallosal connectivity of the hand area in conjunction with reduced IHI could increase activity in the ipsilateral M1 during unimanual hand movements, resulting in unimanual motor commands coming from 1) the contralateral M1 through the normally occurring CST; and 2) the mirror M1 through the pathological ipsilateral CST and contralateral M1 through reduced IHI.

The behavioral consequences of abnormal motor circuitry in DCC/MM+ patients were assessed with a motor learning task. More specifically, it was hypothesized that reduced IHI and involuntary activity in the ipsilateral hand would lead to increased transfer of a newly acquired motor skill. Learning of the motor sequence and transfer of the motor sequence occurred in DCC+/MM+ participants but was not different from that of family members with no CMM or healthy controls. These data suggest that complex unilateral motor behavior is not affected by the presence of mirror movements and that reduced M1-M1 inhibition does not translate into increased behaviorally-relevant interhemispheric transfer of motor information. The task that was used in the present study involved on-line learning of a repeating sequence and the absence of significant group differences does not mean that other motor task may be more sensitive to the abnormalities found in DCC+/MM+ individuals. Nevertheless, despite

the absence of increased transfer, execution of the motor task was found to significantly impact interhemispheric interactions in DCC+/MM+ individuals. Physiological mirror movements increased by approximately 150% immediately after the SRTT in the DCC+/MM+ group whereas it remained stable in MM- and healthy control groups. This suggests that repeated use of the hand may have further reduced inhibition between primary motor cortices leading to interhemispheric overflow of motor activity. This is supported by the fact that MM can arise in healthy individuals when the active hand is performing an effortful task [43] and execution of the SRTT has been shown to modulate IHI [40]. More studies are needed to determine how voluntary motor activity interacts with pathophysiological mechanisms in patients with mirror movements.

5.6 Conclusion

The study of mirror movements in otherwise healthy individuals offers a unique opportunity to better understand the mechanism underlying lateralization of motor control. The present results, in line with previous findings, suggest that accurate motor control relies on proper corticospinal projections connecting motor cortex to appropriate targets in the contralateral hand, but also on appropriate interhemispheric communication. In that regard, the *DCC* gene appears to play a major role in the correct lateralization of the motor system through the establishment of lateralized corticospinal tracts and development of robust transcallosal inhibition.

5.7 Acknowledgements

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5.9 Figures

Figure 1. TMS-induced motor evoked potentials

Legend: **(A)** Ipsilateral MEP coefficient (ipsilateral MEP/contralateral MEP) for the 12 DCC+/MM+ patients. For 5 of the 12 patients with a DCC mutation and mirror movements, ipsilateral MEPs have greater amplitudes than contralateral MEPs. **(B)** Amplitude of ipsilateral and contralateral MEPs elicited from TMS over the dominant and non-dominant M1. The DCC+MM+ group shows no significant difference between ipsilateral and contralateral MEPs. **(C)** Correlation between ipsilateral MEP coefficients from the dominant and non-dominant hemispheres. ***: $p<0.001$.

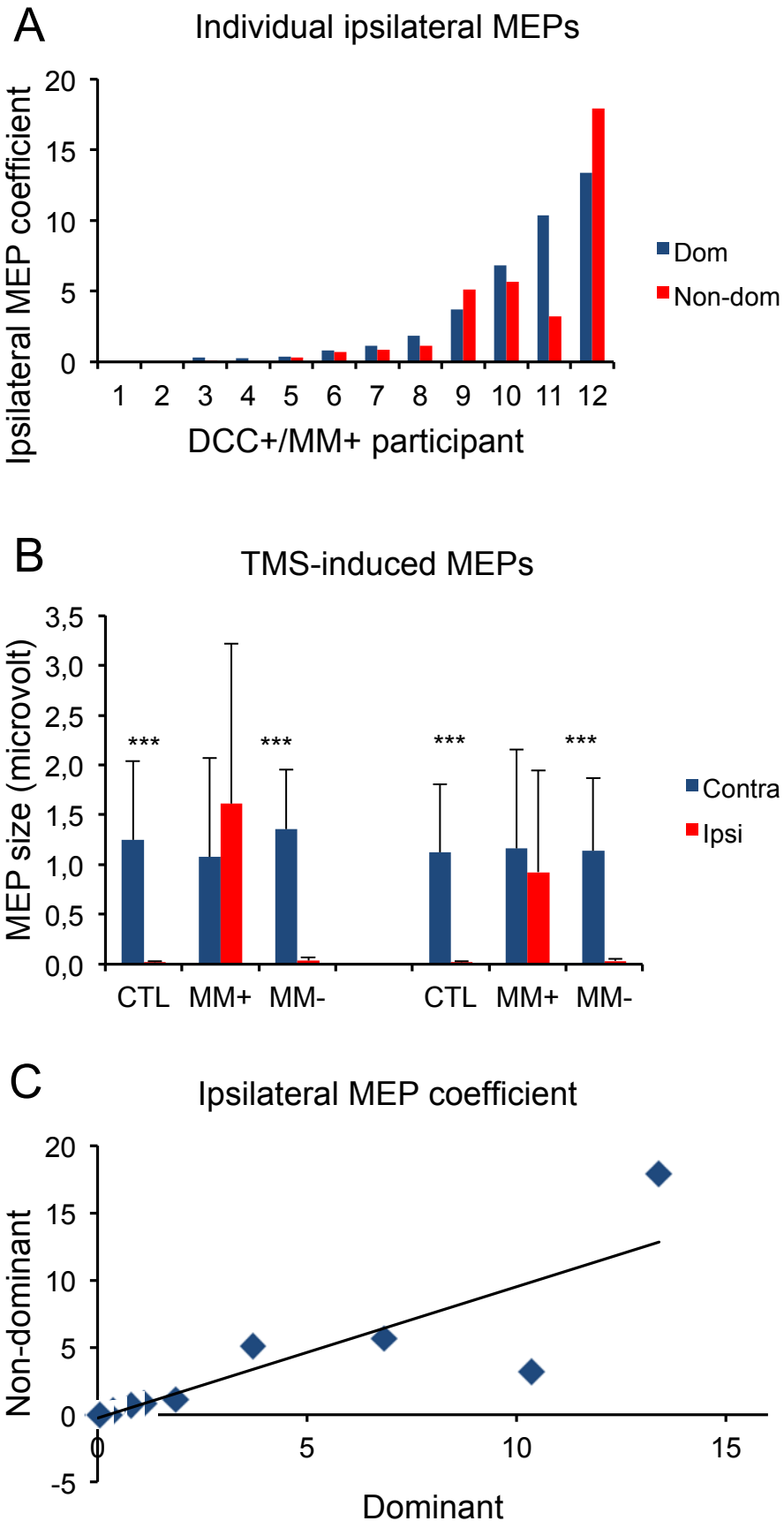

A
Individual ipsilateral MEPs
Ipsilateral MEP coefficient
20
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12
DCC+/MM+ participant
Dom
Non-dom
B
TMS-induced MEPs
MEP size (microvolt)
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
***
***
***
***
CTL MM+ MM-
CTL MM+ MM-
Contra
Ipsi
C
Ipsilateral MEP coefficient
Non-dominant
20
15
10
5
0
-5
0
5
10
15
Dominant

Figure 2. Mirror movements

Legend: **(A)** EMG activity in the dominant and non-dominant mirror hands during phasic contraction of the intended hand. Mirror activity is present only in the DCC+/MM+ group. **(B)** Physiological mirror movements are significantly greater in the DCC+/MM+ group compared to the MM- and control groups. ***: p<0.001.

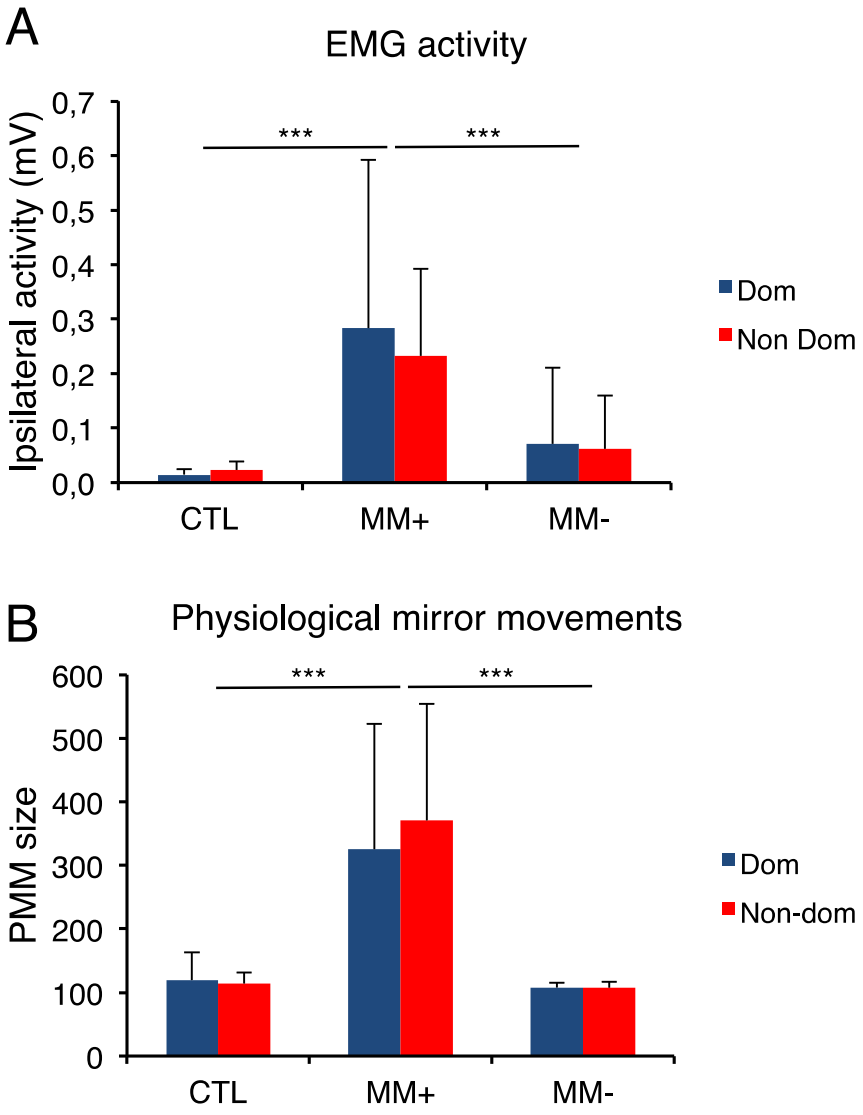
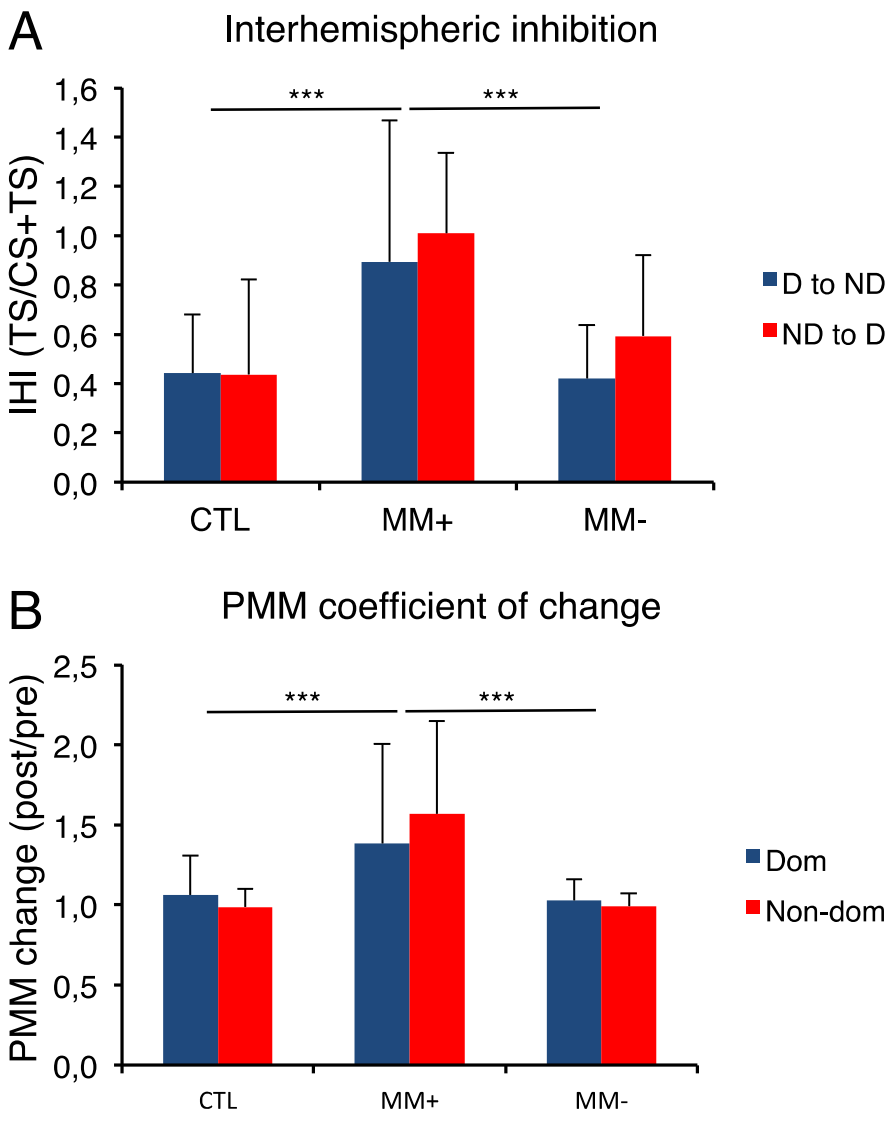


Figure 3. Neurophysiological data

Legend: **(A)** Interhemispheric inhibition is significantly decreased in the DCC+/MM+ group compared to the MM- and control groups. **(B)** After the SRTT, physiological mirror movements significantly increase in the DCC+/MM+ group.



Chapitre 6

Discussion

6.1 Discussion générale

L'objectif global de la présente thèse était d'approfondir les connaissances actuelles quant aux corrélats neuronaux sous-tendant l'exécution de mouvements unilatéraux chez l'humain. La première partie de la thèse avait pour but de réaliser une recension des écrits sur le sujet afin de servir d'assise théorique aux articles expérimentaux qui composent cet ouvrage et est le résultat de l'article 1.

Le premier objectif expérimental de cet ouvrage était de déterminer s'il était possible de moduler, à l'aide d'une technique de stimulation non invasive et accessible, la SÉTcd, le niveau d'activité du CPM dans une population en santé. Le but secondaire était d'évaluer la possibilité d'utiliser la SETcd comme outil permettant de réduire les MMp, ce qui pourrait mener au développement de méthodes permettant de réduire les MM chez des individus présentant une atteinte neurologique telle que la maladie de Parkinson. Ainsi, nous avons tout d'abord cherché à déterminer si une stimulation cathodale du CPM ipsilatéral à la main miroir, à l'instar des études antérieures en SMTr, était associée à une *augmentation* des MMp. En second lieu, une stimulation anodale fut appliquée au CPM ipsilatéral à la main miroir dans le but d'induire une *réduction* des MMp. Ces objectifs font partie de l'article 2 présenté dans cet ouvrage.

Le second objectif expérimental visait à déterminer l'impact de mutations génétiques spécifiques affectant certaines structures importantes sous-tendant la latéralisation du mouvement au niveau anatomique et neurophysiologique. Dans un premier temps, nous avons mesuré l'épaisseur du cortex cérébral dans une population d'individus présentant une agénésie du corps calleux de manière à évaluer la plasticité corticale associée à l'absence de CC et d'inhibition interhémisphérique. Cet objectif est couvert par l'article 3. Dans un deuxième temps, l'objectif était d'évaluer, à l'aide de la SMT et de mesures physiologiques, les interactions interhémisphériques et intrahémisphériques chez des individus présentant des MMC associés à une mutation du gène *DCC*. Cet objectif est au centre de l'article 4.

La présente discussion vise à mettre en contexte les résultats obtenus en fonction des hypothèses présentées dans l'introduction. Dans un premier temps, les objectifs principaux et secondaires seront abordés. En deuxième lieu, une conclusion générale, incluant des perspectives futures, sera présentée.

6.2 Objectif 1 : Modulation de l'activité du CPM par la SÉTcd et son impact sur la latéralisation du mouvement

6.2.1 La SÉTcd bilatérale, un outil similaire à la SMTr pour moduler le réseau de transformation non-miroir

L'article 2 a révélé qu'il était possible d'utiliser la SÉTcd bilatérale dans le but d'augmenter la présence et l'intensité des MMp chez des individus en santé. Dans le protocole bilatéral, la cathode couvre le CPMd ipsilatéral à la main miroir et l'anode couvre le CPMd ipsilatéral à la main active. Ces résultats sont en accord général avec l'idée voulant que la SÉTcd cathodale soit associée à une diminution de l'excitabilité corticospinale (Jacobson, Koslowsky, & Lavidor, 2012; Mordillo-Mateos et al., 2012; Nitsche & Paulus, 2000; Tazoe, Endoh, Kitamura, & Ogata, 2014; voir par contre : Horvath, Forte, & Carter, 2015; O'Shea et al., 2014). Ce résultat obtenu dans l'article 2 rappelle ceux rapportés dans deux études similaires qui ont utilisé la SMTr pour moduler l'activité du CPMd (Cincotta et al., 2004; Giovannelli et al., 2006). Dans ces dernières, l'application de SMTr sur le CPMd à une fréquence de 1Hz était associée à une augmentation significative des MMp tel que mesurée avec la même méthode que celle utilisée dans la présente thèse. Or, il a été démontré de façon convaincante que la SMTr appliquée à une fréquence de 1Hz diminue significativement l'excitabilité corticospinale (Kobayashi & Pascual-Leone, 2003). Pris dans leur ensemble, ces résultats suggèrent que la stimulation cathodale du CPMd ispilatéral à la main miroir pourrait agir sur les MMp de la même manière que la SMTr. On peut donc présumer que la diminution de l'excitabilité corticale du CPMd à la suite de la stimulation cathodale sous-tend, au moins en partie, l'augmentation observée au niveau des MMp.

Toutefois, une importance majeure départage les deux approches dans la manière dont la stimulation module les MMp. En effet, tandis que la SMTr unilatérale est en mesure de moduler significativement les MMp (Cincotta et al., 2004; Giovannelli et al., 2006), les résultats de l'article 2 révèlent qu'une stimulation bilatérale (les deux CPMd sont stimulés simultanément) est nécessaire à la modulation des MMp lorsqu'on utilise la SÉTcd. Ainsi, la modulation significative des MMp n'est survenue que lorsque la stimulation cathodale ciblait le CPMd ipsilatéral à la main miroir et que la stimulation anodale ciblait simultanément le CPMd ipsilatéral à la main active. Aucune modulation significative des MMp n'a été observée lorsque la cathode ciblait le CPMd ispilatéral à la main miroir, tandis que l'anode était placée au niveau supra-orbital de l'hémisphère controlatéral. Ces résultats suggèrent que la modulation des deux CPMd par la SÉTcd est nécessaire pour modifier la capacité d'un individu à exécuter une tâche unilatérale, sans débordement moteur au niveau de la main miroir. Au niveau méthodologique, ces données suggèrent également l'existence de différences fondamentales entre la SMTr et la SÉTcd quant à la manière dont ces techniques parviennent à moduler l'activité d'une région corticale afin d'influencer un comportement donné.

Par ailleurs, l'article 2 suggère que l'utilisation de la SÉTcd bilatérale permet la modulation de l'activité miroir de la main droite, *mais également de la main gauche*, lorsque l'électrode cathodale couvre le CPMd ipsilatéral à la main miroir. Ce résultat suggère fortement que le CPMd gauche est en mesure de restreindre la commande motrice à la main active de manière similaire au CPMd droit. Ceci constitue un élément original, puisque les études précédentes en SMTr ont démontré la contribution du CPMd *droit* dans la restriction de la commande motrice à la main gauche tandis que l'apport du CPMd gauche demeure inconnu (Cincotta et al., 2004; Giovannelli et al., 2006). En ce sens, les résultats de l'article 2 suggèrent qu'une diminution d'activité dans le CPMd gauche, associée à une augmentation de l'activité dans le CPMd droit, résulte en une diminution de la capacité du système moteur à restreindre l'activité motrice au niveau de la main droite, entraînant une augmentation de l'activité miroir dans la main gauche. Il est toutefois nécessaire d'interpréter la contribution du CPMd gauche avec prudence puisque le protocole de stimulation était bilatéral. En effet, dans un tel contexte il est difficile de distinguer la contribution des CPMd droit et gauche dans les résultats obtenus. On peut en effet émettre l'hypothèse contraire, à savoir que la modulation

des MMp est tributaire d'une augmentation d'activité dans le CPMd droit, plutôt qu'une diminution de l'activité dans le CPMd gauche. Des études supplémentaires seront nécessaires pour détermine la contribution relative des CPMd droit et gauche dans la modulation des MMp.

Une autre limite importante et inhérente à tout protocole utilisant la SÉTcd réside dans la taille des électrodes utilisées pour moduler les régions d'intérêt. Dans l'article 2, des électrodes de 25 cm^2 ont été utilisées, ce qui implique qu'en plus de couvrir le CPMd, l'électrode couvrait également l'AMS et le M1, entre autres. Ainsi, l'augmentation observée des MMp pourrait être expliquée, au moins en partie, par une augmentation de l'excitabilité corticospinale dans le M1 controlatéral à la main miroir, recevant une stimulation anodale. Toutefois, puisqu'aucune modulation significative des MMp n'est observée lors de la stimulation unilatérale, cette hypothèse à elle seule semble peu probable.

6.2.2 Capacité de la SÉTcd à réduire les MMp

Les résultats découlant du premier objectif de l'article 2, démontrant la possibilité d'utiliser la SÉTcd bilatérale pour moduler à la hausse les MMp, suggèrent un potentiel clinique à la SÉTcd dans la mesure où celle-ci serait en mesure de produire l'effet inverse, soit une réduction des MMp. Le second objectif de cet article était donc de mettre les bases pratiques d'une approche visant à développer un protocole de SÉTcd pouvant *réduire* les MMp chez des sujets contrôles afin qu'un jour il puisse devenir un traitement dans certaines conditions pathologiques dont les individus atteints souffrent également de MM.

Les résultats obtenus dans l'étude 2 suggèrent que la SÉTcd anodale ipsilatéral à la main miroir (unilatérale ou bilatérale) n'est pas en mesure de réduire les MMp. En effet, malgré l'utilisation de différents protocoles, de différents sites de stimulation et de polarités différentes, aucune réduction significative des MMp n'a été observée dans l'étude 2. Pourtant, le concept sous-jacent à l'utilisation de la SÉTcd anodale pour réduire les MMp est que la stimulation anodale semble être associée à une augmentation de l'excitabilité corticospinale (Jacobson et al., 2012; Nitsche & Paulus, 2000). Ainsi, des études rapportent que la SÉTcd

anodale unilatérale est en mesure de moduler plusieurs éléments de M1, allant de l'inhibition intracorticale (Tremblay, Beaulé, Lepage, & Théoret, 2013) à la concentration GABAergique (Stagg et al., 2009), le résultat le plus probant étant une augmentation de l'excitabilité corticospinale (Horvath et al., 2015). Des résultats similaires ont aussi été rapportés avec la stimulation bilatérale, où une augmentation de l'excitabilité corticospinale a été rapportée sous l'anode (Kidgell, Goodwill, Frazer, & Daly, 2013; Mordillo-Mateos et al., 2012; Tazoe et al., 2014). Il est toutefois important de mentionner que deux études récentes rapportent une absence d'effets d'une stimulation bilatérale sur l'excitabilité corticospinale (O'Shea et al., 2014; Suzuki et al., 2012; Tremblay et al., 2016). De ce fait, l'absence de résultats significatifs pourrait possiblement s'expliquer par un mécanisme neurophysiologique qui ne permet pas de moduler à la baisse les MMp, mais également par des limites inhérentes à la méthode de stimulation.

En effet, de nombreuses études récentes semblent remettre en question la reproductibilité de certains effets associés à la SÉTcd. Une part des divergences quant à l'effet de la SÉTcd semble reposer en partie sur des différences interindividuelles importantes. En effet, deux études prospectives menées auprès de larges échantillons ont montré une grande variabilité de la réponse corticospinale à la SÉTcd (Lopez-Alonso, Cheeran, Rio-Rodriguez, & Fernandez-Del-Olmo, 2014; Wiethoff, Hamada, & Rothwell, 2014). Il est donc possible que l'incapacité de moduler à la baisse les MMp dans l'article 2 est en partie tributaire de cette variabilité. Malgré ces résultats décevants, il est important de mentionner que des modifications mineures des paramètres de stimulation peuvent avoir des impacts importants sur la réponse à la SÉTcd. Par exemple, il a été démontré que l'augmentation de l'intensité de stimulation de 1mA à 2mA résulte en une inversion de l'effet de la stimulation cathodale, passant d'une inhibition à une facilitation (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013), tandis qu'augmenter la durée de stimulation de 13 minutes à 26 minutes résulte en une inversion de l'effet de la stimulation anodale, passant d'une facilitation à une inhibition (Monte-Silva et al., 2013). Ainsi, une évaluation systématique des paramètres de stimulation est nécessaire afin de déterminer le véritable potentiel de la SÉTcd dans la modulation des MMp et de son utilité clinique chez des patients présentant des mouvements miroirs.

6.2.3 Article 2 : conclusion

L'article 2 de la présente thèse démontre qu'il est possible de moduler l'activité du réseau de transformation non-miroir à l'aide de la SÉTcd bilatérale lorsque la cathode est située ipsilatéralement à la main miroir. Toutefois, les résultats de cette étude, de même que les résultats des autres études ayant montré un rôle du CPMd dans la restriction des MMp (Cincotta et al., 2004; Giovannelli et al., 2006), suggèrent que ce rôle est partiel. En effet, bien que la stimulation bilatérale ait augmenté les MMp de manière significative, ces derniers sont demeurés relativement limités, contrairement à ce qui est observé, par exemple, chez l'enfant de moins de 10 ans chez qui les MMp peuvent être visibles à l'œil nu. Par ailleurs, il n'a pas été possible d'augmenter l'efficacité du réseau de transformation non-miroir pour réduire l'intensité des MMp. Le potentiel thérapeutique lié à la SÉTcd reste donc à démontrer.

6.3 Objectif 2 : Investigation de deux populations cliniques présentant des anomalies génétiques affectant le réseau de transformation non-miroir

6.3.1 L'AgCC du corps calleux et son impact sur le développement cortical

6.3.1.1 L'absence du CC lié à un épaississement cortical

Considérant l'absence d'un syndrome de déconnexion, tel qu' observé chez les patients « split brain », et la présence d'une certaine forme de transfert hémisphérique chez les patients nés en l'absence d'un CC, l'article 3 visait à étudier le développement cortical d'individus présentant une AgCC comparativement à des individus contrôles.

Tout d'abord, l'étude a mis en lumière des différences subtiles chez la population AgCC qui se sont reflétées par une augmentation de l'épaisseur corticale au niveau de régions spécifiques, en comparaison à la population contrôle. Ainsi, les analyses ont révélé un épaississement cortical dans les régions somatosensorielles (S1) et visuelles (V1) primaires et au niveau de la région de la main dans M1. Ces résultats sont surprenants et contraires à ce qui

était attendu considérant la littérature existante. En effet, le modèle animal suggérait plutôt qu'un amincissement cortical serait associé à l'AgCC, principalement au niveau des régions recevant normalement d'importantes afférences calleuses (Abreu-Villaca et al., 2002; Ribeiro-Carvalho, Manhaes, Abreu-Villaca, & Filgueiras, 2006). Notons toutefois qu'il existe des différences méthodologiques majeures entre ces études et celle présentée dans l'article 3 qui pourraient, du moins en partie, expliquer ces résultats contradictoires. Dans un premier temps, ces études se sont basées sur un modèle animal (souris) pour déterminer les effets corticaux d'une agénésie calleuse. Dans un deuxième temps, dans l'une de ces études le protocole consistait en l'ablation chirurgicale du CC de la souris dès la naissance (Ribeiro-Carvalho et al., 2006), ce qui peut avoir mené à une mort cellulaire axotomique et ainsi avoir réduit le nombre de neurones normalement présents au niveau de certaines régions cérébrales. Finalement, un autre modèle expérimental pour étudier l'AgCC consiste à analyser des souris porteuses d'une mutation, soit la souche BALB/cCF (Abreu-Villaca et al., 2002). Dans ce cas, la mutation responsable de l'absence du développement du CC pourrait également avoir une influence sur le développement d'autres régions corticales et ainsi expliquer une partie des résultats.

Nonobstant ces études, les résultats de l'article 3 suggèrent que l'absence du CC chez l'humain est associée à une augmentation de l'épaisseur corticale touchant principalement les régions primaires du cerveau. Ces données sont en accord avec la littérature portant sur d'autres troubles congénitaux (Guerrini & Marini, 2006; Guerrini, Sicca, & Parmeggiani, 2003; Hyde et al., 2007). Certains auteurs ont ainsi suggéré que l'épaississement cortical pourrait être le résultat de groupes de neurones n'ayant pas réussi à rejoindre leurs cibles au cours du développement et qui formeraient des revêtements à la surface du cerveau (Guerrini & Marini, 2006; Guerrini et al., 2003; Hyde et al., 2007). L'accumulation de ces nodules causerait l'épaississement du cortex, tel qu'observé dans la présente étude chez les patients AgCC. Un autre mécanisme pouvant expliquer l'épaississement cortical dans certains troubles congénitaux suggère qu'un processus pathologique affecterait le développement des neurones qui suivraient alors un patron de migration aberrant (Chang et al., 2005). Ceci résulterait en une formation corticale « défectueuse », par exemple une polymicrogyrie (quantité anormalement élevée de petites brèches élargissant les sillons). Ces manifestations aberrantes

ont d'ailleurs été identifiées dans l'épilepsie (Guerrini et al., 2003), la dyslexie (Chang et al., 2005) et l'amusie congénitale (Hyde et al., 2007). Considérant ces études et les hypothèses avancées, nous proposons que les régions plus épaisses chez les sujets AgCC traduisent donc l'absence d'afférences calleuses et puissent parallèlement être liées aux déficits comportementaux qui sont rapportés chez les individus AgCC.

6.3.1.2 Lien anatomofonctionnel des différences au niveau de l'épaisseur cortical chez les AgCC

Lorsque l'on considère l'ensemble de la littérature, les déficits comportementaux observés chez les individus AgCC semblent être plus légers que ce à quoi on pourrait s'attendre (Chiarello, 1980; Duquette et al., 2008; Lassonde et al., 1991). Toutefois, un examen plus approfondi des études antérieures met en évidence certaines différences importantes entre individus en santé et patients agénésiques. Ainsi, certains des déficits observés chez les individus agénésiques semblent être liés aux régions cérébrales qui ont été identifiées par l'article 3 comme étant différentes des contrôles. Par exemple, en lien avec l'aire S1, il a été démontré que les individus AgCC avaient plus de mal à discriminer la distance qui sépare deux stimuli sensoriels tactiles (Schiavetto, Lepore, & Lassonde, 1993). Au niveau de V1, certaines études suggèrent que les sujets AgCC présenteraient des déficits de perception de la profondeur, de la distance, des couleurs et de la vision binoculaire (Corballis & Finlay, 2000; Lassonde, Sauerwein, McCabe, Laurencelle, & Geoffroy, 1988; Moes, Schilmoeller, & Schilmoeller, 2009; Saint-Amour, Lepore, Lassonde, & Guillemot, 2004). Des études en imagerie fonctionnelle ont également montré que les patients AgCC présentent une réorganisation du cortex visuel (Bittar, Ptito, Dumoulin, Andermann, & Reutens, 2000). D'ailleurs, Schilmoeller et Schilmoeller (2000) suggèrent que les difficultés visuelles seraient parmi les symptômes les plus fréquemment associés à l'AgCC. En plus des régions sensorielles, l'article 3 suggère que la région corticale responsable du contrôle moteur de la main serait anormale chez les individus AgCC. Ce développement cortical aberrant au niveau de M1 pourrait donc être associé aux difficultés de la motricité manuelle rapportées par la littérature. En effet, les données suggèrent que les enfants AgCC présentent des déficits au niveau de la dextérité fine (Moes et al., 2009) et de la coordination jusqu'à l'âge adulte (de

Guise et al., 1999). D'ailleurs, les individus AgCC sont globalement plus lents au plan moteur que les contrôles (Franz & Fahey, 2007; Mueller, Marion, Paul, & Brown, 2009).

6.3.1.3 Différences sommes toute mineures chez les AgCC

Lorsque l'on prend en considération l'importance du CC au plan anatomique, les résultats de l'article 3 suggèrent tout de même que, malgré des différences sur le plan de l'épaisseur corticale de régions très spécifiques, celles-ci demeurent relativement mineures comparativement à la population contrôle. Ceci n'est pas sans rappeler les résultats d'études antérieures démontrant que les fibres de matières blanches sont très similaires sur le plan de la morphologie, de la structure et du nombre, entre des enfants présentant une dysgénésie du CC et des enfants contrôles (Benezit et al., 2015). De plus, une étude en « resting state » ne rapporte aucune différence entre sujets AgCC et sujets contrôles (Tyszka, Kennedy, Adolphs, & Paul, 2011). Dans la même veine, une étude évaluant la connectivité fonctionnelle d'individus AgCC a rapporté une forte corrélation au niveau de la connectivité des régions homotypiques du cerveau, ce qui suggère la présence d'interactions interhémisphériques relativement normales malgré l'absence du CC (Tyszka et al., 2011). Néanmoins, il serait hasardeux de suggérer que l'absence congénitale du CC a un effet négligeable sur le développement et la maturation du cerveau. En effet, une étude évaluant la connectivité cérébrale rapporte une connectivité globale réduite chez des individus AgCC (Owen et al., 2013). De plus, des études suggèrent également que l'absence du CC pourrait avoir un effet sur des régions dépourvues de connexions calleuses, tandis que la plasticité cérébrale ne restaurerait que partiellement la communication interhémisphérique (Owen et al., 2013). Finalement, il importe de mentionner que le lien possible entre les régions corticales présentant une épaisseur corticale anormale, identifiées dans l'article 3, et les déficits comportementaux rapportés dans la littérature, est spéculatif. D'autres études seront nécessaires pour clarifier le lien entre anomalies structurelles associées à l'AgCC et les difficultés comportementales y étant associées.

6.3.1.4 Article 3: conclusion

En résumé, la présente étude révèle un patron général de développement cortical sensiblement similaire entre individus nés sans CC et la population générale. Toutefois, une

épaisseur corticale significativement plus élevée a été mise en lumière au niveau d'aires corticales spécifiques soit S1, V1 et la région de la main dans M1. Il est aussi possible de faire un parallèle entre ces régions et certains déficits comportementaux qui sont rapportés dans la littérature chez les individus AgCC. Le mécanisme précis, qui rendrait les régions primaires plus vulnérables à l'absence du CC, demeure inconnu.

6.3.2 Les mouvements miroirs causés par une mutation sur le gène *DCC*

6.3.2.1 Description des individus porteurs d'une mutation sur le gène DCC, mais n'ayant pas de MMC apparents

La VCS innerve directement les motoneurones responsables du mouvement des muscles, ce qui en fait le dernier relai entre la commande motrice provenant du cerveau et le mouvement qui lui est associé. Elle joue donc un rôle clé dans la latéralisation du mouvement, puisqu'elle est responsable de l'innervation spécifique des motoneurones des muscles controlatéraux impliqués dans le mouvement sans que le signal n'atteigne le côté ipsilatéral. Les données provenant de la littérature ont démontré qu'une mutation sur le gène *RAD51* est associée à une VCS qui ne traverse pas entièrement la ligne médiane et innerve les motoneurones des deux côtés du corps. Cette mutation affecte la capacité d'un individu à effectuer un mouvement purement latéralisé et cause des MMC (Gallea et al., 2013). Il semble que le développement anormal de la VCS dans cette pathologie affecte également plusieurs processus neurophysiologiques, dont l'IIH. L'objectif de l'article 4 était d'étudier les MMC chez une population présentant une mutation sur le gène *DCC*, lequel est également impliqué dans le croisement de la VCS.

Dans un premier temps, l'article 4 a démontré que les individus porteurs de la mutation génétique sur le gène *DCC*, mais qui ne présente pas de MMC, étaient identiques aux contrôles et aux membres de la famille sans mutation génétique, et ce pour l'ensemble des mesures rapportées. Ces données contredisent une étude antérieure suggérant que certains individus porteurs d'une mutation sur le gène *DCC* ou *RAD51*, mais qui ne manifestent pas de MMC visibles, pouvaient tout de même présenter des MMC subtils lorsqu'évalués avec des appareils sensibles aux micromouvements (Franz et al., 2015). Certaines études suggèrent

également que les individus présentant des MMC peuvent apprendre à supprimer une partie de leurs mouvements involontaires lorsqu'ils augmentent leur focus attentionnel (Kuhtz-Buschbeck, Sundholm, Eliasson, & Forssberg, 2000). On aurait donc pu s'attendre à ce que certains membres de la famille présentant un profil *DCC+/MM-* manifesteraient certaines anomalies motrices similaires à celles observées chez les membres de profil *DCC+/MM+*, mais à un degré moindre. Or, les résultats de l'article 4 démontrent le contraire: les participants *DCC+/MM-* présentent une absence complète de PÉM au niveau de la main miroir, même lorsque l'intensité de la stimulation dépassait largement 1 mV dans la main controlatérale. Bien que surprenantes, ces données sont en accord avec la littérature portant sur la pénétrance du gène *DCC*, laquelle est incomplète dans la famille présentée dans l'article 4 (Meneret et al., 1993). La pénétrance réfère au pourcentage d'individus porteurs d'une mutation génétique spécifique et qui présente le phénotype clinique associé à la mutation (Kumar, Srivastava, & Ganesh, 2000). Dans le cas présent, les membres de la famille étaient porteurs d'une mutation associée à une pénétrance estimée à 50% (Meneret et al., 2014; Meneret et al., 1993; Srour et al., 2010). Ainsi, bien que la mutation sur le gène *DCC* se transmette de manière autosomale dominante (Meneret et al., 1993), les individus hétérozygotes porteurs de la mutation peuvent ne jamais manifester les effets de la mutation et demeurer neurologiquement identiques aux individus *DCC-/MM-* et à la population générale. Toutefois, chez ces individus, la probabilité de transmettre la mutation à la génération suivante est 50%. On peut en partie expliquer ce phénomène par le fait que chaque individu détient deux copies de chaque gène et que le niveau avec lequel un allèle mutant contribue à un phénotype clinique est unique (Kumar et al., 2000). Ce phénomène affecte également le degré avec lequel la manifestation clinique semble se manifester chez les individus *DCC+/MM+*. En effet, l'article 4 a révélé une grande variabilité quant à l'intensité des MMC entre les différents membres de la famille présentant de MMC. Les résultats de l'article 4 suggèrent donc qu'une mutation sur le gène *DCC* n'est pas suffisante en elle-même pour causer un phénotype de MMC et que le degré avec lequel la mutation cause des MMC est unique à chaque individu.

6.3.2.2 Implication de la VCS dans les MMC des individus porteurs d'une mutation sur le gène DCC

L'étude 4 a révélé que la VCS ipsilatérale pathologique des individus *DCC+/MM+* est aussi "excitable" que la VCS controlatérale naturelle. En effet, des PÉM miroirs ont été enregistrés dans 100% des essais de SMT unilatérale, et ce autant lorsque la stimulation ciblait le cortex moteur dominant que le cortex moteur non dominant. Bien que ce résultat corrobore des études antérieures (Cincotta et al., 2003; Depienne et al., 2011; Srour et al., 2009), il contraste avec une étude récente menée chez des individus porteurs d'une mutation sur le gène *RAD51* ayant démontré que la stimulation du M1 dominant produisait des PÉM miroirs dans seulement 33% des effets tandis que la stimulation du M1 non dominant produisait des PÉM miroirs dans 12% des essais (Gallea et al., 2013). On observe donc une différence marquée entre les deux populations, suggérant une contribution plus importante du gène *DCC* à la latéralisation de la VCS que celle du gène *RAD51*, puisque les individus porteurs d'une mutation sur le gène *DCC* ont une VCS ipsilatérale plus "excitable".

Deux explications ont été suggérées pour expliquer le phénomène des MMC (Cincotta et al., 2003). La première suggère que les MMC seraient le résultat d'une VCS ipsilatérale pathologique indépendante de la VCS controlatérale (Cincotta et al., 2003). La seconde suggère que les MMC seraient plutôt le résultat d'un branchement ipsilatéral aberrant provenant de la VCS controlatérale, mais dont une partie ne traverserait pas complètement la ligne médiane au niveau des pyramides (Cincotta & Ziemann, 2008; Gallea et al., 2013; Mayston et al., 1999). Pour ce qui est de la première hypothèse, bien qu'une VCS ipsilatérale et indépendante soit présente chez les nouveau-nés et qu'elle se retire peu après la naissance, le gène *DCC* ne semble pas être impliqué dans un processus de retrait axonal, mais plutôt de guidage axonal (Deiner et al., 1997; Kennedy et al., 1994). Pour cette raison, la seconde hypothèse semble plus probable pour expliquer les MMC chez les individus porteurs d'une mutation sur le gène *DCC*. Ceci va de pair avec plusieurs études ayant démontré que les souris chez qui le gène *DCC* est muté perdent leur capacité à se déplacer normalement et doivent plutôt marcher à la façon d'un kangourou dans un patron similaire à ce qui est observé chez l'humain (Fazeli et al., 1997; Finger et al., 2002). D'ailleurs, une étude en tractographie réalisée chez des patients présentant des MMC et porteurs d'une mutation sur le gène *RAD51* a rapporté la présence d'une plus grande proportion de fibres n'ayant pas croisé la ligne médiane au niveau de la décussation pyramidale que les sujets contrôles (Gallea et al., 2013).

Considérant que les gènes *RAD51* et *DCC* partagent une pathophysiologie similaire et qu'une insuffisance au niveau de la protéine *DCC* semble même être liée à un phénotype plus sévère, il semble plus probable que les MMC chez les individus porteurs d'une mutation sur le gène *DCC* soient le résultat de la seconde hypothèse.

6.3.2.3 Inhibition interhémisphérique et implication dans les MMC

Les données de l'article 4 ont également démontré que les membres *DCC+/MM+* de la famille étudiée présentaient une IIH plus faible que celle observée chez les membres de la famille ne présentant pas de MMC et les participants contrôles. Ces données sont identiques à celles rapportées chez des individus présentant des MMC associés à une mutation sur le gène *RAD51* (Gallea et al., 2013). Tel que mentionné précédemment, l'IIH est un mécanisme fondamental associé à l'exécution de mouvements purement unilatéraux, puisqu'elle permet de diminuer l'activité du M1 devant rester au repos (Giovannelli et al., 2009; Grefkes et al., 2008). Il a été suggéré qu'une réduction de l'IIH chez les individus présentant des MMC pourrait être un mécanisme compensatoire favorisant un meilleur contrôle moteur dans cette population (Gallea et al., 2013). En effet, chez les individus présentant des MMC, chaque main reçoit une afférence motrice provenant des deux M1. Ainsi, une IIH plus importante aurait pour conséquence de réduire l'activité du M1 ipsilatéral, et donc réduire la contribution de la VCS ipsilatérale aberrante connectée à la main volontaire, lors de l'exécution d'un mouvement. Ceci aurait comme contrecoup la diminution de la qualité du contrôle moteur (Gallea et al., 2013). Une autre hypothèse veut que le gène *DCC* soit un acteur important dans le développement du CC, une structure essentielle à l'IIH. En effet, une étude animale a montré que lorsque le gène *DCC* était éteint chez la souris, cela les rendait non viables et entraînait une absence totale de CC (Fazeli et al., 1997). Une autre étude a rapporté des anomalies au niveau du CC chez des individus ayant des MMC causés par une mutation sur le gène *RAD51*, à savoir une plus grande connectivité M1-M1 transitant par le CC (Gallea et al., 2013). Pris dans leur ensemble, ces résultats suggèrent que la réduction d'IIH et le développement anormal du CC pourraient être des mécanismes adaptatifs chez les individus porteurs de MMC. En effet, une réduction de l'IIH et une plus grande connectivité M1-M1 pourraient augmenter la contribution du M1 ispilatéral et de sa VCS aberrante liée à la main active, ce qui augmenterait les capacités motrices des individus ayant des MMC.

6.3.2.4 Article 4 : Conclusion

En résumé, l'article 4 suggère que les individus porteurs d'une mutation sur le gène *DCC*, mais qui ne présentent pas de MMC, sont identique au plan neurophysiologique aux individus non porteurs de la mutation. Par ailleurs, les individus avec des MMC et une mutation sur le gène *DCC* semblent présenter une VCS ipsilatérale plus "excitable" que les individus porteurs d'une mutation sur le gène *RAD51*. Finalement, tel que rapporté dans des études antérieures, l'IIH est réduite chez les individus *DCC+/MM+*, ce qui pourrait être un mécanisme compensatoire permettant un meilleur contrôle moteur de la main active.

6.4 Conclusion générale et perspectives futures

Les trois études composant cette thèse, appuyées par la littérature antérieure portant sur les processus impliqués dans la latéralisation du mouvement, suggèrent la présence d'une contribution significative du CPMd, du CC et de la VCS dans le mouvement unilatéral.

Au plan méthodologique, nous avons montré que le CPMd fait partie du réseau de transformation non-miroir de la commande motrice puisque la diminution de son activité résulte en une augmentation des MMp lors d'un mouvement unilatéral. Considérant que plusieurs pathologies cérébrales sont accompagnées de MM, nuisant ainsi à la qualité de vie des patients, est-ce qu'une augmentation de l'activité du CPMd pourrait réduire l'occurrence des MMp et ainsi offrir une possibilité de traitement dans ces pathologies ? Les résultats du présent ouvrage suggèrent que non. Toutefois, l'utilisation de la SÉTcd comme outil thérapeutique demande davantage d'étude pour élucider son mécanisme d'action et établir des paramètres de stimulation optimaux, stables et reproductibles. Des études utilisant un protocole expérimental différent, la SÉTcd à haute définition (Roy, Baxter, & He, 2014) ou la SMTr à haute fréquence pourraient être utilisées afin de déterminer s'il est possible de réduire les MMp. Dans l'éventualité de résultats positifs chez des individus en santé, des essais cliniques pourraient alors être menés de manière à déterminer si ces méthodes peuvent réduire les MM associés à des pathologies telles que la Maladie de Parkinson.

Par ailleurs, bien que l'IIH semble jouer un rôle important dans la latéralisation du mouvement, il semble que les individus dépourvus de CC, chez qui l'IIH est absente, sont en mesure d'en minimiser l'impact comportemental, contrairement aux individus chez qui le CC a été sectionné à l'âge adulte et qui souffrent d'un syndrome de déconnexion. En effet, le cortex cérébral d'individus AgCC est légèrement différent de celui de la population générale (à tout le moins au niveau de son épaisseur), principalement au niveau des régions primaires S1, V1 et de la région de la main dans M1. Ces différences sur le plan de l'épaisseur corticale ne semblent toutefois pas être exclusivement liées à un processus compensatoire, tel que proposé dans la littérature, mais aussi à certaines des difficultés observées chez les individus AgCC. De plus, l'absence de CC, et donc d'IIH, ne semble pas causer de MM visibles, comme chez l'enfant chez qui le CC est immature et dans d'autres pathologies affectant le CC. D'autres études, utilisant des méthodologies différentes, devront être menées dans cette population afin de déterminer le lien entre les différences sur le plan de la structure du cerveau et le comportement.

Finalement, nous savons que le gène *DCC* est essentiel à la migration des axones au cours du développement cortical, en leur permettant de traverser la ligne médiane. Les individus porteurs d'une mutation sur le gène *DCC*, résultant en une protéine DCC tronquée moins efficace, ont 50% de chance de développer des MMC. Ceux-ci perdent alors la capacité à exécuter un mouvement de manière purement unilatérale, puisque chaque M1 a des projections qui innervent les deux mains simultanément. Cette mutation semble plus sévère que ce qui a été rapporté chez les individus porteurs d'une mutation sur le gène *RAD51*, laquelle cause également des MMC. Il semble également que les individus ayant des MMC et une mutation sur le gène *DCC* présentent une IIH plus faible que celle observée dans la population générale. Ceci pourrait être un mécanisme compensatoire permettant aux deux M1 de contribuer, via la VCS controlatérale naturelle et ipsilatérale aberrante, aux mouvements unilatéraux. Par ailleurs, considérant que des anomalies au niveau du CC ont été rapportées dans des modèles animaux et chez les individus porteurs d'une mutation sur le gène *RAD51*, des études subséquentes devront être réalisée afin de déterminer l'intégrité du CC dans cette population.

En somme, les études du présent ouvrage ont contribué à notre compréhension des mécanismes permettant le contrôle unilatéral de la main et le rôle des structures cérébrales qui y étant associées.

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Annexe 1

Neurophysiological investigation of congenital mirror movements in a patient with agenesis of the corpus callosum

Neurophysiological investigation of congenital mirror movements in a patient with agenesis of the corpus callosum

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Keywords: Corpus callosum; Agenesis; Mirror movements; Transcranial magnetic stimulation; Motor cortex; Neurophysiology

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Abstract

We describe a patient with complete agenesis of the corpus callosum and congenital mirror movements in which primary motor cortex (M1) excitability of both hemispheres was assessed with trancranial magnetic stimulation. Voluntary contraction of the index finger was associated with bilateral electromyographic activity in the first dorsal interosseus muscle. Motor evoked potentials of identical latencies were produced bilaterally following unilateral M1 stimulation. Measures of intracortical inhibition and facilitation were within normal limits bilaterally although a shorter contralateral silent period was found for both hemispheres. Taken together, the present data suggest a pattern of M1 excitability very similar to that found in patients with congenital mirror movements and no other motor abnormality.

Introduction

Congenital mirror movements (CMM) are involuntary movements accompanying voluntary activity in contralateral homologous muscles. CMM have been associated with a number of pathological conditions including Kallman's and Klippel-Feil syndromes (1). Probable mechanisms explaining mirror movements include ipsilateral corticospinal projections, activation of the contralateral motor cortex, and diminished interhemispheric inhibition (1). It has long been known through anecdotal reports that CMM can be present in patients with agenesis of the corpus callosum (ACC) (2,3,4) but detailed neurophysiological investigation of the phenomenon is lacking.

Methods and material

We report the case of a 42-year-old man with ACC and CMM. Patient MG is left-handed, has a global IQ of 77, two older sisters with ACC and absence of CMM (5,6), and no family history of CMM. Complete ACC was confirmed by MRI examination. Five healthy male participants (mean age: 33 years) without ACC or CMM served as controls, as well as patient SG, the sister of MG. SG is right handed, has a global IQ of 84, complete agenesis of the corpus callosum, and no mirror movements. Cortical excitability of bilateral primary motor cortex (M1) was assessed with transcranial magnetic stimulation (TMS) according to established protocols (7). TMS was delivered with a Medtronic Magpro X100 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. 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. Motor evoked potentials (MEPs) were recorded from surface electrodes placed over the first dorsal interosseus (FDI) muscle bilaterally. For short interval intracortical inhibition (SICI), conditioning stimulus (CS) intensity was set at 90% active motor threshold (aMT) and test stimulus (TS) intensity at 120% resting motor threshold (rMT). A conditioning pulse intensity of 90% aMT was selected to avoid short interval

intracortical facilitation (SICF) from contaminating SICI measures (8), which may have occured in a previous report of the same patients (6). For intracortical facilitation (ICF), conditioning stimulus (CS) intensity was set at 80% rMT and TS intensity at 120% rMT. SICI and ICF were tested at interstimulus intervals of 3 and 12 ms, respectively. Cortical silent period durations were produced at an intensity of 120% rMT. Single-pulse stimulations were applied over M1 while participants maintained a voluntary isometric muscle contraction of the FDI at 20% maximum force. For long interval intracortical inhibition (LICI), intensity of the CS and TS was adjusted to induce MEPs of approximately 1mV peak-to-peak amplitude at an interstimulus interval of 100 ms. Interhemispheric inhibition was measured according to the method described by Ferbert and collaborators (9) using two 50 mm custom-made coils, one over each hemisphere, connected to two Magstim 200 stimulators (The Magstim Company, Wales, UK). Bilateral stimulation at all intervals was controlled by an iMac (Apple, Cupertino, USA) running Psyscope software and timing accuracy was verified with an oscilloscope (Tektronix, Beaverton, USA).

Results

Contrary to controls, voluntary contraction of the left or right index finger produced bilateral EMG activity (Fig 1a) and single pulse TMS of either hemisphere produced bilateral MEPs of identical latency in patient MG (Fig 1b). Mirror movements were more prominent during voluntary contraction of the left hand and ipsilateral MEPs were much more easily evoked following stimulation of the right hemisphere compared to the left hemisphere. Contralateral MEPs were consistently larger than ipsilateral MEPs. Ipsilateral MEPs could not be elicited in patient SG from either hemisphere and EMG activity was absent in the contralateral FDI during voluntary contraction. Mean TMS values for controls and patients MG and SG are given in Table 1. In patient MG, paired-pulse measures of intracortical facilitation revealed increased MEP amplitude bilaterally compared to single pulse TMS for both hemispheres that was within normal limits. Paired-pulse measures of SICI were also within normal limits bilaterally. Similarly, long interval intracortical inhibition was present bilaterally for both hemispheres and was of similar magnitude to that found in control

participants (Fig 1c). A similar pattern was observed in patient SG, except for ICF at 12ms in the left hemisphere, which resulted in slight inhibition.

The duration of the contralateral CSP following unilateral stimulation of the right or left hemisphere was shorter in patient MG compared to controls and SG, predominantly in the left hand (Table 1). An ipsilateral silent period, explained by the presence of the uncrossed corticospinal projection, could only be induced during right hemisphere stimulation at an intensity producing MEPs of 1mV peak-to-peak amplitude at rest. In that case, CSP durations were of very similar durations ipsi- and contralaterally. Whereas bilateral M1 stimulation was associated with reduced CSP duration compared to unilateral stimulation in control participants and patient SG, bilateral stimulation induced slight CSP duration increases in patient MG. In contrast to control participants, in whom stimulation of the left or right M1 reduced the amplitude of MEPs elicited by stimulation of the contralateral primary motor cortex 10 or 40 ms later, interhemipheric inhibition was absent in patient MG and SG in both directions (Fig 1d). Genetic testing was performed in patient MG to detect the presence of mutations in the DCC (deleted in colorectal carcinoma) gene that have been associated with familial CMM (10). No DCC mutation was found.

Discussion

The present case report suggests that the corpus callosum has little influence on the neurophysiology of congenital mirror movements. Similarly to patients with CMM and no other motor abnormalities (1), the onset of voluntary and mirror movements was simultaneous in patient MG and TMS-induced bilateral MEPs had the same latency. This provides strong evidence for the existence of a fast conducting ipsilateral corticospinal pathway originating from both hemispheres in this patient. Furthermore, the absence of ipsilateral MEPs in patient SG, the sister of MG with ACC and no CMM, shows the specificity of patient MG. Normal SICI values were also found in the two acallosal patients using a conditioning pulse intensity that is not subject to contamination from SICF (8), confirming previous data (6). Abnormal activity in the M1 ipsilateral to the intended movement also appears to be involved in MM (1).

For example, Cincotta and collaborators (11) found reduced CSP durations that significantly increased during simultaneous bilateral stimulation of the motor cortex and functional magnetic resonance imaging has revealed increased signal levels in the mirror M1 during sequential finger movements (12). The present data showing shorter CSP durations in patient MG are in keeping with these findings (11), although the fact that CSP lengthening produced by bilateral stimulation with respect to unilateral stimulation was somewhat marginal may be due to the physical interaction of the two simultaneously discharging coils (13).

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Dr Lepage reported no biomedical financial interests or potential conflicts of interest.
Mr Beaulé reported no biomedical financial interests or potential conflicts of interest.
Dr Srour reported no biomedical financial interests or potential conflicts of interest.
Dr Rouleau reported no biomedical financial interests or potential conflicts of interest.
Dr Pascual-Leone reported that he serves on the scientific advisory board for Nexstim, NeoSync, Neuronix, and Starlab.
Dr Lassonde reported no biomedical financial interests or potential conflicts of interest.
Dr Théoret reported no biomedical financial interests or potential conflicts of interest.

All authors acknowledge that the conflict of interests are complete for both themselves and their co-authors, to the best of their knowledge.

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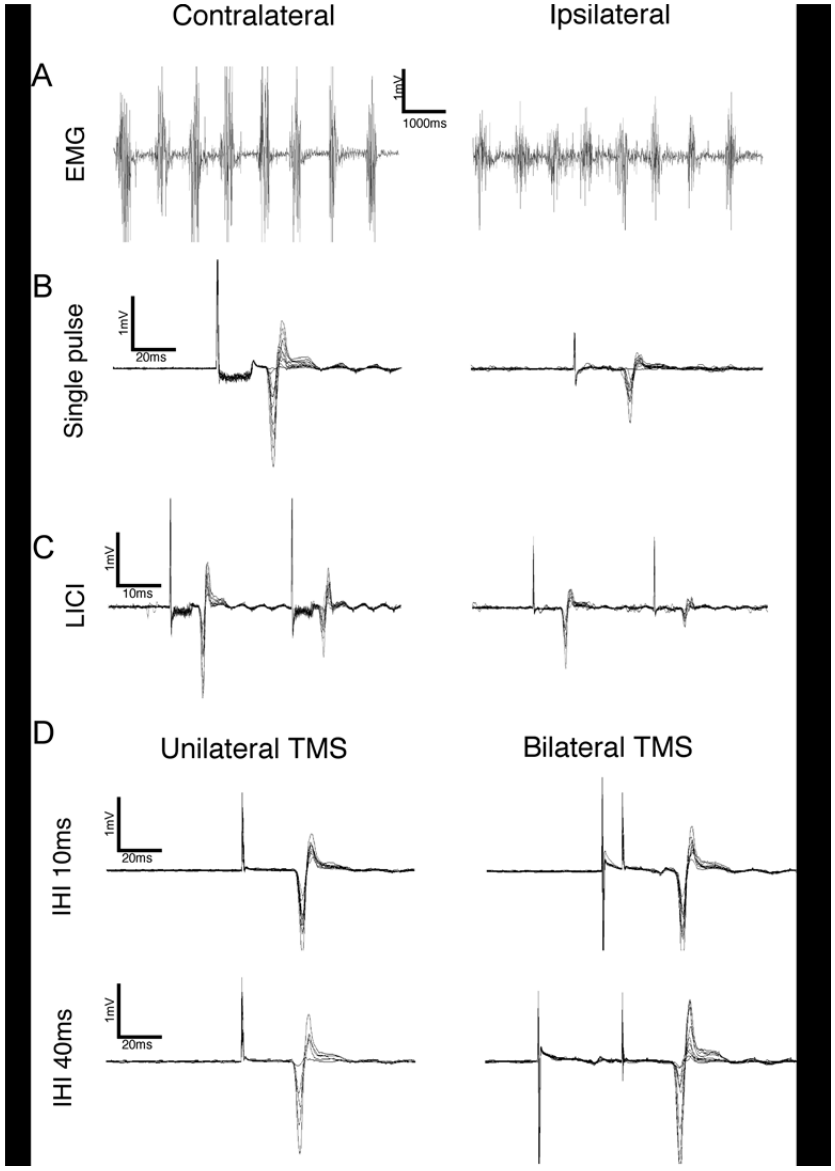
Figure

Figure 1: Bilateral EMG recordings

Legend: **(a)** during repeated unimanual contraction (1Hz) of the left FDI; **(b)** following single pulse TMS over right M1; **(c)** following paired-pulse TMS (LICI protocol) over right M1. **(d)** EMG recordings from the left hand during unilateral or bilateral stimulation of M1 to assess interhemispheric inhibition (IHI) at interstimulus intervals of 10 ms and 40 ms.



Annexe 2

Microcephaly, intellectual disability and hypogenesis of the corpus callosum in the child of an acallosal mother with compound heterozygous variants in *CDK5RAP2*

Microcephaly, intellectual disability and hypogenesis of the corpus callosum in the child of an acallosal mother with compound heterozygous variants in *CDK5RAP2*

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Abstract

The corpus callosum (CC) is the major commissure of the brain, ensuring transfer and integration of information between the cerebral hemispheres. Disruption in its development can cause agenesis of the CC (AgCC). It has been reported compound heterozygous variants in the *CDK5RAP2* gene could explain some cases of AgCC. *CDK5RAP2* is known to cause autosomal recessive primary microcephaly, intellectual disability, and abnormalities in callosal development. We describe two probands (son and daughter) of a mother with AgCC and compound heterozygous variants in the *CDK5RAP2* gene. The son presented the phenotype usually associated with mutations affecting *CDK5RAP2* with microcephaly, intellectual disability and hypogenesis of the CC, whereas the daughter was normal on all measures. Sanger sequencing revealed, in both probands, one compound heterozygous mutation found in the mother, without other genetic mutations affecting *CDK5RAP2*.

Introduction

The corpus callosum (CC) is the principal commissure of the brain with over 190 million axons. Its major role is the transfer and integration of information between homologous regions of the cerebral hemispheres. Early disruption in the maturation of the CC can lead to agenesis of the corpus callosum (AgCC), ranging from complete absence to hypogenesis [1]. AgCC is a relatively frequent congenital malformation affecting 1:4000 individuals [2] and can be related to other neurological conditions such as hydrocephalus [3], severe microcephaly [4] or foetal alcohol syndrome [5]. Because AgCC is a heterogeneous condition, affected individuals display a wide range of symptoms, from seemingly normal to severe impairment in every day living [6, 7]. It has been suggested that specific genes can contribute to AgCC independently of other brain conditions, such as Disrupted-in-Schizophrenia 1 (DISC1), in which a possibly pathogenic variant was found [8]. More recently, Jouan et al. [9] performed whole exome sequencing in three French Canadian acallosal siblings and identified compound heterozygous variants in *CDK5RAP2* (cyclin-dependant kinase 5 regulatory protein 2) as a candidate gene for isolated AgCC. They suggested that a combination of two missense heterozygous mutations affecting both alleles of the *CDK5RAP2* gene (mutations : p.[Gly94Arg] and p.[Asn1232Ser]) could result in an abnormal phenotype (AgCC). Indeed, deleterious mutations in *CDK5RAP2*, also called *MCPH3*, are known to cause autosomal recessive primary microcephaly, intellectual disability, and abnormalities in callosal development [10, 11]. One of the three French Canadian acallosal siblings described in Jouan et al. [9] is the mother of two children, one daughter and one son, both born from the same father. We herein describe these two children, one of which presents with hypogenesis of the corpus callosum, microcephaly, intellectual disability, but no paternally inherited *CDK5RAP2* deleterious mutation. This is an unusual case where the mother does not have the complete phenotype associated with a *CDK5RAP2/MCPH3* mutation (no microcephaly) whereas the son presents the full phenotype without bi-allelic pathogenic *CDK5RAP2* mutation.

Case presentation

The probands are two French Canadian siblings, one daughter (III-1) and one son (III-2), both born from the same mother (II-2) and father (II-A) (Fig. 1). For complete description of the three French Canadian family members with full AgCC, refer to [9].

II-2 : The mother is a 55 year-old woman with complete AgCC, a global IQ of 78 (PIQ of 97 and VIQ of 61) and normal head circumference (10^{th} centile, low average) [12, 13] and height (table1).

II-A: The father is a 55 year-old man with a global IQ of 71 (WAIS-IV: PIQ of 85 and VIQ of 58) and normal head circumference (63^{rd} centile, average) [12, 13] and height (table 1).

III-1: The daughter is a 25 year-old right-handed woman with a global IQ of 77 (WAIS-IV: PIQ of 98 and VIQ of 63) and normal head circumference (39^{th} centile, average) [12, 13] and height (Table 1). Brain MRI revealed no major abnormalities and an intact CC (Fig. 2).

III-2: The son is a 24 year-old right-handed man with intellectual disability, revealed by an IQ of 62 (*mild intellectual disability*) on the WAIS-IV (PIQ of 70 and VIQ of 63: Table 1). The patient also presents with microcephaly, with head circumference (52cm) well below the 1^{st} centile [12, 13]. MRI examination revealed the presence of callosal hypogenesis (Fig. 2). Although the global IQ of both parents is near intellectual disability (78 for the mother and 71 for the father; cut-off at 70), it is likely that intellectual disability in case III-2 is at least partly linked to his condition, rather than strictly inherited from the parents. Indeed, both parents have a PIQ ranging from normal to low average (97 for the mother and 85 for the father) whereas the son's PIQ is well below (70).

CDK5RAP2 screening was performed by Sanger sequencing on the two siblings using thirty-nine primers of all coding exons and flanking intronic boundaries. One heterozygous missense mutation in *CDK5RAP2* (NM_018249.5; NG_008999.1) p.[Gly94Arg] was found in the affected son and one heterozygous missense mutation in *CDK5RAP2* (NM_018249.5; NG_008999.1) p.[Asn1232Ser] was found in the asymptomatic daughter, both mutations transmitted by the affected mother. EXAC total frequencies are 8.237e-06 and 8.238e-06 for

the first and the second variant respectively (Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org) [December 2016]). No additional potentially causative mutation was found in this gene in either case.

Discussion

We describe two probands, both born from the same mother and father. It was found that the son was carrying one of the two heterozygous *CDK5RAP2* missense mutations (p.[Gly94Arg]) present in the mother [9]. Interestingly, although he only carries one missense mutation, the proband displayed a more severe phenotype than his mother, including intellectual disability, microcephaly and partial agenesis of the CC. The other unaffected sister was within normal limits on all measures. One heterozygous missense mutation in *CDK5RAP2* (NM_018249.5; NG_008999.1) p.[Asn1232Ser] was found in this unaffected sister, transmitted by the affected mother. The grandfather also carries the same mutation.

The *CDK5RAP2* gene plays a critical role in neocortical expansion during brain development. There is evidence of centrosomal dysfunction associated with *CDK5RAP2* mutations leading to increased apoptosis that can result in microcephaly and CC abnormalities [9]. Microcephaly resulting from a *CDK5RAP2* mutation is rare in non-consanguineous Caucasians (1/1 000 000) [14]. Jouan and collaborators [9] have suggested that a combination of two missense mutations p.[Gly94Arg] and p.[Asn1232Ser] affecting both alleles of the *CDK5RAP2* gene is associated with isolated AgCC and could affect brain development. The binding site of the CDK5RAP2 protein is located between amino acids 58-90. Mutations in this domain or near could affect protein function [15]. Therefore, the p.[Gly94Arg] variant affecting the 94th amino acid, which is very close to the active binding site, could affect protein function slightly by interacting or modulating final protein organization [9].

Interestingly, the affected case (III-2) displayed the expected phenotype associated with homozygous nonsense or frameshift mutation of the *CDK5RAP2* gene. However, though he had one of the two heterozygous mutations carried by his mother, Sanger sequencing did

not identify any additional mutations in the *CDK5RAP2* gene that could explain his condition. This suggests that *CDK5RAP2* plays a partial role in AgCC and that an additional mutation harbored by a different non-MCPH gene also contributes to his AgCC, intellectual disability and microcephaly. The phenotype in case III-2 may be caused by a double hit mechanism, where a mutation in a gene regulating brain and CC development inherited from his father interacts with the *CDK5RAP2* mutation to cause the observed phenotype. Alternatively, we cannot exclude that a deletion or a duplication of *CDK5RAP2* affects gene function. A Whole Genome Sequencing (WGS) of the affected son would help us to address these questions.

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Conflict of interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Figure

Figure 1. Pedigree of the ACC family.

Legend: Square symbols represent men, circles represent women and filled symbols represent affected individuals.

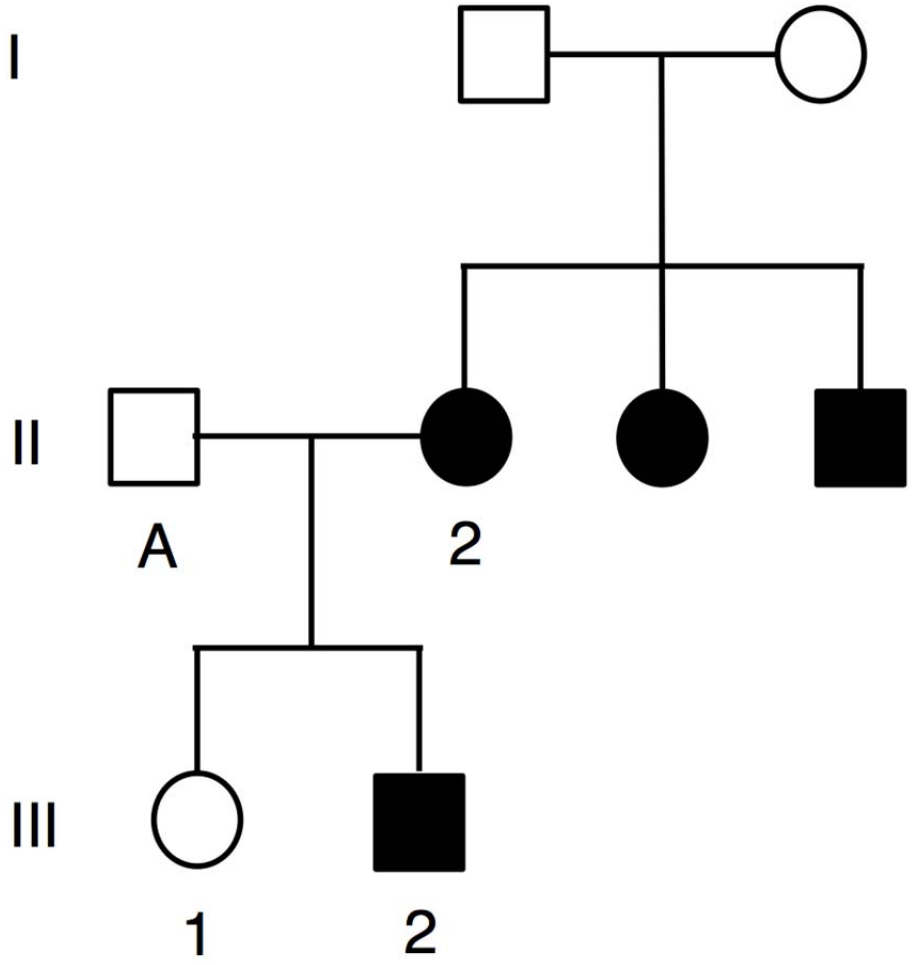
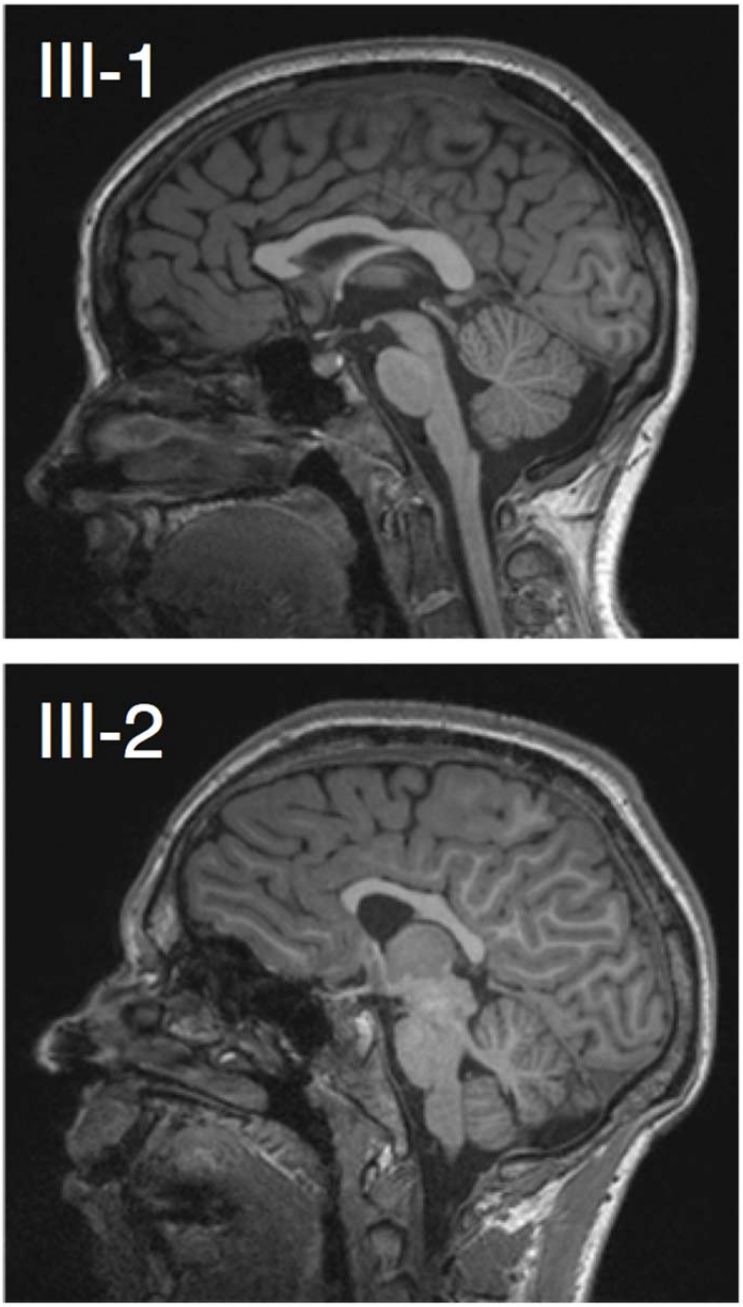


Figure 2. Midsagittal MRI of the daughter (A) and son (B).



Table

Table 1. Demographic data.

Participant	Age	PIQ	VIQ	WMI	PSI	FSIQ	Height	Circum. (centile)
II-2 : Mother	55	97	61	-	-	78	160	53 (10)
II-A: Father	55	85	58	82	79	71	175	58 (63)
III-1 : Daughter	21	98	63	82	85	77	163	55 (39)
III-2 : Son	24	70	63	76	66	62	168	52 (<1)

PIQ: performance IQ; VIQ: verbal IQ; WMI: working memory index; PSI: Processing speed index. FSIQ: full-scale IQ.

Annexe 3

Contribution scientifique

1. Occlusion of LTP-Like Plasticity in Human Primary Motor Cortex by Action Observation (2012)

Jean-François Lepage, Olivier Morin-Moncet, **Vincent Beaulé**, Louis de Beaumont, François Champoux, Hugo Théoret

2. Relationship between transcranial magnetic stimulation measures of intracortical inhibition and spectroscopy measures of GABA and glutamate+glutamine (2012)

Sara Tremblay, **Vincent Beaulé**, Sébastien Proulx, Louis de Beaumont, Małgorzata Marjannska, Julien Doyon, Alvaro Pascual-Leone, Maryse Lassonde, and Hugo Théoret

3. Anodal transcranial direct current stimulation modulates GABAB-related intracortical inhibition in the M1 of healthy individuals (2012)

Sara Tremblay, **Vincent Beaulé**, Jean-François Lepage and Hugo Théoret

4. The Use of Magnetic Resonance Spectroscopy as a Tool for the Measurement of Bi-hemispheric Transcranial Electric Stimulation Effects on Primary Motor Cortex Metabolism (2014)

Sara Tremblay, **Vincent Beaulé**, Sébastien Proulx, Louis-Philippe Lafleur, Julien Doyon, Małgorzata Marjańska, Hugo Théoret

6. Multimodal assessment of primary motor cortex integrity following sport concussion in asymptomatic athletes (2014)

Sara Tremblay, **Vincent Beaulé**, Sébastien Proulx, Sébastien Tremblay, Małgorzata Marjańska, Julien Doyon, Maryse Lassonde, and Hugo Théoret.

6. The effects of bi-hemispheric M1-M1 transcranial direct current stimulation on primary motor cortex neurophysiology and metabolite concentration (2016)

Sara Tremblay, Louis-Philippe Lafleur, Sébastien Proulx, **Vincent Beaulé**, Alex Latulipe-Loiselle, Julien Doyon, Małgorzata Marjanska and Hugo Théoret