Université de Montréal

Transfert et traitement de l'information visuomotrice dans le cerveau autiste : intégrité et hétérogénéité

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Thèse présentée à la Faculté des études supérieures et postdoctorales
en vue de l'obtention du grade Philosophiae Doctor (Ph.D.)
en sciences biomédicales
option sciences psychiatriques

décembre 2014

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Faculté des études supérieures et postdoctorales

Cette thèse intitulée :

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Résumé

En plus de la triade de symptômes caractérisant l'autisme, ce trouble neurodévelopmental est associé à des particularités perceptives et motrices et, au niveau cérébral, par une connectivité atypique entre les différentes régions du cerveau. Au niveau anatomique, un des résultats les plus communs est la réduction du corps calleux. Toutefois, des effets directs de cette altération anatomique sur l'intégrité et l'efficacité du transfert interhémisphérique restent à être démontrés. Pour la présente thèse, trois différentes études investiguent différents aspects du traitement de l'information visuomotrice : le transfert interhémisphérique entre les régions bilatérales motrices et visuelles, la vitesse de traitement perceptif, et les habiletés motrices visuellement guidées.

Dans la première étude, le paradigme visuomoteur de Poffenberger a été utilisé pour mesurer le temps de transfert interhémisphérique (TTIH). L'imagerie par résonnance magnétique fonctionnelle (IRMf) et structurale ainsi que l'imagerie de diffusion ont aussi été utilisées pour étudier les réseaux cérébraux impliqués dans la tâche de Poffenberger. Les autistes ont été comparés à un groupe d'individus à développement typique. La deuxième étude avait pour but d'investiguer la vitesse de traitement perceptif en autisme. Dans la troisième étude, deux tâches motrices (Purdue et Annett) ont été utilisées pour examiner la nature et l'importance des déficits moteurs. La tâche de Purdue inclut deux conditions bimanuelles utilisées comme indice additionnel d'intégration interhémisphérique. Dans les études 2 et 3, le groupe d'autistes a aussi été comparé à un groupe d'individus Asperger afin de voir si, et comment, les deux sous-groupes peuvent être distingués en ce qui concerne le traitement visuel et les déficits moteurs.

Aucune différence entre les groupes n'a été observée en termes de TTIH. Les résultats de l'étude IRMf révèlent des différences d'activations corticales en lien avec la tâche de Poffenberger. Dans les groupes d'autistes et de typiques, l'efficacité de la communication interhémisphérique était associée à différentes portions du corps calleux (frontales/motrices chez les typiques, postérieures/visuelles chez les autistes). De façon globale, les résultats de cette étude démontrent un patron atypique de transfert interhémisphérique de l'information

visuomotrice en autisme, reflétant un rôle plus important des mécanismes visuels dans le comportement sensorimoteur possiblement en lien avec une réorganisation cérébrale.

Les résultats des études comportementales 2 et 3 indiquent que les autistes excellent dans la tâche mesurant la vitesse de traitement perceptif alors que les Asperger accomplissent la tâche à des niveaux similaires à ceux des typiques. La nature des déficits moteurs diffère aussi entre les deux sous-groupes; la dextérité et la coordination bimanuelle est affectée chez les individus Asperger mais pas chez les autistes, qui eux sont plus atteints au niveau de la rapidité unimanuelle. Les sous-groupes d'autistes et de syndrome d'Asperger sont caractérisés par des profils cognitifs différents dont les particularités perceptives et motrices font partie intégrante.

Mots-clés : autisme, corps calleux, transfert interhémisphérique, imagerie par résonance magnétique (IRM), imagerie de diffusion (DTI), habiletés motrices, vitesse de traitement perceptif, syndrome d'Asperger

Abstract

In addition to the triad of symptoms characterizing autism, this neurodevelopmental condition is characterized by visual and motor atypicalities and, at the cerebral level, by atypical connectivity between the different brain areas. Anatomically, one of the most replicated finding is a reduction of the corpus callosum. However, evidence of a direct effect of the corpus callosum reductions on integrity and efficiency of interhemispheric transfer is lacking. Three different studies were designed to investigate different aspect of visuo-motor processing: interhemispheric transfer between bilateral motor and visual brain areas, perceptual processing speed, visually guided motor performance.

In the first study, the visuo-motor Poffenberger paradigm was used to measure interhemispheric transfer time (IHTT). Structural and functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) were also used to study the brain networks involved in the Poffenberger task. Autistics were compared to typically developing individuals. The second study investigates whether perceptual processing speed (Inspection Time task) is atypical in autism. In the third study, two visually-guided motor tasks (the Purdue pegboard and Annett peg moving task) were used to verify the nature and magnitude of motor deficits. The Purdue task includes two bimanual conditions used as additional measures of interhemispheric communication integrity. Moreover, in studies 2 and 3, behavioral differences between autistic and Asperger individuals were investigated in order to see if and how the two subgroups can be distinguished in terms of perceptual processing and motor deficits.

No group difference was observed in terms of IHTT. The fMRI results reveal a different pattern of cortical activations associated to the Poffenberger task. In the autism and typical groups, the efficiency of interhemispheric communication was associated with different portions of the corpus callosum (frontal/premotor in typicals, posterior/visual in autistics). These results demonstrate an atypical pattern of interhemispheric visuo-motor information transfer, possibly reflecting a more prominent role of visual mechanisms guiding sensorimotor behavior in autism, related to cerebral reorganizations.

Results of the behavioral studies indicate that autistics have an excellent visual processing speed while Asperger individuals performed like typicals. Motor impairments also differed between the two subgroups; dexterity and bimanual coordination was impaired in Asperger individuals but not in autistics, who presented more difficulties in unimanual conditions. Autism and Asperger subgroups are characterized by different cognitive profiles in which visual processing and motor deficits are important factors.

Keywords : autism, corpus callosum, interhemispheric transfer, magnetic resonance imaging (MRI), diffusion imaging (DTI), motor skills, perceptual processing speed, Asperger syndrome

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Annexe I

Liste des sigles et abbréviations

TED-NS: Trouble envahissant du développement non spécifié

DSM: Diagnostic and Statistical Manual of Mental Disorders

TSA: Trouble du spectre autistique

ADI: Autism Diagnostic Interview

WCC: Weak Central Coherence

EPF: Enhanced Perceptual Functioning

RPM: Raven's Progressive Matrices

QIV: Quotient intellectuel verbal

QIP: Quotient intellectuel de performance

QIG: Quotient intellectuel global

EEG: Électroencéphalographie

IRM: Imagerie par résonnance magnétique

MEG: Magnétoencéphalographie

DTI: Diffusion Tensor Imaging

FA: Fractional Anisotropy

MD: Mean Diffusivity

AD: Axial Diffusivity

RD: Radial Diffusivity

IVT: Indice de vitesse de traitement

IRMf: Imagerie par résonnance magnétique fonctionnelle

ADOS: Autism Diagnostic Observation Schedule

TTIH: Temps de transfert interhémisphérique

CUD: Crossed-Uncrossed Difference

BOLD: Blood-Oxygen-Level-Dependent

dHb: déoxyhémoglobine

IT: Inspection Time

TTT: Trigger-Threshold-Target

VBM: Voxel-based Morphometry

à Téo.

Remerciements

Tout d'abord, je tiens à remercier mon directeur de recherche, Laurent Mottron, sans qui j'aurais terminé une maitrise depuis longtemps. Mais grâce à votre passion contagieuse pour la science et la recherche à votre confiance me voilà à terminer un doctorat. Merci d'encourager la curiosité, tant scientifique que pour la dégustation culinaire....

Merci à mes collaborateurs et à mes spécialistes en neuroimagerie: Adrianna Mendrek, Tom Zeffiro, John Lewis, Julien Doyon et Habib Benali pour la si précieuse expertise et ce que vous m'avez appris.

Aux Mottronettes bien sur qui ont fait de ces années dans le labo un plaisir quotidien et sont devenues des partenaires de voyage et des amies. À mes Brain Sisters, Isabelle et Fabienne, aussi éternelle partenaire d'hôtel, de fou rires et de bedaine! Sans oublier Patricia, Andrée-Anne avec qui j'ai parcouru les derniers miles, Jessica, Valérie, Marie-Pier et compagnie. J'aurais fait un doctorat de 15 ans avec vous! N'oubliez jamais que l'important dans la vie c'est de ne pas aller en prison!

À mes ami(e)s pour les soupers du vendredi, pour les soupers avec les petits, pour tous ces moments, merci de rendre ma vie si riche et remplie de...vous!

À mes chers parents qui m'ont supportée et toujours encouragée malgré mes choix de parcours plutôt hétéroclites et surement durs à suivre. Merci pour le côté artistique qui donne un équilibre essentiel à ma vie scientifique. Merci pour la soif d'apprendre, la créativité et l'originalité.

Finalement, mes deux amours, le premier, Yan, merci d'être là, merci de ta patience quotidienne, mais aussi celle d'attendre qu'un jour je ne sois plus étudiante. Merci de faire que ma vie ne soit pas un long fleuve tranquille. Et le plus récemment arrivé dans ma vie, mon petit Téo, mon petit chéri, ma petite boule d'énergie.... merci d'être toujours là tous les deux pour mettre de la joie et de la vie dans mes journées. Et une mention spéciale, à une toute petite fille qui m'a accompagnée durant les derniers mois. Je vous aime xxx

Chapitre 1. Contexte théorique

1.1 Traitement de l'information visuomotrice dans le cerveau

Les cinq sens sont pour le cerveau la porte d'entrée lui permettant de percevoir l'information de l'environnement et d'interagir avec ce dernier afin de permettre les fonctions complexes du cerveau humain, telles que la cognition, l'organisation, le langage, la conscience et le mouvement. Afin d'accomplir une tâche motrice (attraper un objet par exemple), le cerveau doit analyser et intégrer l'information visuelle de l'environnement afin de s'ajuster et de produire le mouvement approprié. Le traitement de l'information visuomotrice comprend donc différentes étapes. Le processus commence par la perception, et, éventuellement, l'information visuelle est transférée aux régions motrices du cerveau qui produiront une réponse motrice.

1.1.1 Le système visuel : organisation croisée

L'œil, plus précisément la rétine, capte l'information visuelle et la transforme en influx nerveux qui se rend, par le nerf optique, jusqu'à un premier relais dans le cerveau : le corps genouillé latéral du thalamus. Cette structure sous-corticale relaie ensuite l'information, via le tractus optique, aux aires visuelles corticales dans le lobe occipital, à l'arrière du cerveau. Le cerveau étant divisé en deux, chacun des hémisphères, le gauche et le droit, a son thalamus, donc, son corps genouillé, qui ne reçoit pas la même information visuelle. En effet, le corps genouillé droit reçoit l'information du champ visuel gauche capté par la rétine nasale de l'œil gauche et la rétine temporale de l'œil droit et l'inverse est vrai pour le corps genouillé gauche (Figure 1). Chaque œil envoie une moitié de l'information qu'il reçoit dans un hémisphère du cerveau, et la deuxième moitié dans l'autre. Celle venant des rétines temporales reste ipsilatérale à l'œil alors que l'information des rétines nasales de chaque œil doit traverser la ligne médiane du cerveau. Cette décussation a lieu au chiasma optique. Par ce processus, si une personne garde son regard au centre du champ visuel, les aires visuelles corticales de l'hémisphère gauche ne percevront que l'information présentée dans le champ visuel droit et vice versa. Les lobes occipitaux gauches et droits travailleront ensuite de concert, avec la collaboration du corps calleux. Cette structure principale de matière blanche permet les

échanges entre les hémisphères pour traiter et interpréter les différents aspects de l'information visuelle tels que la forme, la couleur, le mouvement, la position dans l'espace, etc. Le cortex visuel peut être divisé en différentes régions ayant des fonctions spécifiques quant au type d'information à traiter et à son niveau de complexité, selon une organisation hiérarchique. L'aire visuelle primaire (V1) traite les aspects les plus élémentaires de l'information visuelle, l'information progresse ensuite vers les régions secondaires (V2) et associatives (V3, V4, V5) permettant une analyse plus globale intégrant ces éléments primaires.

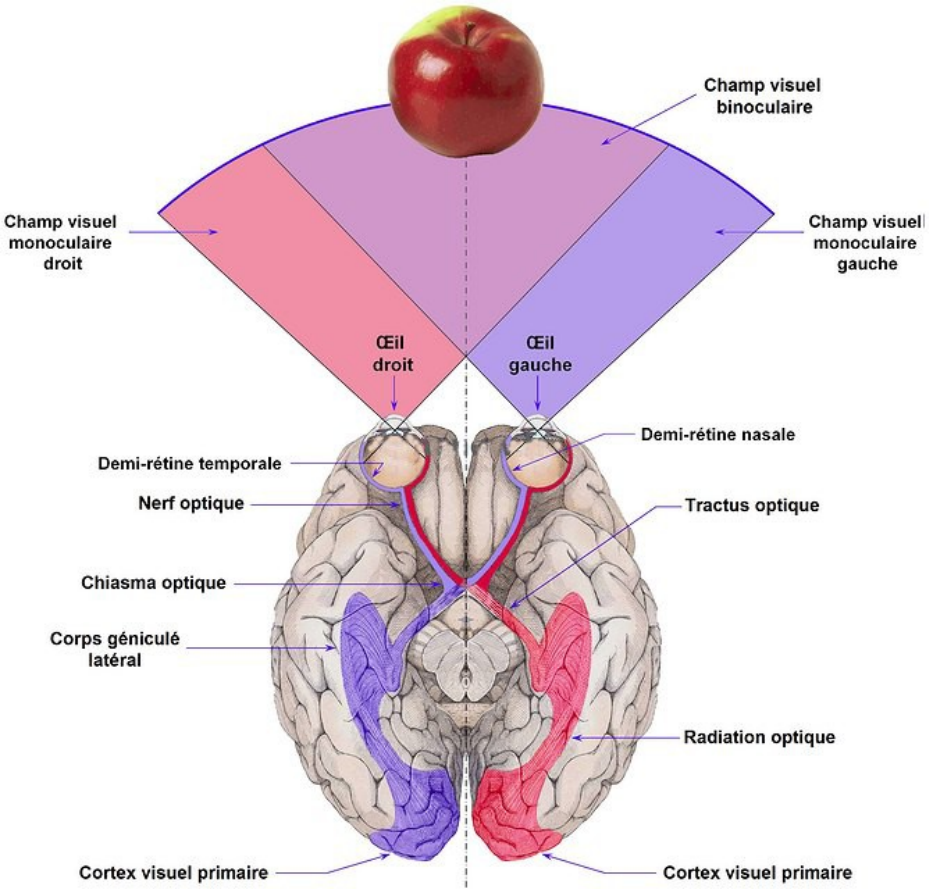


Figure 1. Schématisation du système visuel. Tirée de http://www.cinenow.fr/tutorials/2110-de-loeil-au-cerveau-des-chemins-qui-se-croisent.

1.1.2 La réponse motrice

Si, une tâche nécessite une réponse ou une exécution motrice, le cortex visuel devra transmettre l'information au cortex moteur situé dans le lobe frontal, qui à son tour enverra la

commande aux membres devant effectuer l'action. Le cortex moteur est aussi divisé en différentes aires : le cortex moteur primaire et, situées plus rostralement, l'aire prémotrice, qui intègre l'information sensorielle et guide les mouvements, et l'aire motrice supplémentaire, qui est impliquée dans la planification et la coordination bimanuelle des mouvements. Comme l'information visuelle, l'information motrice descendante suit aussi une organisation croisée et doit traverser la ligne médiane du corps au niveau du tronc cérébral avant de rejoindre la moelle épinière du côté du membre concerné. De cette façon, le cortex moteur gauche contrôle la main droite et le cortex moteur droit contrôle la main gauche. Dans une tâche visuomotrice, l'information doit donc suivre un chemin indirect entre la perception visuelle et la réponse motrice. Ce trajet est parsemé de relais et de croisements nécessitant une bonne coordination et une bonne communication entre les différentes du système nerveux qui sont impliquées.

1.2 Autisme

1.2.1 Définition

L'autisme est un trouble envahissant du développement caractérisé par des atteintes dans trois aires du développement : la communication, les interactions sociales, et la variété des comportements. De plus, pour recevoir un diagnostic d'autisme, une personne doit présenter un retard ou des anomalies perceptibles avant l'âge de trois ans, soit sur le plan des interactions sociales, du langage nécessaire à la communication sociale, ou du jeu symbolique ou de l'imagination. Concernant la communication, en plus de l'usage répétitif et stéréotypé du langage (écholalie, inversion pronominale) et de la difficulté à communiquer, l'autisme est caractérisé par un retard dans le développement de la parole et parfois même par une absence de développement du langage oral. Sur le plan social, on note des difficultés sur le plan des relations interpersonnelles et de la réciprocité, de l'usage et de l'interprétation des comportements non verbaux et du partage des intérêts et des émotions. Des comportements répétitifs et stéréotypés peuvent se manifester tant au niveau des intérêts, des habitudes et de la routine, qu'au niveau des mouvements et de l'usage des objets.

Selon la 4e version du Manuel diagnostique et statistique des troubles mentaux (Diagnostic and Statistical Manual of Mental Disorders, ou DSM-IV (APA, 1994)), l'autisme

fait partie des troubles envahissant du développement (TED) qui incluent aussi le trouble envahissant du développement non spécifié (TED-NS) et le syndrome d'Asperger. Ce dernier se distingue de l'autisme par le fait que pour son diagnostic on ne doit pas déceler de retard significatif sur le plan du langage, ni au niveau du développement cognitif, des capacités d'autonomie, du comportement adaptatif (sauf social) ou de la curiosité pour l'environnement.

Les déficits moteurs peuvent aussi différentier l'autisme du syndrome d'Asperger. Ils sont fréquemment observés dans les TED et l'outil principal de diagnostic, le Autism Diagnostic Interview (ADI: Lord, Rutter, & Le Couteur, 1994), basé sur les critères du DSM, inclut des items concernant la motricité, tels que la démarche, la posture et aussi la coordination. Au niveau empirique, plusieurs études documentent l'observation de déficits moteurs sur plusieurs plans : la vitesse d'exécution, la posture, la coordination, le contrôle, la planification et l'anticipation des mouvements (Dowd, McGinley, Taffe, & Rinehart, 2011; Dziuk, Gidley Larson, Apostu, Mahone, Denckla, & al., 2007; Forti, Valli, Perego, Nobile, Crippa, & Molteni, 2011; Glazebrook, Elliott, & Lyons, 2006; Mostofsky, Burgess, & Gidley Larson, 2007; Rinehart, Bradshaw, Brereton, & Tonge, 2001; Rinehart et al., 2006). De nombreuses études font état d'une différence marquée entre les deux sous-groupes en ce qui a trait à la motricité, tant sur le plan des aspects de la motricité qui sont affectés que de la sévérité des atteintes (Behere, Shahani, Noggle, & Dean, 2012; Gillberg, 1998; Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995; Rinehart et al., 2001; Szatmari, Tuff, Finlayson, & Bartolucci, 1990). Dans le DSM-IV, l'autisme et le syndrome d'Asperger étaient d'ailleurs distingués en terme de maladresse ou retards de motricité et d'anomalies de posture (APA, 1994). Toutefois, la distinction autisme-Asperger au niveau du diagnostic est maintenant désuète depuis l'application du nouveau DSM-5 (APA, 2013). Celui-ci a une approche plus dimensionnelle que catégorielle faisant disparaître les termes de syndrome d'Asperger et de TED-NS. On retrouve maintenant un diagnostic unique de trouble du spectre autistique (TSA) pouvant présenter différents niveaux de sévérité. Des spécificateurs permettent ensuite de mieux caractériser le diagnostic en ce qui a trait au niveau d'intelligence, au langage et aux conditions associées. Le nouveau DSM-5 considère entre autres le trouble développemental moteur et de coordination comme condition associée possible. Par contre, le DSM-5, contrairement au DSM-IV, ne précise pas si les déficits moteurs sont distribués uniformément

dans tout le spectre de l'autisme, ni s'ils peuvent être associés à l'un ou l'autre des spécificateurs, tel que le niveau d'intelligence ou de langage, plus qu'à un autre. L'importance des particularités motrices est aussi soulignée par le fait qu'avec les particularités perceptives (voir section 1.2.2) et certains signes sociaux comme à non-réponse à son nom et ne pas regarder dans les yeux, les comportements moteurs inhabituels sont d'important marqueurs précoces de l'autisme (Rogers, 2009). La pertinence de ces signes précoces est importante considérant que selon les dernières données du Center for Disease Control and Prevention (CDC, 2014), les TSA ne sont diagnostiqué qu'après l'âge de quatre ans en moyenne.

1.2.2 La perception en autisme

La présence de particularités sensorielles auditives, visuelles et tactiles fait partie des critères diagnostiques du DSM-5 pour les TSA (APA, 2013). Bien que les particularités auditives soient fréquemment observées (O'Connor, 2012), sous la forme par exemple d'une hypersensibilité auditive (Gomes, Rotta, Pedroso, Sleifer, & Danesi, 2004; Matsuzaki et al., 2012), d'aptitudes musicales (Bouvet, Simard-Meilleur, Paignon, Mottron, & Donnadieu, 2014; Mottron, Pertez, & Ménard, 2000) ou de supériorité à discriminer et identifier les sons purs (Bonnel et al., 2003; Bonnel et al., 2010; Heaton, Hudry, Ludlow, & Hill, 2008), les particularités visuelles sont particulièrement documentées et importantes. Une perception visuelle atypique a été mentionnée dès les toutes premières descriptions de l'autisme (Kanner, 1943) et est maintenant une caractéristique importante du phénotype autistique (Belmonte et al., 2004; Dakin & Frith 2005). Une perception atypique est observée entre autres sous la forme de supériorités pour traiter l'information visuelle, par exemple dans la performance à des tâches de figures cachées consistant à extraire une forme simple dissimulée dans une image plus complexe (Jarrold, Gilchrist, & Bender, 2005; Jolliffe & Baron-Cohen, 1997; Shah & Frith, 1983). Elle est aussi notée dans des tâches de recherche visuelle où une cible doit être repérée parmi des distracteurs (Kaldy, Kraper, Carter & Blaser, 2011; O'Riordan, 2004)), et dans le sous-test Blocs des échelles de Wechsler, qui nécessite la segmentation visuelle de blocs pour reproduire un modèle (Caron, Mottron, Berthiaume, & Dawson, 2006; Siegel, Minshew, & Goldstein, 1996; Shah & Frith, 1993). L'importance des particularités perceptives en autisme est aussi mise en évidence par des études soulignant leur pertinence comme marqueur précoce de l'autisme. On observe en effet des comportements visuels atypiques très

tôt dans le développement (Ozonoff et al., 2008). Ils incluent entre autres une durée de fixation plus élevée des objets et la tendance à fixer des objets particuliers ou des parties d'objets (Zwaigenbaum et al., 2005) et un intérêt pour objets brillants (Leekam, Nieto, Libby, Wing, & Gould, 2007). On observe aussi des regards latéraux vers les objets ou les visages à une fréquence plus élevée chez les enfants autistes que non-autistes (Mottron et al., 2007; Kaldy et al., 2011). Quantifier les forces perceptives en autisme pourrait aussi avoir d'importantes implications prédictives du potentiel intellectuel de jeunes autistes non-verbaux, considérés comme ayant un très bas potentiel cognitif. On pourra ainsi cibler mieux et plus précocement les approches éducatives adaptées pouvant leur être bénéfiques (Courchesne, Meilleur, Poulin-Lord, Dawson & Soulières, soumis).

Selon la revue de littérature de Dakin et Frith (2005), deux principaux modèles perceptifs de l'autisme ont été élaborés pour expliquer ces particularités perceptives. Bien que la perception atypique soit impliquée dans un grand nombre de traits autistiques, comme les symptômes sociocommunicatifs (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006), ces modèles n'expliquent pas tous les aspects du phénotype. D'autres modèles plus récents ont été élaborés pour tenter tenir compte de toute l'hétérogénéité des symptômes et de leur lien avec les aspects neurobiologiques. On peut penser par exemple à l'Intense World Theory (Markram & Markram, 2010), au modèle Trigger-Threshold-Target (TTT; Mottron, Belleville, Rouleau, & Collignon, 2014) et au modèle du cerveau prédictif dysfonctionnel (Gomot & Wicker, 2012; Sinh, et al., 2014; Van de Cruys et al., 2014) qui seront présentés dans la section 5.3.8. En 1989, la première de ces théories cognitives de l'autisme a été développée. C'est le modèle de faible cohérence centrale ou Weak Central Coherence (WCC), décrit la tendance des autistes à traiter les aspects plus locaux de l'information visuelle au détriment de l'analyse globale (Frith, 1989). Les individus au développement typique quant à eux, auraient plus tendance à traiter l'information de façon globale par défaut pour en retirer une signification. On dit par exemple que l'on voit la forêt alors que les autistes voient des arbres. Cette emphase sur les aspects locaux serait d'ailleurs responsable de la supériorité des autistes dans les tâches de figures cachées. Une mise à jour du modèle WCC (Happe & Frith, 2006) qualifie toutefois cette tendance au traitement perceptif local de *biais* local, plutôt que comme conséquence d'un déficit de traitement global. En effet, les autistes seraient tout à fait capables

de traiter l'information de façon globale lorsque la tâche le requiert explicitement (Caron, Mottron, Berthiaume, & Dawson, 2006; Lahaie et al., 2006). Le traitement perceptif particulier des autistes a aussi été décrit par le modèle du surfonctionnement perceptif ou Enhanced Perceptual Functionning (EPF; Mottron et al., 2006). Ce modèle souligne par ailleurs le rôle supérieur de la perception dans la cognition autistique, tant au niveau social que non-social, perception qui serait orientée localement avec une discrimination de bas-niveau accrue avec laquelle les traitements de plus haut-niveau interfèrent moins que chez les individus à développement typique. Les processus perceptifs seraient donc plus autonomes chez les autistes. De plus, le modèle EPF met l'emphase sur un surfonctionnement des régions cérébrales perceptives en autisme. Cette activité cérébrale accrue dans les aires visuelles chez les autistes a été observée dans de nombreuses études de neuroimagerie (voir Samson, Mottron, Soulieres, & Zeffiro, 2012 pour une méta-analyse). L'hyperactivation occipitale a effectivement été observée lors de tâches cognitives variées, tant de natures perceptives, comme dans une tâche visuospatiale (Kana et al., 2013), que non-perceptive, par exemple, dans une tâche de traitement du langage (Shen et al., 2012) ou de raisonnement (Soulieres et al., 2009).

Le rôle de la perception et des habiletés visuospatiales dans l'intelligence et le raisonnement autistique n'est pas négligeable. Une récente étude en imagerie par résonnance magnétique fonctionnelle, à laquelle nous avons participé (Soulieres et al., 2009, voir Annexe II), a investigué les activations cérébrales associées à la résolution du test des Matrices progressives de Raven (Raven's Progressive Matrices, RPM), un test couramment utilisé pour estimer les habiletés de raisonnement. Pour accomplir le test, les autistes, contrairement aux non-autistes, avaient davantage recours à certaines régions postérieures visuelles du cerveau et moins à certaines régions frontales plus analytiques. Les régions associées aux processus visuels de haut niveau pourraient donc jouer un rôle plus important dans le raisonnement chez les personnes autistes. Une plus importante activation visuelle associée à moins d'activation frontale a été observée dans des tâches de figures cachées (Ring et al., 1999) et de recherche visuelle (Manjaly et al,. 2007), mais aussi dans des tâches cognitives plus complexes comme de compréhension de phrases (Kana, Keller, Cherkassky, Minshew, & Just, 2006) et de mémoire de travail (Koshino et al., 2005). Ces différences dans le patron d'activations

cérébrales chez les autistes étaient associées à des performances aux tâches égales ou supérieures à celles des individus typiques. Les résultat de l'étude des matrices de Raven en IRMf pourraient donc potentiellement se généraliser aux capacités cognitives au sens large. Ils remettent en question l'idée reçue selon laquelle les capacités de raisonnement complexe seraient déficitaires chez les autistes, tout en suggérant des mécanismes de raisonnement différents chez ces derniers. L'autisme a été décrit dans le passé comme un trouble du traitement de l'information complexe (Minshew & Goldstein, 1998) or, les forces, notamment en perception, ne seraient pas nécessairement attribuées à des déficits cognitifs de plus haut niveau comme il a déjà été suggéré (Happé & Frith 2006). Les surfontionnements perceptifs seraient possiblement associés, soit à une façon « par défaut » de traiter l'information de façon efficace ou au fait que les régions visuelles dépendent moins d'un traitement de plus haut niveau (Soulières et al., 2009), et ce, en lien avec l'implication moindre du lobe frontal et la connectivité plus faible entre celui-ci et le reste du cerveau.

1.2.3 Intelligence

L'idée que l'intelligence soit atypique en autisme date de ses toutes premières descriptions (Asperger, 1944/1991; Kanner, 1943) et des études empiriques ont rapporté des performances inégales tant entre les épreuves d'un même test (Rutter, 1966) qu'entre les différents tests d'intelligence (Bartak, Rutter, & Cox, 1975). Il est maintenant bien établi que les mesures d'intelligence en autisme varient selon l'instrument utilisé (Magiati & Howlin, 2001; Mottron, 2004). L'intelligence générale est souvent estimée en utilisant le test des échelles de Wechsler qui combine le score à différents sous-tests pour estimer le quotient intellectuel verbal (QIV), le QI non verbal (ou de performance, QIP) et finalement le QI global (QIG). Dans la population typique, les normes du test font en sorte que des performances similaires seront obtenues pour les trois mesures. Toutefois, le QIV étant fondé sur la compréhension et la production verbale, les difficultés des autistes au niveau du langage tirent leurs performances au QIV vers le bas et biaisent leur QIG. Par ailleurs, leurs bonnes habiletés perceptives et visuospatiales leur donnent des pics relatifs de performances (aptitudes supérieures au niveau de fonctionnement général de l'individu) pour des sous-tests non verbaux comme celui des Blocs, contrastant avec une faiblesse au sous-test Compréhension (Ehlers et al., 1997; Lockyer & Rutter, 1970; Stevenson & Gernsbacher, 2013). Cela résulte en

un profil inégal au Wechsler, profil qui varie selon les sous-groupes du spectre autistique (Figure 2). En effet, en plus des spécificateurs du DSM-5 et des déficits moteurs, ces pics d'habiletés sont considérés comme un autre aspect important de la cognition discriminant les autistes ayant un retard de langage des Asperger sans retard de langage. Alors que les autistes présentent de bonnes habiletés perceptives et visuospatiales, les Asperger montrent des forces au point de vue verbal, par exemple pour les sous-tests Vocabulaire, Similitudes et Compréhension des échelles verbales d'intelligence de Wechsler, (Soulieres, Dawson, Gernsbacher, & Mottron, 2011).

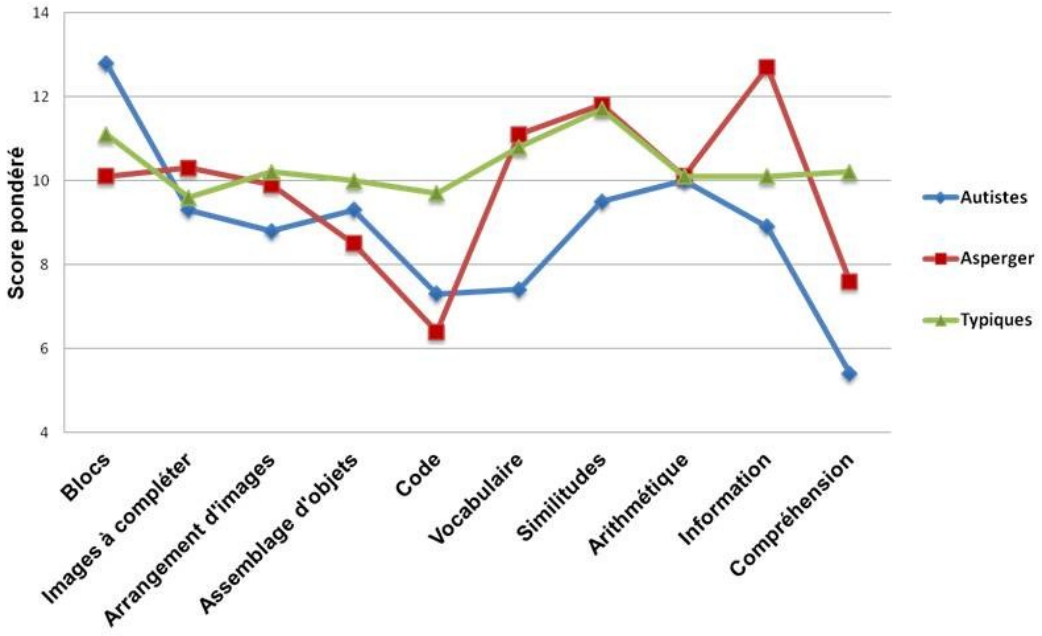


Figure 2. Profil cognitif des individus autistes, Asperger et typiques. Scores pondérés aux différents sous-tests des échelles de Wechsler (WISC-III). Traduit de Nader, Jelenic & Soulières (soumis), avec permission.

Les individus Asperger, n'ayant pas de pics perceptifs, présentent donc plutôt un bon QIV du fait de leurs pics langagiers. On questionne donc la validité des tests de Wechsler pour estimer l'intelligence des autistes. Il existe un test alternatif pour estimer l'intelligence générale et auquel les autistes excellent: le test des Matrices Progressives de Raven. Ce test, qui évalue les habiletés de raisonnement, ne nécessite aucune réponse ou instruction verbale. Il présente

des problèmes uniques sous la forme d'une matrice de motifs visuels qui doivent être résolus en identifiant parmi un choix de réponses la partie manquante. Le test présente une progression allant d'un niveau relativement facile et purement perceptif à des niveaux analytiques difficiles nécessitant l'inférence de règles et un haut niveau d'abstraction. Chez les individus à développement typique, les tests de Wechsler et RPM donnent des mesures d'intelligence comparables alors que chez les autistes, la performance au RPM est souvent significativement supérieure à celle du Wechsler et reflèterait les résultats des sous-tests du Wechsler les plus hauts, tels que ceux aux Blocs (Dawson, Soulieres, Gernsbacher, & Mottron, 2007). Chez les Asperger par contre, les sous-tests des échelles verbales seraient plus représentatifs de leur performance au RPM (Soulieres, Dawson, Gernsbacher, & Mottron, 2011).

1.2.4 Pourquoi différencier les autistes des Asperger?

En plus de l'hétérogénéité qui existe entre les sous-groupes du TSA sur le plan du profil cognitif et des forces et faiblesses langagières, perceptives et motrices, un argument en faveur d'une meilleure distinction des sous-groupes provient des études de neuroimagerie. Malgré le très petit nombre d'études ayant investigué spécifiquement les sous-groupes autres que l'autisme, il a été démonté que les sous-groupes du TSA peuvent effectivement être discriminés, non seulement au niveau comportemental ou cognitif, mais aussi au niveau neuroanatomique. Par exemple, des différences entre les Asperger et les autistes ont été observées au niveau des volumes moyens de matière grise, plaçant cette variable chez les typiques, les Asperger et les autistes sur un continuum. Les différents sous-groupes différeraient aussi au niveau des corrélations cerveau-comportement (Lotspeich et al., 2004). Les différences régionales de volume entre les autistes et les individus à développement typiques versus entre les individus Asperger et les typiques se trouveraient dans des régions cérébrales différentes. Les individus Asperger auraient des volumes plus petits de matière blanche autour des régions sous-corticales alors que les autistes auraient des diminutions de volume au niveau frontal (McAlonan et al., 2009). Une méta-analyse (Yu, Cheung, Chua, & McAlonan, 2011) a aussi démontré qu'en ce qui concerne les volumes de matière grise, les différences, comparativement au groupe contrôle, seraient plus importantes chez les autistes que chez les Asperger. De plus, les deux groupes seraient caractérisés par des patrons distincts

de diminutions et d'augmentations de matière grise. Cette étude rapporte aussi que les deux sous-groupes se distingueraient dans la localisation de ces différences et de leur latéralisation. McAlonan et ses collègues (2009) ont d'ailleurs rapporté que la matière blanche était principalement affectée dans l'hémisphère droit chez les Asperger alors que les atypicalités de matière blanche ont été principalement observées dans l'hémisphère gauche chez les autistes. Or, beaucoup d'études utilisent des critères d'inclusion comprenant, l'autisme, le syndrome d'Asperger et le TED-NS. De telles études avec des groupes mixtes incluant des phénotypes moins sévères pourraient diminuer les tailles d'effet des résultats (Lotspeich et al., 2004). Cela biaiserait les résultats en faveur de différences non significatives entre les groupes du spectre autistique et les groupes témoins, d'où l'importance d'une meilleure caractérisation des sous-groupes.

D'un point de vue plus clinique, certains sont d'avis qu'un diagnostique de TSA non catégoriel, surtout en jeune âge, serait suffisant quand le but premier est l'intervention précoce et que tous les enfants sur le spectre bénéficient grandement de ces interventions (Szatmari et al., 2000; Matson, 2007). Toutefois on peut aussi penser que s'il existe différents sous-groupes, distincts au niveau cognitif et cérébral, le fait de décortiquer leurs forces et faiblesses respectives serait bénéfique au niveau d'interventions et de stratégies d'apprentissages mieux ciblées. Par exemple, un individu avec des forces verbales ne bénéficiera pas également d'une même intervention qu'un individu dont on connait les faiblesses à ce niveau, mais qui a d'importantes forces perceptives.

De plus, il existe aussi des différences au niveau psychologique et émotionnel. En effet, les individus avec syndrome d'Asperger seraient significativement plus anxieux que les autistes (Thede & Coolidge, 2007) et montreraient plus de comportements perturbateurs et plus de difficultés au niveau des interactions sociales (Tonge, Brereton, Gray, & Einfeld, 1999). Tonge et collègues (1999) suggèrent que ces différences significatives au niveau psychopathologique appuient une différentiation diagnostique et mettent l'emphase sur l'importance de différents traitements ou thérapies adaptés à chacune des deux conditions. Selon Damiano et ses collègues (2014), une des causes du lent développement des traitements psychosociaux et pharmacologiques pour les TSA est justement l'hétérogénéité phénotypique rendant peu probable qu'un même traitement fera pour tous. La caractérisation des conditions

et caractéristiques qui co-existent est donc critique tant pour la recherche que pour le développement de meilleurs traitements et interventions plus personnalisés (Ousley & Cermak, 2014).

Pour l'instant les traitements existants visent principalement à contrôler les symptômes ou les comportements problématiques associés aux TSA afin d'améliorer le fonctionnement des individus. Ces symptômes incluent l'anxiété, les troubles d'attention ou d'hyperactivité, l'agressivité, les comportements obsessifs compulsifs et les troubles de sommeil. Il existe aussi différentes méthodes comportementales d'intervention précoces visant à favoriser l'apprentissage et à modifier les comportements, dont la plus populaire est l'ABA ou Applied Bahavioural Analysis. Toutefois, beaucoup de recherche est encore nécessaire quant à leur efficacité (Schreibman, 2000) et leur pertinence.

1.2.5 Neurobiologie de l'autisme

1.2.5.1 Origines génétiques

L'autisme est un trouble neuro-développemental d'origine génétique (Abrahams, & Geschwind, 2008; Betancur, 2011; Ronemus, Iossifov, Levy, & Wigler, 2014). Par contre, la concordance monozygotique non complète suggère l'implication de facteurs environnementaux. Ces facteurs incluent entre autres l'exposition à des stress ou toxines environnementales, l'exposition à des stress, infections ou toxines prénatales et l'âge maternel et paternel avancés (Herbert, 2010; Kolevzon, Gross, & Reichenberg, 2007; Gardener, Spiegelman & Buka, 2009 pour revues de littératures et méta-analyse des facteurs de risque prénataux et périnataux). De plus, les facteurs environnementaux interagiraient avec la génétique par des mécanismes d'épigénétique (Pepsico & Bourgeron, 2010).

La grande variabilité au niveau des profils cognitifs et symptomatiques, du comportement, de la sévérité et des trajectoires développementales de l'autisme est en partie explicable par cette origine génétique. L'une des sources de cette hétérogénéité phénotypique vient en effet de la grande variabilité des polymorphismes et des régions chromosomales associées à l'autisme. En plus de cette grande variabilité au niveau des mutations de novo ou hérités, il existe de multiples combinaisons de mutations ayant été ciblées comme prédisposant à l'autisme. Malgré tout, une récente revue de littérature (Huguet, Ey, & Bourgeron, 2013)

conclut que les mutations génétiques identifiées ont des implications au niveau de plusieurs fonctions cellulaires qui convergeraient toutes vers des déficits au niveau de l'homéostasie neuronale et synaptique. Plusieurs des gènes impliqués dans l'autisme sont reliés à des mécanismes de plasticité synaptique en lien avec l'activité des neurones (Ebert & Greenberg, 2013). Une plus grande plasticité pourrait, en plus d'être liée aux altérations microstructurales dans le cerveau autistique (Markram & Markram, 2010), expliquer en partie les mécanismes de réallocation corticale observés en autisme. Entre autres, la plus grande implication des fonctions visuelles chez les autistes pourrait être issue de modifications développementales du cerveau, qui seraient d'origine génétique.

1.2.5.2 Différences corticales anatomiques et fonctionnelles

Comme peu d'études distinguent les sous-groupes, il sera question ici de trouble du spectre autistique au sens large. Bien qu'il existe une grande hétérogénéité dans les résultats d'études neuroanatomiques quant à de potentielles atteintes locales en autisme, plusieurs récentes revues de littérature soulignent toutefois certaines différences volumétriques de la matière grise. Au niveau de la matière grise corticale, comparativement aux individus à développement typique, de plus grands volumes ont été principalement observés dans le lobe frontal, pariétal et temporal (Amaral, Schumann & Nordahl, 2008: Anagnostou & Taylor, 2011; Brambilla et al., 2003; Courchesne, Redcay, & Kennedy, 2004). Des volumes élevés ont aussi été rapportés fréquemment dans le cervelet et le noyau caudé (Amaral et al., 2008; Anagnostou & Taylor, 2011; Penn, 2006; Standfield et al., 2008). Des volumes anormaux de l'amygdale sont aussi observés et ont été associés aux symptômes émotionnels, Baron-Cohen et collègues (2000) ont même suggéré une « Amygdala theory of autism » pour expliquer les difficultés émotionnelles des personnes autistes. Les anomalies du cervelet ont aussi été identifiées comme élément clé pouvant expliquer plusieurs symptômes de l'autisme donc certains symptômes attentionnels, langagiers, mais surtout moteurs (Penn, 2006). Les anomalies du noyau caudé ont aussi été associées à des symptômes moteurs, plus particulièrement aux comportements répétitifs (Penn, 2006, Standfield et al., 2008). Vu leur implication dans la planification et le contrôle des mouvements volontaires, les fonctions exécutives et les comportements répétitifs les différences du striatum combinées aux différences très consensuelles dans le lobe frontal ont aussi mené à qualifier l'autisme de

trouble fronto-striatal (Bradshaw & Sheppard, 2000). Nick-Jockshat et al. (2012) se sont penchés spécifiquement sur les résultats de Voxel Based Morphometry (VBM) et leur méta-analyse a localisé des différences principalement dans les régions occipitales et pariétales, mais aussi frontales et temporales. Ecker et ses collèges (2012) ont quant à eux conclut de leur méta-analyse des études VBM de populations d'autistes adultes à des augmentations de volume dans les régions temporales, frontales et péricentrales, mais à des diminutions dans les régions occipitales et pariétales. Ces deux dernières études soulignent le rôle important de l'âge dans l'hétérogénéité des résultats. De plus, selon Haar et al. (2014) dans leur revue de littérature, les différences anatomiques entre les groupes TSA et les groupes témoins sont petites relativement à la grande variabilité interindividuelle et la valeur scientifique et clinique des mesures anatomiques cérébrales pour comprendre la neuropathologie du TSA est faible. Les auteurs soulignent l'importance de la recherche de sous-groupes TSA plus homogènes.

De façon générale, bien que l'hétérogénéité phénotypique et le facteur de l'âge jouent un rôle important dans la variabilité des résultats, il est probable que le phénotype autistique ne puisse être entièrement expliqué par des atteintes cérébrales locales, mais devrait plutôt être considéré comme un trouble distribué impliquant le cerveau de façon globale (Anagnostou & Taylor, 2011), ou comme *distributed disorder* (Muller, 2007). Cela s'applique aussi aux études de neuroimagerie fonctionnelle. Les études observant des différences fonctionnelles sont nombreuses, et celles-ci sont présentes pour une large variété de tâches et distribuées dans pratiquement tout le cerveau. En plus des suractivations visuelles déjà mentionnées, la plupart des régions où l'on trouve des différences anatomiques révèlent aussi des atypies fonctionnelles. Dans leur revue de littérature des études en neuroimagerie fonctionnelle, Minshew et Keller (2010) concluent aussi à un *distributed neural system disorder* ce qui a mené à la phase plus récente et de valeur explicative plus prometteuse vers les études en connectivité fonctionnelle supportant des dysfonctions au niveau des réseaux plutôt qu'au niveau local. Muller (2007) suggère aussi qu'il est plus prometteur de se pencher sur des approches plus globales investiguant la connectivité entre ces différentes régions. De plus, les facteurs de risque génétiques suggèrent des atteintes développementales de multiples réseaux cérébraux (Muller 2007). En effet, les modifications génétiques au niveau de la synapse et de

la plasticité synaptique mentionnées précédemment pointent vers des implications à plus grande échelle sur la connectivité cérébrale.

1.2.5.3 Théories de connectivité

Bien que beaucoup d'études de connectivité s'attardent sur l'intégrité de communication entre deux régions spécifiques, par exemple, les régions activées lors d'une tâche, il existe aussi une abondance de littérature concernant la connectivité fonctionnelle au repos. En autisme, une connectivité cérébrale altérée en absence de tâche cognitive (la plupart du temps les yeux fermés, voir Maximo, Cadena, & Kana, 2014 pour une revue de littérature sur la connectivité cérébrale en autisme) suggère une réorganisation intrinsèque des circuits neuronaux.

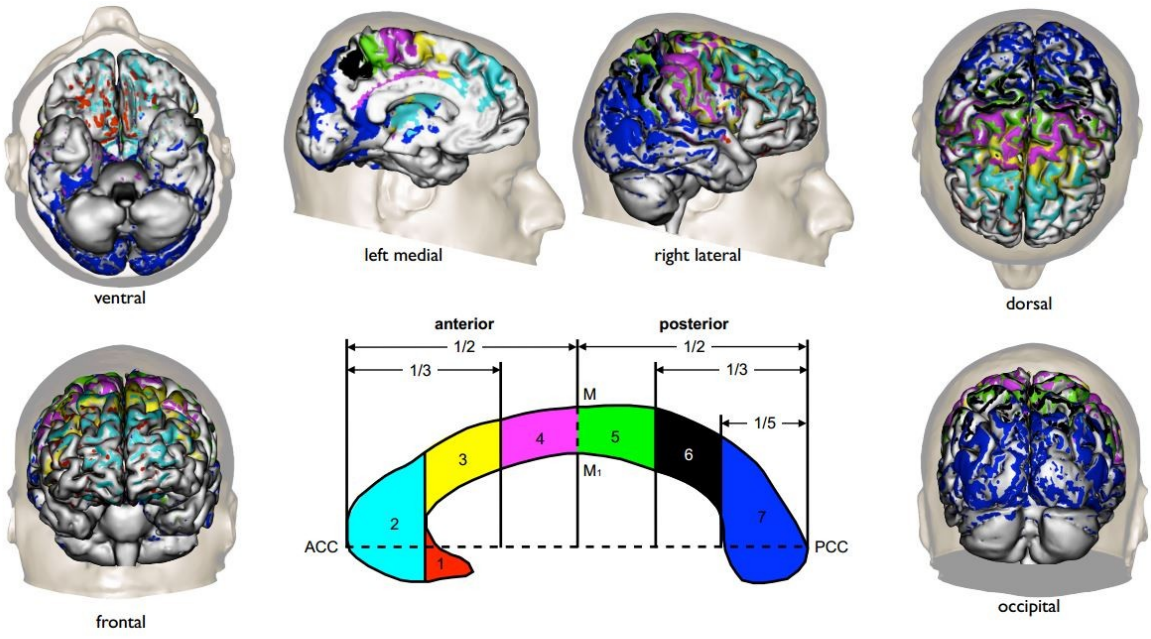
Récemment, les résultats d'études cognitives et d'imagerie cérébrale décrivent l'autisme comme un trouble de la connectivité. Ces théories de connectivité de l'autisme font état d'une connectivité atypique entre les différentes régions du cerveau, associée à une plus grande indépendance ou autonomie de certaines régions cérébrales (Just, Keller, Malave, Kana, & Varma, 2012) et, entre autres, au fonctionnement perceptif accru (Kana et al., 2013). Plus précisément, les théories de sous-connectivité basées sur la distance décrivent une sous-connectivité fronto-postérieure (longue distance), associée à une surconnectivité locale (de courte distance) (Just, Cherkassky, Keller, Kana, & Minshew, 2007; Just, Cherkassky, Keller, & Minshew, 2004). Bien que les approches méthodologiques très variables causent une grande variabilité dans les résultats de connectivité fonctionnelle (Muller et al., 2011), les revues de littérature récentes sont cohérentes avec ces théories. La majorité des études de connectivité fonctionnelle, tant dans des contextes de tâches cognitives qu'au repos, observent la sous-connectivité de longue distance, particulièrement avec le lobe frontal (Schipul, Keller, & Just, 2011; Uddin, Supekar, & Menon, 2013; Vissers, Cohen, & Geurts, 2012).

Toutefois, plusieurs études rapportent aussi une hyperconnectivité en autisme, entre autres lorsque les régions visuelles sont impliquées, et ce, peu importe la distance des connexions. Notre groupe a été le premier à montrer cette plus grande connectivité avec les régions occipitales dans une étude de cohérence électroencéphalographique (EEG) en sommeil (Léveillé et al., 2010, voir Annexe III). Ce résultat a été plusieurs fois répliqué depuis dans des

études de connectivité fonctionnelle en imagerie par résonnance magnétique (IRM) (Di Martino et al., 2011; Keown et al., 2013; Shen et al., 2012; Supekar et al., 2013) et en magnétoencephalographie (MEG: Dominguez, Velazquez, & Galan, 2013). Cela suggère des théories de connectivité basées sur la fonction plutôt que sur la distance, et supporte la grande variabilité dans les conclusions rapportées dans les études de connectivité fonctionnelles, selon la présence ou non (repos) de tâche, la tâche utilisée et les régions d'intérêts investiguées (Vissers et al., 2012).

1.2.5.4 Connectivité et matière blanche : le corps calleux

On ne peut parler de communication cérébrale sans parler de la matière blanche. Les fibres la composant sont formées d'axones permettant le transfert de l'information d'un neurone à l'autre, et donc d'une région corticale (ou sous-corticale) à l'autre. Selon la longueur et le diamètre de ces axones et leur niveau de myélinisation, la gaine permettant une meilleure conduction, l'information sera transmise plus ou moins rapidement dans le cerveau. Les axones sont regroupés en faisceaux de matière blanche divisés en trois types différents selon les régions cérébrales qu'ils connectent. Les fibres dites associatives connectent des régions corticales d'un même hémisphère dans une orientation antéropostérieure; les fibres de projection connectent le cortex aux structures sous-corticales; et finalement, les fibres commissurales connectent les deux hémisphères du cerveau. Le principal faisceau de fibres commissurales, et le plus gros du cerveau, est le corps calleux. De façon générale, la portion antérieure (genu), connecte les régions préfrontales et orbitofrontales, transférant entre autres l'information motrice. La section centrale (body), connecte les régions frontales précentrales et pariétales, et la portion postérieure (splénium), connecte les régions occipitales (Catani & Thiebaut de Schotten, 2012) en transférant l'information visuelle d'un hémisphère à l'autre. Il existe de multiples façons de parceller le corps calleux, par exemple, la méthode Witelson (1989) le divise en sept régions. La Figure 3, décrit de façon plus détaillée les sous-régions du corps calleux et leurs fonctions.



Region	Anatomical label	Cortical region	
		Monkey (axonal tracing)	***Human (tractography)***
1	Rostrum	Caudal/orbital prefrontal, inferior premotor	Orbital and polar frontal
2	Genu	Prefrontal	Prefrontal, premotor, polar, and orbital frontal
3	Rostral body	Premotor, supplementary motor	Motor and premotor
4	Anterior midbody	Motor	Motor, somatosensory, premotor
5	Posterior midbody	Somatosensory, posterior parietal	Somatosensory, parietal, motor
6	Isthmus	Superior temporal, posterior parietal	Parietal and someasthesic
7	Splenium	Occipital, inferior temporal	Occipital, posterior temporal and parietal

Figure 3. Topographie du corps calleux selon la division de Witelson et les projections corticales correspondantes. Tirée de « Atlas of the Human Brain Connections» par Catani & Thiebaut de Schotten, 2012, p. 348. Avec permission.

Les études neuro-anatomiques en autisme appuient aussi la notion d'une connectivité atypique. Des atypicalités de la matière blanche ont été observées dans différentes régions du cerveau, selon l'âge des groupes étudiés. Même si des réductions dans le volume de matière blanche ont été observées (Lainhart, 2006), les résultats les plus consensuels sont des grossissements régionaux de matière blanche, observés dans les régions temporales et pariétales, mais principalement dans le lobe frontal (Amaral et al., 2008). Toutefois, le résultat le plus consensuel dans l'étude des volumes de la matière blanche en autisme est la réduction du corps calleux (voir Frazier & Hardan, 2009 pour une méta-analyse).

En 1985, Witelson suggérait qu'un plus petit corps calleux serait associé à moins de connectivité anatomique entre les hémisphères, en lien avec un plus petit nombre d'axones, ou résultant d'axones de plus petit diamètre ou étant moins myélinisés. Les techniques d'imagerie de diffusion telles que l'imagerie du tenseur de diffusion ou Diffusion Tensor Imaging (DTI) documentent les différentes propriétés microstructurales de la matière blanche assurant la communication neuronale et permettent d'examiner son intégrité. Les techniques d'imagerie de diffusion mesurent le déplacement des molécules d'eau le long des fibres de matière blanche. Par exemple, des fibres organisées selon une direction cohérente favoriseront le mouvement des molécules d'eau suivant l'orientation des fibres, alors que des fibres entrecroisées favoriseront une diffusion plus aléatoire, de même que des fibres moins densément organisées favoriseront une diffusion de l'eau perpendiculaire aux fibres, entre celles-ci. L'une des mesures obtenues en imagerie de diffusion est l'anisotropie fractionnelle (Fractional Anisotropy (FA)). Une diffusion plus anisotropique, donc une valeur de FA plus élevée, indique soit une plus grande cohérence dans la direction des fibres (Keller, Kana, & Just, 2007), soit, une plus grande densité d'axones, ou plus de myélinisation et/ou une myéline moins perméable (Madden et al., 2004). Les diminutions de la diffusivité moyenne ou « Mean Diffusivity » (MD), souvent associées aux augmentations de FA, reflèteraient aussi moins de cohérence dans les fibres de matière blanche ou moins de myélinisation (Basser, 1995). La diffusivité peut aussi être mesurée dans des directions plus spécifiques, soit en termes de diffusivité radiale (RD; perpendiculaire aux fibres), ou axiale (AD; parallèle aux fibres). La RD serait plus modulée par la myéline alors que l'AD le serait par l'intégrité des axones (Alexander et al., 2007). De plus, des augmentations de RD impliquent une diminution de densité des fibres, de la myéline ou un plus grand diamètre des axones (Lewis et al., 2013; Song et al., 2002). En plus des propriétés macro-anatomiques de la matière blanche, comme le volume, mesuré à l'aide de l'IRM anatomique, les techniques d'IRM de diffusion permettent donc d'investiguer sa microstructure plus en détail. Toutefois, la DTI reste un outil indirect. Cette technique permet de relever des différences de microstructure de la matière blanche, mais ces dernières restent pour l'instant difficilement interprétables quant à la nature exacte ou la cause de ces différences de mesures.

Les études de DTI en autisme corroborent les études anatomiques et montrent des altérations dans la microstructure du corps calleux. Une récente revue de littérature (Vissers et al., 2012) rapporte que la majorité des études observent une connectivité structurelle plus faible en autisme, spécialement dans le lobe frontal et temporal et dans le corps calleux (principalement des réductions de FA). De plus, le corps calleux des autistes serait composé de moins de fibres (Thomas, Humphreys, Jung, Minshew, & Behrmann, 2011). Travers et ses collègues (2012), dans une autre revue des études de DTI, concluent que les enfants (> 4 ans) et les jeunes adultes autistes auraient des diminutions de FA souvent accompagnées par des augmentations de MD et RD dans différents faisceaux de matière blanche, principalement dans le corps calleux, le cingulum et les faisceaux connectant le lobe temporal. Une méta-analyse (Aoki, Abe, Nippashi, & Yamasue, 2013) des études de tractographie (DTI) conclut aussi à des réductions de FA et des augmentations de MD dans le corps calleux et le fascicule longitudinal supérieur, connectant le lobe frontal aux régions postérieures du cerveau (occipitales, temporales et pariétales), et des diminutions de FA dans le fascicule unciné connectant le lobe frontal et temporal.

Outre l'hétérogénéité des critères diagnostiques, une autre source très importante de variabilité dans les résultats d'études en neuroimagerie est l'âge. Pour une même région, les résultats de différence entre un groupe autiste et un groupe typique pourraient aller dans des directions opposées selon l'âge des participants (Nick-Jockschat et al. 2012). Les augmentations du volume de la matière blanche chez les autistes, comparativement aux typiques, sont principalement présentes chez les enfants. La trajectoire développementale du cerveau des autistes est en effet caractérisée par une surcroissance précoce (principalement frontale, les régions occipitales étant les moins affectées), surtout durant la première année de la vie et jusqu'à 2-3 ans. Ces grossissements, tant de matière blanche que de matière grise, ont pour conséquence que vers 3 ans le cerveau des autistes serait dix pour cent plus gros. Cette croissance accélérée serait suivie par un ralentissement de croissance (Courchesne, Redcay, Morgan, & Kennedy, 2005) et une fois à l'adolescence le cerveau des autistes ne serait qu'un à deux pour cent plus gros (Redcay & Courchesne, 2005). Ces atypies de croissance cérébrale à un très jeune âge durant une période développementale de différenciation neuronale et de formation de circuits (Courchesne et al., 2005) auraient des conséquences sur la connectivité,

les circuits et leurs fonctions, entrainant avec eux des effets au niveau comportemental. Les investigations en DTI corroborent aussi les études anatomiques au niveau développemental et suggèrent que les diminutions de FA en autisme seraient précédées par une augmentation rapide de la FA à un très jeune âge (Travers et al., 2012 pour une revue de littérature). En effet, les études portant sur des jeunes enfants (≤ 5 ans) montrent plutôt des augmentations de FA dans le corps calleux (Ben Bashat et al., 2007; Weinstein et al., 2011; Wolff et al., 2012).

La macrocéphalie est un important facteur à considérer, car elle n'est pas sans lien avec les diminutions du corps calleux en autisme. Premièrement, le cerveau plus volumineux des autistes serait aussi associé à un plus grand nombre de neurones (Casanova et al., 2006). Au niveau de l'organisation cellulaire, en plus des neurones plus nombreux, il y aurait un plus grand nombre de petits circuits neuronaux locaux interconnectés, soit des groupes de neurones qui ont des fonctions similaires et répondent à une même stimulation, se regroupant en colonnes de neurones dans le cerveau. Ces circuits, appelés mini-colonnes, seraient aussi plus étroits (Casanova, Buxhoeveden, Switala, & Roy, 2002; Casanova et al., 2006; Courchesne, Redcay, & Kennedy, 2004). De façon intéressante, ces différences micro anatomiques se trouveraient aussi principalement dans les régions frontales (Casanova et al.,2006; Courchesne et al. 2004). Le fait d'avoir plus de neurones dans des mini-colonnes qui sont aussi plus nombreuses créerait une plus grande compétition entre les cellules pour les ressources d'énergie nécessaires à leur fonctionnement (Casanova et al., 2006). En effet, Piven et ses collègues (1997) suggéraient que des régions corticales plus grosses et comprenant un plus grand nombre de neurones, auraient pour effet que ces derniers seraient en compétition pour les facteurs trophiques qui ont pour fonction de maintenir le neurone en vie et de faciliter la croissance de ses prolongements. Cette compétition favoriserait les projections ipsilatérales de courte distance (demandant moins de ressources et d'énergie) au détriment des longues projections incluant celles pointant vers l'hémisphère controlatéral. Cela résulterait en un plus petit corps calleux (Piven et al., 1997) et un ratio de la connectivité intra vs interhémisphérique biaisé vers la connectivité intrahémisphérique (Vidal et al., 2006).

1.2.6 Conséquences comportementales des atypicalités de matière blanche en autisme

1.2.6.1 Motricité

Le lobe frontal est l'une région où l'on observe le plus d'atypies chez les autistes, tant au niveau fonctionnel qu'au niveau des augmentations de volume de matière grise (Courchesne, Redcay, & Kennedy, 2004), et de matière blanche (Amaral et al., 2008). Mostofsky et ses collègues (2007) suggèrent que les déficits des fonctions motrices observés chez les enfants autistes seraient fortement prédits par l'augmentation de volume de la matière blanche dans l'hémisphère gauche au niveau des régions motrices et prémotrices (frontales). Les auteurs expliquent ces déficits comme étant une conséquence de la trajectoire développementale atypique du cerveau autistique, plus particulièrement de l'augmentation rapide du volume de matière blanche suivi d'un arrêt (contrairement aux enfants typiques, chez qui le développement graduel de la matière blanche laisse le temps à la dextérité manuelle de se développer). Bien que la relation entre les déficits moteurs et les propriétés de la matière blanche n'ait pas été investiguée de façon extensive en autisme, on peut s'attendre à d'autres relations possibles. Par exemple, l'intégrité d'autres régions de matière blanche comme la capsule interne, la capsule externe et la matière blanche du cervelet serait corrélée à la performance motrice, plus précisément aux mouvements fins des doigts uni et bimanuels (Sullivan, Rohlfing, & Pfefferbaum, 2008). Les anomalies de matière blanche en autisme permettent aussi d'émettre l'hypothèse que les atteintes motrices seraient en lien avec un ralentissement de la vitesse de traitement de l'information par le cerveau, ce qui affecterait la motricité sur le plan de l'intégration sensorimotrice, de l'ajustement postural et de l'anticipation (Gepner & Feron, 2009).

1.2.6.2 Vitesse de traitement

En autisme, les altérations de la matière blanche ont effectivement été liées à des diminutions de vitesse de traitement de l'information par le cerveau (Travers et al., 2014). Selon Schmitz et al. (2007), la densité atypique de matière blanche du lobe frontal causerait des ralentissements de la vitesse de traitement. Dans cette étude les auteurs ont utilisé une tâche de type Go/NoGo consistant à appuyer sur un bouton rapidement en réponse à des

stimuli (lettres) cibles, seulement lorsqu'ils sont précédés d'un autre stimulus spécifique. Des temps de réponse plus lents chez les autistes étaient corrélés à la densité de matière blanche frontale. Les échelles d'intelligence de Wechsler comprennent certains sous-tests qui, combinés, forment un Indice de vitesse de traitement (IVT). Sur le plan comportemental, des études montrent que les autistes, comparativement aux individus typiques, ont des IVT plus lents qui sont associés aux symptômes de l'autisme (Oliveras-Rentas, Kenworthy, Roberson, Martin, & Wallace, 2012). De plus, Alexander et ses collègues (2007) ont montré une association entre l'IVT et l'intégrité du corps calleux (FA, RD). Cet IVT des échelles de Wechsler en tant que mesure de la vitesse de traitement est toutefois questionnable puisqu'il comprend une composante motrice importante. Les sous-tests composant l'IVT impliquent, entre autres, le dessin rapide de petites formes requérant une bonne motricité fine et une bonne dextérité. Une mauvaise coordination de l'écriture souvent notée chez les autistes ainsi qu'une tendance obsessive à reproduire les symboles de façon trop exacte pourrait biaiser l'indice. La question de la vitesse de traitement réelle ainsi que son implication dans l'intelligence autistique restent donc à être clarifiées.

1.2.7 Conséquences possibles des diminutions anatomiques du corps calleux

1.2.7.1 Que nous apprend l'agénésie du corps calleux?

Outre le transfert direct de l'information d'un hémisphère à l'autre pour les fonctions motrices bimanuelles, qui ont été corrélées avec l'intégrité de la matière blanche le composant (Johansen-Berg, Della-Maggiore, Behrens, Smith, & Paus, 2007), le corps calleux est impliqué dans diverses fonctions cognitives plus complexes comme le langage (Gazzaniga, 2000). La littérature sur l'agénésie du corps calleux, ou absence développementale de cette structure, permet d'en savoir plus sur la nature de ses fonctions. Bien que l'absence totale du corps calleux chez ces personnes ait un impact étonnamment limité sur leurs habiletés cognitives générales, certains déficits sont observables. Ils incluent la compréhension et l'usage de la syntaxe et des aspects pragmatiques du langage tels que la prosodie et les proverbes, mais aussi de l'humour et des formes non littérales du langage. De plus, on rapporte des déficits au niveau de la résolution de problèmes, du raisonnement abstrait, de la généralisation et de la vitesse de traitement (Paul et al., 2007; Paul, Corsello, Kennedy, &

Adolphs, 2014). De façon plus générale, on observe aussi des déficits sur le plan social ainsi qu'en ce qui touche la représentation et la conscience de soi (Uddin, 2011). Une autre étude (Badaruddin et al., 2007) note des déficits dans le transfert interhémisphérique de l'information sensorielle complexe et dans l'apprentissage, la coordination motrice bimanuelle, la résolution de nouveaux problèmes complexes, le traitement des aspects sémantiques et phonétiques subtils du langage, la compréhension de la signification de second ordre du langage, et la compréhension de la psychologie et du comportement. En ce qui concerne l'aire de la compréhension du comportement et de la psychologie, les parents rapportent souvent des déficiences dans le fonctionnement social impliquant un jugement social pauvre, un parlé avec une tendance à l'écholalie ou un parlé en cliché, une difficulté à comprendre les expressions faciales et parfois une tendance à ne pas comprendre les blagues ou les histoires (Badaruddin et al., 2007). De façon intéressante, tous ces symptômes s'apparentent à ceux de l'autisme. Sans que les personnes avec agénésie du corps calleux en aient nécessairement le diagnostic, cette condition est tout de même un facteur de risque important de l'autisme (Paul et al., 2014) et un tiers des adultes avec agénésie du corps calleux présenteraient des comportements concordant avec un TSA.

1.2.7.2 Corps calleux et autisme : lien entre anatomie et fonction

En autisme, les conséquences directes qu'ont les diminutions du corps calleux sur sa fonction restent à être investiguées. Comme on l'a vu plus haut, les diminutions de FA et les augmentations de RD associés au diamètre et myélinisation des axones, et donc à leur vitesse de conduction (Madden et al., 2004), prédisent une communication moins efficace entre les neurones connectés par ces fibres.

Bien que les récentes revues de littératures en connectivité fonctionnelle soulignent principalement la connectivité antéropostérieure (intrahémisphérique) réduite, il existe aussi certains arguments empiriques en faveur d'une connectivité interhémisphérique atypique en autisme. Ces évidences proviennent entre autres d'études de cohérence en EEG, qui observent des diminutions généralisées chez les autistes, surtout entre les régions bilatérales frontales et temporo-pariétales (Carson, Salowitz, Scheidt, Dolan, & Van Hecke, 2014; Catarino et al., 2013; Coben, Clarke, Hudspeth, & Barry, 2008; Lazarev, Pontes, Mitrofanov, & Deazevedo, 2013), mais aussi entre les régions visuelles bilatérales (Clawson, Clayson, South, Bigler, &

Larson, 2013; Isler, Martien, Grieve, Stark, & Herbert, 2010; Lazarev et al., 2013). Cette connectivité interhémisphérique atypique a aussi été observée à l'aide de la spectroscopie proche infrarouge (Zhu, Fan, Guo, Huang, & He, 2014) et de l'IRM fonctionnelle (IRMf). Parmi les études de connectivité fonctionnelles IRM en autisme, celle de Dinstein et al. (2011) a mis en évidence des diminutions de connectivité interhémisphérique entre les régions langagières chez des enfants durant le sommeil. Verly et al. (2014) ont observé une diminution entre les régions de Broca bilatérales, les aires motrices supplémentaires et les régions dorsolatérales préfrontales. Anderson et al. (2011) ont aussi observé des réductions de connectivité interhémisphérique entre les régions frontales sensorimotrices, l'insula frontale et les régions pariétales supérieures, et les régions temporales et prémotrices inférieures. Ces auteurs ont investigué le lien entre ces réductions de connectivité et les réductions anatomiques du corps calleux chez les autistes. Ils ont observé que les deux étaient associés, mais pas significativement corrélés. D'ailleurs peu d'études ont mis en relation ou même tenté de mettre en relation les diminutions de corps calleux avec ses fonctions.

Les réductions de corps calleux ont été associées à des aspects neurocognitifs incluant le traitement sensorimoteur et les fonctions exécutives (Tour de Hanoi), impliquant les régions frontales bilatérales (Keary et al., 2009) ainsi que l'IVT des échelles de Wechsler (Alexander et al., 2007). Les diminutions du corps calleux ont aussi été reliées à la sévérité des symptômes autistiques. Les propriétés microstructurales du corps calleux seraient négativement corrélées aux scores de communication et interactions sociales réciproques du Autism Diagnostic Observation Schedule (l'ADOS-G, Hanaie et al., 2014), et aux scores de sévérité des symptômes mesurés à l'aide du Childhood Autism Rating Scale (CARS). Elles ont aussi été reliées aux scores de l'ADI dans les trois sphères d'atteinte, soit les interactions sociales réciproques, la communication et les comportements restreints, répétitifs et stéréotypés (Cheung et al., 2009), ainsi qu'aux habiletés langagières (Billeci, Calderoni, Tosetti, Catani, & Muratori, 2012).

Seulement quelques études ont établi un lien direct entre les propriétés du corps calleux et la connectivité fonctionnelle réduite. Les réductions volumétriques du corps calleux antérieur ont été mises en relation avec une connectivité fronto-pariétale (donc intrahémisphérique) plus basse, et les propriétés du corps calleux ont été interprétées comme

indexant les anomalies plus générales de la matière blanche, imposant des contraintes sur la connectivité fonctionnelle (Damarla et al., 2010; Just et al., 2007). Des liens ont aussi été notés entre la grosseur du corps calleux et la connectivité fonctionnelle réduite entre les régions bilatérales occipitales et temporales, ainsi qu'entre les régions frontales gauches et pariétales droites (Kana et al., 2006), entre les régions frontales gauches et temporales droites (Mason, Williams, Kana, Minshew, & Just, 2008), entre les régions bilatérales parahippocampiques et la connectivité antéropostérieure dans l'hémisphère gauche (Cherkassky, Kana, Keller, & Just, 2006). De plus, McGrath et ses collègues (2013) ont souligné qu'il existe définitivement un lien en autisme entre les réductions d'organisation microstructurales de la matière blanche et les anomalies de connectivité fonctionnelles. Toutefois l'effet direct des diminutions du corps calleux sur l'efficacité et la rapidité des communications entre les régions cérébrales connectées par ses fibres reste à être investiguée.

1.3 Mesurer la connectivité interhémisphérique

1.3.1 Le paradigme de Poffenberger

Le temps de transfert interhémisphérique (TTIH) peut être indexé par le temps de réaction simple en réponse à des stimuli visuels latéralisés, ce que mesure le paradigme de Poffenberger (Poffenberger, 1912). Ce paradigme consiste à mesurer la différence de temps de réponse qui existe selon que le participant répond avec la main droite ou gauche et selon que le stimulus est présenté dans le champ visuel droit ou gauche. En soustrayant le temps de réponse du circuit non croisé (réponse de la main ipsilatérale au champ visuel stimulé) du temps de réponse plus long du circuit croisé (réponse de la main controlatérale au champ visuel stimulé), on obtient la différence *croisé-non croisé* ou Crossed-Uncrossed Difference (CUD). Cette mesure reflète le TTIH, ou temps nécessaire pour que l'information visuomotrice traverse, via le corps calleux, d'un hémisphère à l'autre, ce qui nécessite moins de temps aux essais non croisés, qui peuvent être traités avec un seul hémisphère (aire visuelle activée ipsilatérale à l'aire motrice). Le CUD a été mesuré à de nombreuses reprises dans des populations typiques. Il a été estimé lors d'une méta-analyse des études du paradigme de Poffenberger à 3-4 ms avec une étendue de 1 à 10 ms (Marzi, Bisiacchi, & Nicoletti, 1991). Les études de lésion confirment l'importance de l'implication du corps calleux dans ce

transfert de l'information. En l'absence de cette structure, dans l'agénésie du corps calleux par exemple, le CUD est significativement plus lent (Marzi et al., 1991) et est encore plus long (jusqu'à 96 ms) chez les individus ayant subi une section du corps calleux, à laquelle on a parfois recours dans des cas graves d'épilepsie (Clarke & Zaidel, 1989; Marzi et al., 1991).

1.3.2 Localisation du transfert dans le corps calleux : moteur ou visuel?

Plusieurs études ont utilisé des variantes du paradigme de Poffenberger en manipulant l'information visuelle (luminance, excentricité) et motrice (position de la main, du bras) pour tenter de déterminer quels aspects influençaient le TTIH et donc, si l'information traverse d'un hémisphère à l'autre au niveau visuel ou moteur (Figure 4). Si la manipulation des paramètres moteurs de la tâche affecte le CUD, mais pas la manipulation des paramètres visuels, le transfert aurait par conséquent lieu au niveau moteur. Ces études ainsi que des études de lésions partielles du corps calleux suggèrent que, dans la population typique, le transfert de l'information aurait lieu dans la partie du corps calleux reliant les régions prémotrices gauches et droites (Berlucchi, Heron, Hyman, Rizzolatti, & Umilta, 1971; Clarke & Zaidel, 1989; Corballis, Hamm, Barnett, & Corballis, 2002; Tettamanti et al., 2002). Les études de lésions partielles suggèrent en effet que les lésions du corps calleux antérieur épargnant le splénium (postérieur) causent des CUD anormalement plus longs (Iacoboni & Zaidel, 1995; Marzi, Bongiovanni, Miniussi, & Smania, 2003). Toutefois certaines études montrent aussi des ralentissements lors de lésions de la partie postérieure du corps calleux (Marzi et al., 2003), et même un CUD normal, que la lésion soit antérieure ou postérieure (Berlucchi, Aglioti, Marzi, & Tassinari, 1995). Ces études supportent une théorie alternative stipulant que le transfert pourrait avoir lieu à différents endroits et que, tant les fibres motrices que visuelles seraient capable de transférer l'information. Selon le modèle *horse race* (Bisiacchi et al., 1994), l'information visuomotrice serait transférée au niveau prémoteur ET visuel, et le CUD refléterait le transfert transcallosal « gagnant », soit le plus rapide, donc celui déclenchant la réponse motrice mesurée. Bien que ce site « gagnant » dépendrait de plusieurs variables (Iacoboni & Zaidel, 1995; Weber et al., 2005), un transfert plus rapide en moteur qu'en visuel est plus probable (Clarke & Zaidel, 1989; Martuzzi et al., 2006). La composition des fibres du corps calleux supporte aussi un transfert plus rapide au niveau moteur puisque les régions du corps calleux connectant les aires sensorimotrices comprennent les fibres de plus large

diamètre et plus myélinisées et donc les fibres conduisant l'information le plus rapidement (Aboitiz, Lopez, & Montiel, 2003). Caminiti et collègues (2009) ont aussi montré que le délai de conduction des axones du corps calleux reliant les régions prémotrices gauches et droites était moins grand que celui des fibres connectant les régions visuelles. De plus, à l'aide de techniques de DTI, on a observé que dans une population typique, le TTIH mesuré à l'aide du paradigme de Poffenberger corrélait positivement avec la constante de diffusivité dans la région antérieure du corps calleux, connectant les régions motrices bilatérales (Schulte, Sullivan, Muller-Oehring, Adalsteinsson, & Pfefferbaum, 2005). Le modèle *horse race* est cohérent avec les études en électrophysiologie observant des mesures de CUD comportementales et électrophysiologiques ne concordant pas ensemble (Bisiacchi et al., 1994). Par exemple, certaines études ont observé un CUD estimé en comportemental ne concordant pas avec un CUD plus lent, mesuré au niveau électrophysiologique entre les électrodes occipitales (Lines, Rugg, & Milner, 1984; Saron & Davidson, 1989).

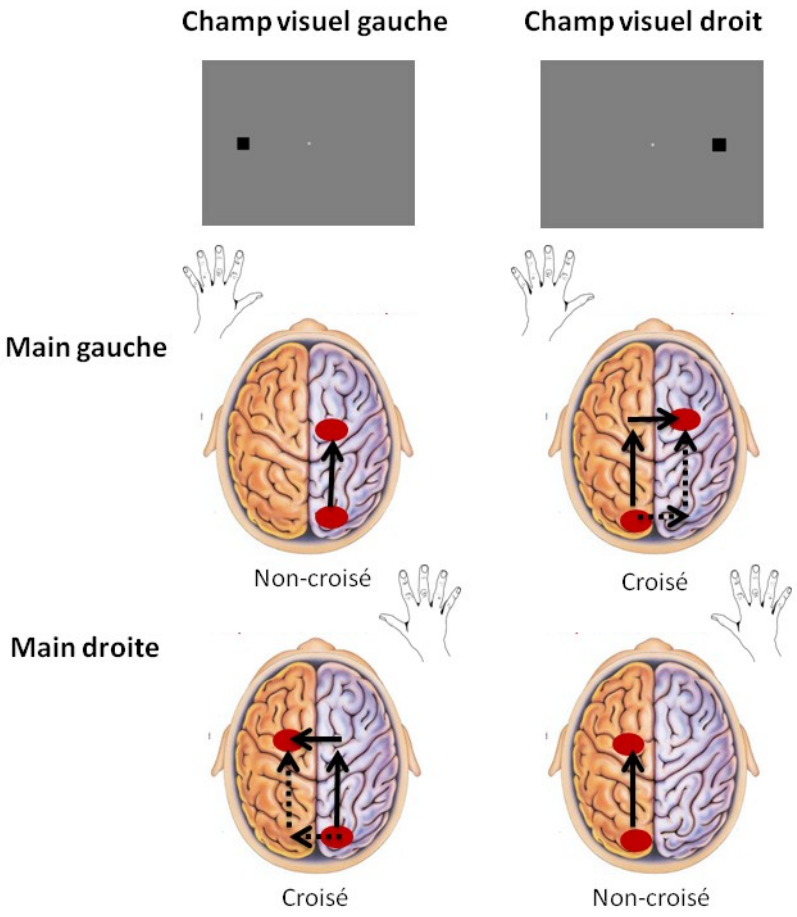


Figure 4. Illustration des quatre conditions du paradigme de Poffenberger : transfert de l'information au niveau moteur (ligne pleine) ou visuel (ligne pointillée) pour les conditions croisées.

1.3.3 Les bases neuronales du paradigme de Poffenberger

Plusieurs études d'imagerie cérébrale fonctionnelle ont investigué les bases neuronales du paradigme de Poffenberger. À l'aide de l'IRMf, il est possible d'avoir des indices sur la localisation du transfert de l'information par le corps calleux en observant l'activité bilatérale dans les régions corticales adjacentes au corps calleux, desquelles et vers lesquelles l'information transite. Aussi, des différences en niveaux d'activation (intensité du signal) entre les régions corticales homologues refléteraient des déficits de l'intégration interhémisphérique

de l'information. Il a été montré en effet, à l'aide d'une tâche visuelle d'intégration spatiale, que des enfants (entre 7 et 13 ans) avec connexions interhémisphériques immatures (index de myélinisation bas) montreraient des activations IRMf dans l'hémisphère gauche seulement. Les enfants ayant des fibres du corps calleux plus myélinisées montreraient quant à eux des activations bilatérales (Fornari, Knyazeva, Meuli, & Maeder, 2007). Dans le paradigme de Poffenberger, en plus des activations reliées aux effets principaux de la tâche, soit visuelles et motrices, plusieurs études IRMf dans des populations typiques ont investigué les régions activées spécifiquement en lien au transfert de l'information. La différence d'intensité du signal (entre les circuits croisés et non croisés) dans les régions corticales impliquées dans le transfert serait corrélée avec la mesure de CUD (Iacoboni & Zaidel, 2004; Omura et al., 2004). Bien que quatre études n'aient observé aucune activation corticale spécifique à la condition croisée (Gawryluk, Brewer, Beyea, & D'Arcy, 2009; Gawryluk, D'Arcy, Mazerolle, Brewer, & Beyea, 2011; Martuzzi et al., 2006; Omura et al., 2004), plusieurs autres études observent des activations pour la condition croisée comparée à la condition non croisée. Weber et al. (2005) ont observé de l'activation à droite dans le cunéus seulement et Tettamanti et al. (2002) ont observé plus d'activité bilatérale dans les régions prémotrices, l'insula, le gyrus cingulaire et le cortex frontal mésial et le lobule postcentral (pariétal). Iacoboni and Zaidel (2004) ont observé, spécifiquement à la condition croisée, de l'activité bilatérale frontale, prémotrice et pariétale droite et le CUD était corrélé avec l'intensité du signal de la région pariétale. Le cortex pariétal a donc été crédité d'un rôle clé dans l'intégration visuomotrice du paradigme de Poffenberger (Iacoboni & Zaidel, 2004; Martuzzi et al., 2006; Marzi et al., 1991).

Une particularité des études de la tâche de Poffenberger en IRMf est qu'une activation cérébrale dans la matière blanche est souvent rapportée. Sur sept études, cinq rapportent une activité dans le corps calleux, reliée aux conditions croisées de la tâche (Gawryluk et al., 2009; Gawryluk et al., 2011; Omura et al., 2004; Tettamanti et al., 2002; Weber et al., 2005). Cette activation est localisée plus précisément dans la partie antérieure du corps calleux, reliant les régions préfrontales et prémotrices, ce qui suggère que ces activations de la matière blanche ne sont pas aléatoires, mais concordantes avec la tâche (Gawryluk et al., 2009). Or, le signal IRMf observé dans la matière blanche est très discutable et sa validité peu consensuelle considérant les facteurs qui permettent le signal dépendant des niveaux d'oxygène sanguin

ou Blood-Oxygen-Level-Dependent (BOLD). Le signal BOLD est en effet plus probable et habituellement observé dans la matière grise où se trouvent les corps neuronaux et les synapses. Le signal BOLD est une mesure indirecte de l'activité électrique et chimique des neurones. Cette activité nécessite une augmentation de l'apport d'oxygène et de glucose par les vaisseaux sanguins et donc une augmentation du débit sanguin dans les régions où l'activité neuronale a lieu et permet ainsi à l'oxygène, transporté par l'hémoglobine, de rejoindre les neurones. La susceptibilité magnétique de l'hémoglobine, c'est-à-dire sa capacité à être affectée un champ magnétique, est l'élément clé pour l'IRMf. Quand elle est liée à l'oxygène, elle est moins susceptible au champ magnétique, alors que quand elle est séparée de l'oxygène (déoxyhémoglobine (dHb)), est affectée par le champ magnétique de façon plus importante. La dHb paramagnétique est présente à l'intérieur des cellules de globules rouges et contraste avec le milieu extracellulaire générant ainsi des gradients de champ magnétique. Selon les variations de la concentration de dHb dans le sang, il se crée de l'inhomogénéité dans le champ magnétique et ce sont ces changements de signal BOLD qui sont détectés en IRMf. Lorsqu'il y a activité neuronale donc, le débit sanguin augmente dans cette région pour un plus grand apport en glucose et en oxygène, toutefois, la consommation d'oxygène est proportionnellement moins élevée que l'apport sanguin (Fox & Raichle, 1986), entrainant une diminution de la concentration de dHb. Le contraste entre les milieux intra et extracellulaires diminue donc et le champ magnétique est moins perturbé, ce qui se traduit par une plus grande intensité du signal BOLD. La consommation d'énergie nécessaire à l'activité des neurones prenant place au niveau de la synapse lors de potentiels post-synaptiques, l'absence de corps neuronal et de synapse dans la matière blanche la rendent peu propice à produire le signal IRMf. Toutefois, il existe aussi des mécanismes nécessitant la consommation d'énergie dans la matière blanche étant associés à la propagation de potentiels d'actions qui pourraient, bien que de façon plus faible, déclencher du signal BOLD. De plus, le fait que le volume et le débit sanguin soient beaucoup plus bas dans la matière blanche diminue certainement aussi la force d'un possible signal BOLD (Gawryluk et al., 2009; Gawryluk et al., 2011). C'est pourquoi d'ailleurs les activations dans la matière blanche ne sont seulement observées qu'à des seuils de significativité plus bas (ex.: seuils non corrigés de $p<.005$). Gawryluk et ses collègues (2011) ont toutefois montré que ce signal peut être optimisé en utilisant des séquences d'acquisition différentes. Aussi, en appui à la véracité des activations de matière blanche dans

les tâches de transfert interhémisphérique, une étude a confirmé, à l'aide de la tractographie, qu'elles étaient associées à des activations de matière grise correspondantes (Mazerolle, D'Arcy, & Beyea, 2008). Bien que l'activation fonctionnelle dans la matière blanche soit une piste intéressante à explorer, compte tenu des aspects techniques du signal IRMf et des propriétés électrophysiologiques du cerveau, la validité du signal BOLD dans la matière blanche reste à être montrée.

1.3.4 Poffenberger et autisme

Le paradigme de Poffenberger n'a jamais été utilisé avec une population autiste. Toutefois, Nydén et al. (2004) ont étudié des tâches perceptives visuelles (ex: nommer ou pointer des objets vus), auditives (nommer des voyelles entendues) et tactiles (nommer le doigt touché) impliquant un transfert par le corps calleux. Selon les auteurs, les performances inférieures des autistes dans ces tâches neuropsychologiques nécessitant un certain niveau de traitement, et impliquant un transfert interhémisphérique, suggèrent des altérations des fonctions du corps calleux. Clawson et al. (2013) ont utilisé une tâche mesurant le temps de transfert interhémisphérique, mais n'ont obtenu aucune différence significative entre les autistes et les typiques, tant sur le plan comportemental qu'électrophysiologique. Ils suggèrent que le transfert de base de l'information visuelle est intact, mais que des différences pourraient possiblement être observées avec des tâches plus complexes requérant plus d'intégration par le corps calleux. Ils mentionnent aussi que la tâche utilisée étant simple, il est possible que les limites du corps calleux des autistes n'aient pas été mises au défi. Ces résultats suggèrent que malgré les diminutions de corps calleux, les autistes pourraient avoir des performances normales en ayant recours à différentes trajectoires neuronales (Clawson et al., 2013). L'observation de mécanismes neuronaux différents en autisme malgré une performance similaire à une tâche donnée n'est pas quelque chose de nouveau. On a vu par exemple, le plus grand rôle des régions visuelles dans différentes tâches pour lesquelles aucune différence de performance n'a été notée. Pierce et ses collègues (2001) ont noté par ailleurs une altération des allocations cérébrales typiques, dans ce cas pour le traitement des visages, suggérant que les régions cérébrales activées pour une même tâche différeraient entre les autistes et les typiques malgré une performance égale à la tâche (temps de réponse et exactitude).

1.4 Objectifs et hypothèses

Plusieurs particularités cognitives et comportementales propres au phénotype autistique, entre autres au niveau du traitement de l'information et de la motricité, sont associées à une connectivité cérébrale intra et interrégionale atypique. Elles sont reliées à des différences anatomiques au niveau de la matière blanche. Particulièrement, l'importance des réductions du corps calleux en autisme suggère une connectivité atypique entre les hémisphères. Toutefois, l'effet direct sur le transfert de l'information entre les régions homologues bilatérales reste à être montré. Dans la première étude, la tâche de Poffenberger permet, à l'aide de sa mesure de temps de transfert interhémisphérique (TTIH), de déterminer si les réductions potentielles de corps calleux affectent directement l'efficacité de sa fonction de communication de l'information d'un hémisphère à l'autre. Ce paradigme implique un traitement de l'information visuelle, un transfert de l'information aux régions motrices du cerveau permettant une réponse motrice signalant la détection du stimulus visuel. La tâche implique aussi un transfert de l'information visuomotrice d'un hémisphère à l'autre. À l'aide de l'imagerie cérébrale, les propriétés volumétriques et microstructurales du corps calleux sont aussi mesurées chez les mêmes participants. Cela permet de déterminer si, dans un groupe d'autistes composé d'adolescents et d'adultes, on retrouve les réductions attendues du corps calleux, et si ces réductions peuvent être localisées particulièrement dans les régions transférant l'information visuelle et motrice. La tâche de Poffenberger est aussi investiguée en IRMf afin d'identifier les régions visuelles et motrices impliquées et d'identifier des possibles différences de localisation du transfert de l'information via le corps calleux. Finalement, les mesures comportementales de temps de transfert (TTIH) sont mises en relation avec les mesures macrostructurales (IRM structurelle) et microstructurales (DTI) du corps calleux. Considérant l'impact des réductions du corps calleux sur la vitesse de conduction de ses axones, un temps de transfert interhémisphérique plus long est attendu chez les autistes. Toutefois, la variabilité et la plasticité souvent observées en autisme pourraient mener à une absence de différences comportementales associées tout de même à des différences anatomiques ou de localisation des activations cérébrales.

Des atypicalités de la matière blanche au niveau intrahémisphérique sont aussi notées en autisme et ont été mises en relation avec les particularités de traitement de l'information

visuelle et de motricité. Une meilleure description de ces composantes est particulièrement pertinente vu leur implication dans la tâche visuomotrice de Poffenberger. Par exemple, les déficits ou les ralentissements moteurs observés en autisme pourraient influencer les résultats obtenus, puisqu'un aspect crucial de la tâche de Poffenberger est la réponse motrice qui consiste à appuyer sur un bouton le plus rapidement possible. Le deuxième volet de la présente thèse consiste donc à évaluer, toujours chez les mêmes participants, la vitesse de traitement perceptif, mesurée à l'aide d'une tâche de temps d'inspection (Inspection Time ou IT) ainsi que les aptitudes motrices, évaluées avec les tests de *Purdue pegborard* et *Annett peg moving*.

La deuxième étude consiste donc à investiguer un aspect précis de la perception autistique : la vitesse de traitement de l'information présentée visuellement. Cette étude permet de préciser l'implication de la vitesse de traitement perceptif dans la cognition autistique et les surfonctionnements perceptifs qui la caractérisent. Dans la troisième étude, deux tâches motrices guidées visuellement sont utilisées afin de caractériser la nature et l'importance des déficits moteurs en autisme. Les tâches impliquent la motricité fine et globale, la dextérité et la coordination œil-main. De plus, la tâche de Purdue comprend deux conditions bimanuelles nécessitant l'implication du corps calleux. Elles sont utilisées comme mesures supplémentaires d'indice d'intégrité de communication interhémisphérique à être mises en relation avec les propriétés du corps calleux. Par ailleurs, considérant la littérature existante sur les possibles différences entre les autistes et les Asperger en termes d'habiletés motrices et de traitement de l'information visuelle et leur valeur discriminante potentielle, ces deux dernières études comprennent des groupes distincts d'autistes et d'Asperger. Les deux sous-groupes sont comparés entre eux ainsi qu'au groupe à développement typique. Une importance particulière du traitement perceptif dans la cognition est attendue dans le sous-groupe d'autistes spécifiquement. De plus, étant donné les différences cliniques, comportementales et cérébrales observées entre les deux sous-groupes TSA, des déficits moteurs de différente nature et/ou de différente sévérité sont prédits.

De façon générale l'objectif de la présente thèse est donc d'investiguer, à l'aide de tâches visuomotrices, l'intégrité du traitement de l'information visuomotrice et des réseaux cérébraux impliqués avec une emphase particulière sur la communication interhémisphérique.

Chapitre 2. Article 1: A greater role of perception in interhemispheric transfer in autism: fMRI, DTI and behavioral evidences

A greater role of perception in interhemispheric transfer in autism: fMRI, DTI and behavioral evidences

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ABSTRACT

A small corpus callosum (CC) is one of the most replicated neurobiological findings in autism. However, its effect on interhemispheric (IH) communication is unknown. We combined structural (CC area and DTI), functional (task-related fMRI activation) and behavioral (Poffenberger and Purdue task) measures to investigate IH integration in adult autistic individuals of typical intelligence. Despite similar behavioral IH transfer time and performances in bimanual tasks, the CC subregions connecting frontal and parietal cortical areas were smaller in autistic than in non-autistic individuals, but those connecting visual regions were similar. The activation of visual areas was lower in autistic than in non-autistic individuals during the presentation of visual stimuli. Behavioral IH performances were related to the properties of CC subregions connecting motor areas in non-autistic individuals, but to the properties of posterior CC regions in autistic individuals. Thus, visual IH transfer plays an important role in visuo-motor tasks in autistic individuals. These findings extend the well established enhanced role of perception in autistic cognition to visuo-motor IH information transfer.

Keywords: corpus callosum, Poffenberger, Purdue, visuo-motor integration

The observation that the corpus callosum (CC) is smaller in autistic individuals than in non-autistic individuals is among the most replicated neurobiological findings in autism. A meta-analysis of structural studies [Frazier et al., 2009], two reviews of diffusion tensor imaging (DTI) studies [Travers et al., 2012; Vissers et al., 2012] and one meta-analysis of diffusion tractography studies [Aoki et al., 2013] support the conclusion that structural connectivity is altered in the corpus callosum of autistic individuals. Early investigations examining alterations of functional connectivity in autistic individuals found evidence of low intrahemispheric, fronto-posterior long-distance connectivity, [Schipul et al., 2011; Uddin et al., 2013; Vissers et al., 2012] associated with short distance (or local) over-connectivity [Just et al., 2007; Just et al., 2004]. Recent reconsideration of these findings emphasizes the dependence of functional connectivity results on the methodology used [Muller et al., 2011] and differences in methods to account for brain volume and intelligence in anatomical corpus callosum investigations [Lefebvre et al., 2014].

Several other studies have observed higher connectivity in autism involving perceptual areas, regardless of the distance [Di Martino et al., 2011; Dominguez et al., 2013; Keown et al., 2013; Léveillé et al., 2010; Shen et al., 2012; Supekar et al., 2013]. Besides alterations of corpus callosum volume, alterations of intrahemispheric frontal, temporal and parietal white matter volume [Amaral et al., 2008; Anagnostou et al., 2011; Just et al., 2012] and diffusion properties [Aoki et al., 2013; Travers et al., 2012; Vissers et al., 2012] also suggest that widespread alterations of connectivity occur in autism.

The corpus callosum is the main white matter bundle connecting the two brain hemispheres; therefore, morphological and microstructural alterations of this brain region should negatively influence interhemispheric (IH) connectivity. EEG signal coherence between bilateral frontal and temporoparietal regions [Carson et al., 2014; Catarino et al., 2013; Coben et al., 2008; Lazarev et al., 2013] and between bilateral visual regions [Clawson et al., 2013; Isler et al., 2010; Lazarev et al., 2013] is lower in autistic than in non-autistic individuals. In addition, MRI functional connectivity studies also report that IH connectivity is impaired between bilateral several frontal regions [Verly et al., 2014] and between sensorimotor frontal areas, frontal and parietal superior insula, and temporal and inferior

premotor areas in autistic individuals [Anderson et al., 2011]. Alterations of functional connectivity are related to anomalies in the microstructural properties [McGrath et al., 2013] and reduction in size [Cherkassky et al., 2006; Damarla et al., 2010; Just et al., 2007; Kana et al., 2006; Mason et al., 2008] of the corpus callosum. The size of the corpus callosum in autistic individuals is also correlated with their neurocognitive performance [Alexander et al., 2007; Keary et al., 2009], the numbers and magnitude of autistic signs [Billeci et al., 2012; Cheung et al., 2009; Hanaie et al., 2014].

Direct evidence supporting a link between atypical structure, IH information transfer and behavioral performance is nonetheless lacking and the effect of alterations of corpus callosum size on the speed and efficiency of IH communication remains to be investigated. Information transfer between brain hemispheres can be investigated by a simple reaction time paradigm in response to lateralized visual stimuli, the Poffenberger paradigm [Poffenberger, 1912]. The relevant variable of this paradigm is the Crossed/Uncrossed Difference (CUD), which is obtained by subtracting the response time to a stimulus presented in the uncrossed circuit (i.e. the response of the hand ipsilateral to the stimulated visual hemifield) from that of the crossed circuit (i.e. the response of the hand contralateral to the visual hemifield). Uncrossed trials can be processed by visual and motor areas of the same hemisphere, whereas crossed trials necessitate a transfer of information from one hemisphere to the other. The CUD therefore reflects the time needed for the visuo-motor information to cross from one hemisphere to the other via the corpus callosum. The Poffenberger paradigm has been used in populations of non-autistic individuals, in conjunction with fMRI, to identify the motor and visual cortical areas involved in information transit through the corpus callosum. These studies have revealed that the CUD is correlated with the signal intensity difference between the crossed and the uncrossed circuits [Iacoboni et al., 2004; Omura et al., 2004]. The Poffenberger paradigm has never been applied to autistic populations, either in behavior tests or in neuroimaging studies. Behavioral performance under the dependence of IH communication is also assessed by bimanual coordination tasks. The Purdue pegboard is a test that examines gross and fine motor skills. It comprises two bi-manual conditions requiring the coordinated movement of both hands to place little pieces into the pegboard in a simultaneous or sequential manner. This task also requires hand-eye coordination. Bimanual motor skills are

dependent on the integrity of the corpus callosum [Johansen-Berg et al., 2007] and are affected in people with corpus callosum agenesis [Badaruddin et al., 2007].

The aim of this study was to establish whether the alterations of the size of the corpus callosum observed in autism affect IH transfer, and whether the cortical areas involved in IH information transfer differ in autistic and non-autistic individuals. We used anatomical and diffusion weighted MRI of the corpus callosum, coupled with two measures of IH transfer, the Poffenberger paradigm and the Purdue pegboard task, to investigate IH integration**.** IH transfer was expected to be slower in autistic than in non-autistic individuals, because corpus callosum size is thought to affect the speed of IH transfer. However, variability in the allocation of cortical regions involved in visuo-motor tasks in autistic individuals [e.g., Pierce et al., 2001; Poulin-Lord et al., 2014] as well as the use of plastic cortical rededication [see Mottron et al., 2014 for review] may result in anatomical brain differences without deleterious consequence on IH transfer.

MATERIALS AND METHODS

Participants

Thirty-four autistic and 33 non-autistic individuals aged between 14 and 37 years old participated in this study. Participants were randomly recruited from the research database of the Specialized Clinic for the Diagnosis and Evaluation of Pervasive Developmental Disorders at the Rivière-des-Prairies Hospital (Montreal, Canada). Exclusion criteria for all participants were uncorrected visual impairment, the use of drugs or alcohol exceeding two drinks per day, and a Full Scale Intellectual Quotient (Wechsler FSIQ) score inferior to 75. Two autistic participants took medication (one quetiapine, one methylphenidate). Twenty-seven out of 34 autistic participants were diagnosed by the Autism Diagnostic Interview-Revised [ADI-R; Lord et al., 1994] and the Autism Diagnosis Observation Schedule module 3 or 4 [ADOS-G; Lord et al., 2000], combined with an expert interdisciplinary clinical assessment. Seven participants were characterized according to expert interdisciplinary judgment alone (one participant) or in combination with the ADOS-G (two participants) or the ADI-R (four participants). None of the autistic participants had comorbid genetic, neurologic, or DSM-IV Axis 1 psychiatric conditions, except for hyperactivity and language disorders, which are

present in a large proportion of autistic individuals at some point during their development. Non-autistic participants were screened through a questionnaire to exclude individual or familial neurological, psychiatric, or medical conditions known to affect brain function.

Handedness was measured with the Edinburgh inventory [Oldfield, 1971] and the Hand Preference Demonstration Test [Soper et al., 1986]. The findings of these two measures were consistent for all participants. Handedness affects corpus callosum size and function in typically developing populations [Witelson, 1985, 1989]. Left and right-handed people display different patterns of IH transfer time with the left and the right hand [Marzi et al., 1991]; therefore, only right-handed people were included in this study.

Written informed consent was obtained from all participants in accordance with the Regroupement Neuroimagerie/Québec IRB approved protocol 08-09-003 and the research ethics committee of the Rivière-des-Prairies Hospital, Montréal, Canada. All participants received compensation for their participation. Autistic and non-autistic groups were comparable in terms of sex, age (14-37 years old), IQ (77-127), RPM percentile (10-100) and handedness (Edinburgh: 17-100). A subsample of 22 autistic and 24 non-autistic MRI-compatible individuals, matched according to the same variables as the overall group, were included in the MRI part of the experiment. Table 1 shows the socio-demographic charateristics of the participants. One autistic and two non autistic participants were excluded because of artifacts in the data associated with a large amount of head motion. One more participant in each group was removed because of their performance in the tasks (see data analysis section). The final group included in the fMRI second level analysis comprised 20 autistic and 21 non-autistic individuals matched for PIQ, Raven percentile and age.

Table 1. Characteristics of participants in the non-autistic (nAUT) and autistic (AUT) group for the behavioral study (outside the scanner) and the MRI study.

	Behavioral study			MRI study		
	AUT	nAUT	*p*	AUT	nAUT	*p*
N	32 (3F)	31 (3F)		22 (3F)	24 (3F)	
Age (SD)	21.5 (5.9)	21.5 (5.2)	.991	20.3 (5.5)	22.7 (5.3)	.149
Range	14-34	15-37		14-33	15-38	
FSIQ (SD)	99.8 (12.7)	106.7 (11.6)	.030	98.6 (10.7)	108.1 (13.0)	.010
Range	78-126	87-127		78-126	87-127	
PIQ (SD)	105.3 (11.3)	103.5 (11.87)	.555	104.7 (12.3)	106.1 (13.2)	.714
Range	77-127	82-122		77-127	82-122	
VIQ (SD)	96.3 (16.3)	108.5 (11.4)	.001	96.1 (15.0)	108.8 (12.2)	.003
Range	67-128	91-127		67-124	91-127	
RPM %tile (SD)	73.5 (22.2)	69.6 (23.7)	.508	70.4(20.9)	72.1 (25.6)	.803
Range	10-100	25-98		10-100	25-100	
Edinburgh	81 (21.9)	77 (20.1)	.532	83 (20.5)	86 (11)	.640
Range	27-100	17-100		29-100	62-100	

Stimuli, apparatus and procedure

The Poffenberger task

Behavioral task outside the scanner. The task consisted of detecting a black square that randomly appeared on the gray background either to the right or to the left of a central fixation cross (figure 1). The black stimulus had an eccentricity of 8°. In each experimental block, subjects were presented with 50 stimuli to the right and 50 to the left of the central fixation cross. Each stimulus lasted 50 ms, which is shorter than a visual saccade [~200 ms: Rayner, 1998]. This ensured that each stimulus was presented to only one cerebral hemisphere. The interstimulus interval varied randomly from 1000 to 3500 ms to avoid anticipation. The testing session consisted of three right and three left hand blocks (each lasting about 4 minutes) of 100 trials each, for a total of 600 trials. The order of blocks varied for each participant and was balanced across groups. There were 150 trials in each of the four conditions (Left hand-Left visual field: LH-LVF, Left hand-Right visual field: LH-RVF, Right hand-left visual field: RH-LVF, Right hand-Right visual field: RH-RVF). A practice block of 16 trials (eight left and eight right stimuli) for each hand was administered before the task.

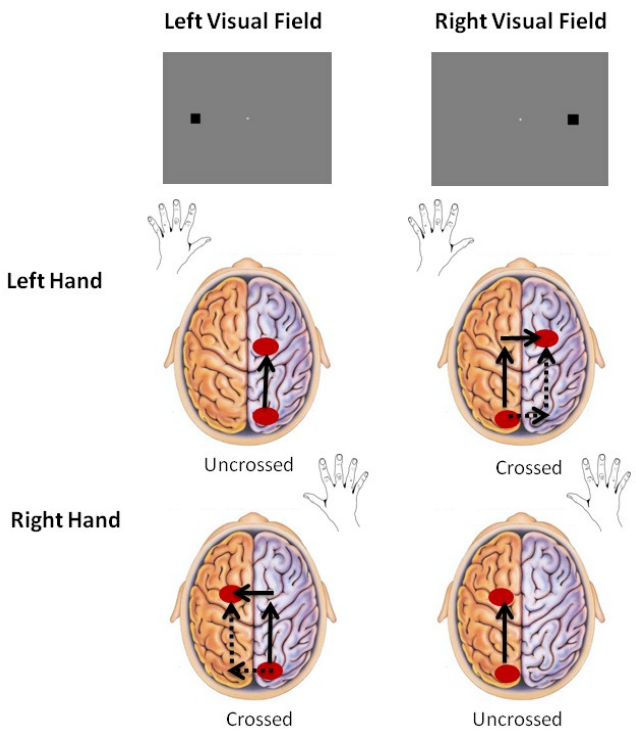

Figure 1. Stimuli presentation in the left visual field (LVF) and in the right visual field (RVF).

The participants were seated in a quiet and dimly lit room with black wooden panels on each side and one in front with an opening for the computer screen, to minimize visual distraction. A chin rest minimized head movement and maintained the viewing distance at 73 cm from the screen. The response box was placed either to the right or left of the participants to ensure a 90° angle of the responding arm. Participants were instructed to keep fixating their eyes on the cross throughout the task, and to press the button as quickly as possible with one of their index fingers every time they saw a black square, regardless of the side it appeared.

The experiment was carried out with *E-prime* software Version 1.2 (Psychology Software Tools Inc.) on a 19 in. CRT monitor, with a 120 Hz refresh rate. Monitor luminance was checked with a photometer before each session. The manual response was recorded with the PST Serial Response box that has a 0 ms debounce period.

Behavioral task inside the scanner. The Poffenberger paradigm was adapted to suit to a single-event paradigm and to favor high levels of blood oxygen level dependent (BOLD) activation in the visual cortex. Easily discernible, black and white checkerboard stimuli were presented on a gray background, and presentation time was increased to 100 ms, which is still

shorter than a visual saccade. The interstimulus intervals (ISI) were longer than in tasks outside the scanner, which allowed the hemodynamic response to return to baseline between trials. The ISI was varied pseudo-randomly between 5000 and 12000 ms as follows: 6x5000 ms, 5x6000 ms, 4x7000 ms, 3x8000 ms, 1x10000 ms, 1x11000 ms, 1x12000 ms, with an average of about 7000 ms. In motor related areas, fMRI activation decays linearly over time during the repeated execution of motor response paradigms [Mancini et al., 2009]; therefore, an event related design was chosen to optimize the detection sensitivity. Long ISIs improve the sensitivity of the signal [Price et al., 2006] and their variable durations reduce predictability. There were 84 trials per block and four blocks (two with each hand) lasting about 9 min each. Before each block, participants were told which hand they should use throughout the block, and were instructed to press the button as fast as possible with the index finger as soon as they saw the stimulus. The participants were lying in a supine position in the scanner, and held a MRI-compatible Fiber Optic Response Pad (Current design INC.) in each hand. The response box was connected to a computer equipped with a parallel port to improve the accuracy of timing. Visual stimuli were presented with *E-prime,* Version 2.0, and were presented to participants though a mirror installed on the head coil, which allowed them to see the stimuli on a screen installed at the back of the scanner.

Measurements of the Poffenberger effect in the scanner are less accurate than those outside the scanner due to the resolution of the MRI-compatible response box and screen, the suboptimal (less ergonomic) position of the participants arms which may have affected the participant's response times, and the presence of distractors (e.g. noise, immobility). Moreover, it was suggested that brain processes are slower under the influence of the magnetic field [Foucher et al., 2008]. Although both tasks yielded similar results, only the task outside the scanner was considered for behavioral analysis.

The Purdue pegboard test

The Purdue pegboard test (Model 32020, Lafayette Instrument Co., IL, USA) assesses fine and gross motor skills, dexterity and coordination and was performed outside the scanner. It has two bimanual conditions in which participants have to move small pegs and place them in small holes. This is done with both hands (BH) working simultaneously in the BH condition, or with each hand working in a coordinated but sequential manner in the assembly (As) condition. Detailed methods and behavioral results are presented in a separate publication

[Barbeau et al., in press]. Absolute performance in the bimanual conditions of this task (Purdue BH and As measures) as well as the relationship between these conditions (number of pegs placed in 30 seconds) and the properties of the corpus callosum were relevant measures for this study.

MRI Image acquisition

Images were acquired on a 3T Siemens Tim Trio scanner with a 32 channel phased-array head coil at the "Unité de Neuroimagerie Fonctionnelle" (University of Montreal). The scanning session included an anatomical T1-weighted structural brain image obtained with an ME-MPRAGE 4-Echo sequence (176 slices, $1mm^3$ voxels, TR = 2530 ms, TE = 1.64/3.5/5.36/7.22ms, flip angle = 7°), which has a low distortion and high signal-to-noise ratio [van der Kouwe et al., 2008]. Functional data were acquired with an echo planar imaging (EPI) pulse sequence (150 acquisitions, TR = 3330ms, 60 slices, matrix size 80x80 voxel size 2.5x2.5x2 mm^3, slice thickness: 2mm with a 0.5mm gap, TE = 30ms, flip angle = 90°). Gradient echo phase and magnitude field maps were then acquired (60 slices, matrix size = 80x80, voxel size 2.5x2.5x2.0mm^3, slice thickness = 2mm with a 0.5mm gap, TR = 488ms, TE short = 4.92ms, TE long = 7.38ms, flip angle = 60°) for the correction of image distortions and the improvement of co-registration accuracy with the field map toolbox in SPM. Diffusion weighted images (DTI) were acquired with an echo-planar sequence (TR = 8740 ms; TE = 83 ms; 70 axial slices; FOV 256 mm; matrix = 128x128; 2 mm interleaved slices; 128 directions; b values = 0 and 700 s/mm^2). Field maps matched to the diffusion-weighted images were also acquired.

Data analysis

Behavioral task

Trials with a response time (RT) under 150 ms or above 500 ms (outside the scanner) or 800 ms (inside the scanner), for a total of 2.3% of trials, were considered as commission and omission errors, respectively and were removed. Median RT was computed for each of the four conditions (LH-LVF, LH-RVF, RH-LVF, RH-RVF) and for each participant. A repeated measure ANOVA was conducted with Hand (left and right) and Visual field (left and right) as within factors and Group as a between factor. The Crossed-Uncrossed Difference (CUD) was individually computed by subtracting the RT of the two uncrossed conditions from the RT of

the crossed conditions of both hands. Participants within each group with CUD values >2 SD from group average were considered as outliers and removed from the analysis. For trials outside the scanner, two participants in each group were excluded to give a final total of 32 autistic and 32 non-autistic individuals. For trials inside the scanner, one participant in each group was excluded because they missed more than 20% of the trials and another participant in each group was excluded because they had an outlier CUD value.

T1 structural and DTI Image analysis

The T1-volumes were processed with CIVET, a fully automated structural image analysis pipeline developed at the Montreal Neurological Institute. CIVET corrects intensity non-uniformities by non-parametric non-uniform intensity normalization [N3: Sled et al., 1998]; aligns the input volumes to the Talairach-like ICBM-152-nl template, with an affine transformation followed by a non-linear transformation [Collins et al., 1994]; classifies the input volumes into white matter, gray matter, cerebrospinal fluid, and background [Zijdenbos et al., 2002]; and extracts the white-matter and pial surfaces [Kim et al., 2005]. The CIVET non-linear transformation was then refined with the minctracc program, and the result was used to warp a parcellated (25 subregions) template of the corpus callosum (CC), defined on the ICBM-152-nl template, to overlay each subject's T1-volume. This procedure ensured that subregions of the CC were comparable among participants. The size of each CC subregion was then measured and this value was divided by the surface area of the portions of cortex connected via each CC subregion to provide a measure of the *relative* size of each CC subregion (RelCC) to account for the amount of gray matter it connects. The surface atlas was produced from an independent sample in which probabilistic tractography was used to map surface vertices to CC subregions [the procedure is illustrated in supplementary figure 1 and described in detail in Lewis et al., 2013]. This surface atlas was registered to each participant to provide the measures of cortical surface area connected by each subregion of the CC. The 25 CC subregions, numbered from anterior to posterior, were then divided into five different groups to investigate the properties of the CC connecting particular functionally related cortical areas: CC 1-3 (prefrontal cortical areas), CC 4-9 (frontal areas), CC 10-16 (para-central areas), CC 17-21 (parietal areas), CC 22-25 (occipital areas).

Field maps were used to correct the diffusion-weighted images for distortions caused by inhomogeneities in the magnetic field and the images were converted to 4D volumes. The diffusion volumes were motion corrected and cleaned of artifacts. The resulting volumes were processed with FSL's *dtifit* to calculate fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD), and with *bedpostx* to calculate the orientation distribution function at each voxel. The T1 was registered with the b0 diffusion volume, which allowed diffusion-based measures to be calculated for each CC subregion, and provided the transformation necessary to carry out probabilistic tractography with masks derived from the T1 volume. The CIVET results were used to construct the seed, stop, and target masks for use with FSL's *probtrackx* [Behrens et al., 2007]. Tracts are seeded from all white matter voxels. Stop masks determine where tract propagation is halted; stop masks were voxels on the boundary of white-matter, including the ventricles and subcortical gray matter. Target masks determine the mapping from voxels of the stop masks to brain regions; target masks were the voxels at the boundary of white matter and the cortex in the following five bilateral regions of interest of the Automatic Anatomical Labeling (AAL) atlas [Tzourio-Mazoyer et al., 2002]: the precentral (PC) gyrus, the supplementary motor area (SMA), the superior occipital (SO) gyrus, the middle occipital (MO) gyrus, and the inferior occipital (IO) gyrus (Figure 2). FSL's dtifit was used to produce FA, AD, RD and MD volumes. Mean FA, AD, RD and MD within each of the five CC subregions were measured. An example of the tracts resulting from the probabilistic tractography is displayed in Figure 3.

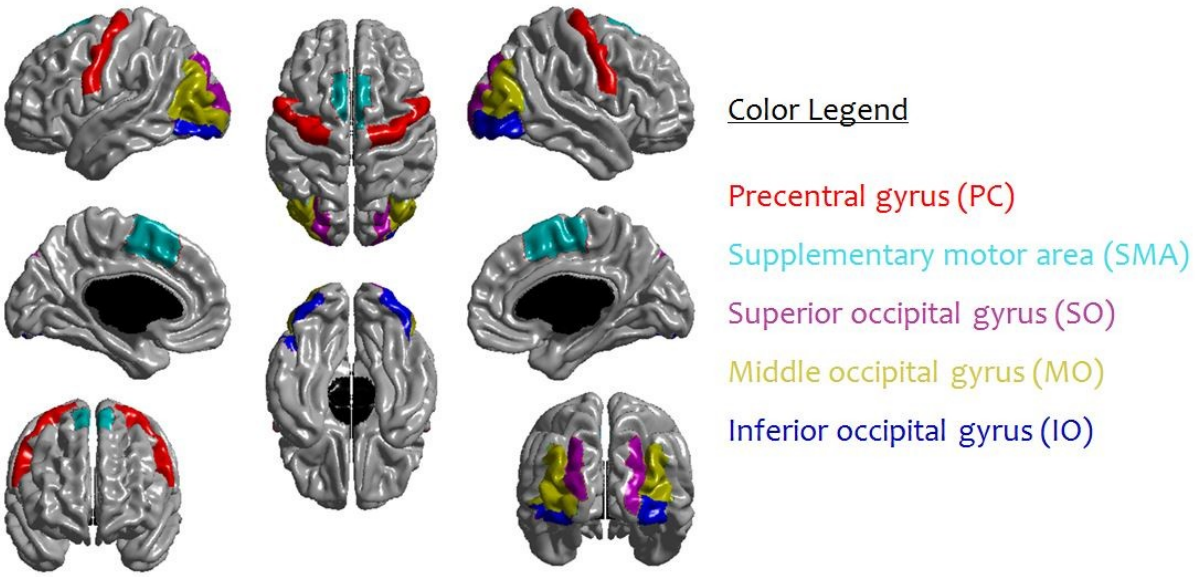

Figure 2. The five bilateral AAL regions of interest used as target masks for the probabilistic tractography

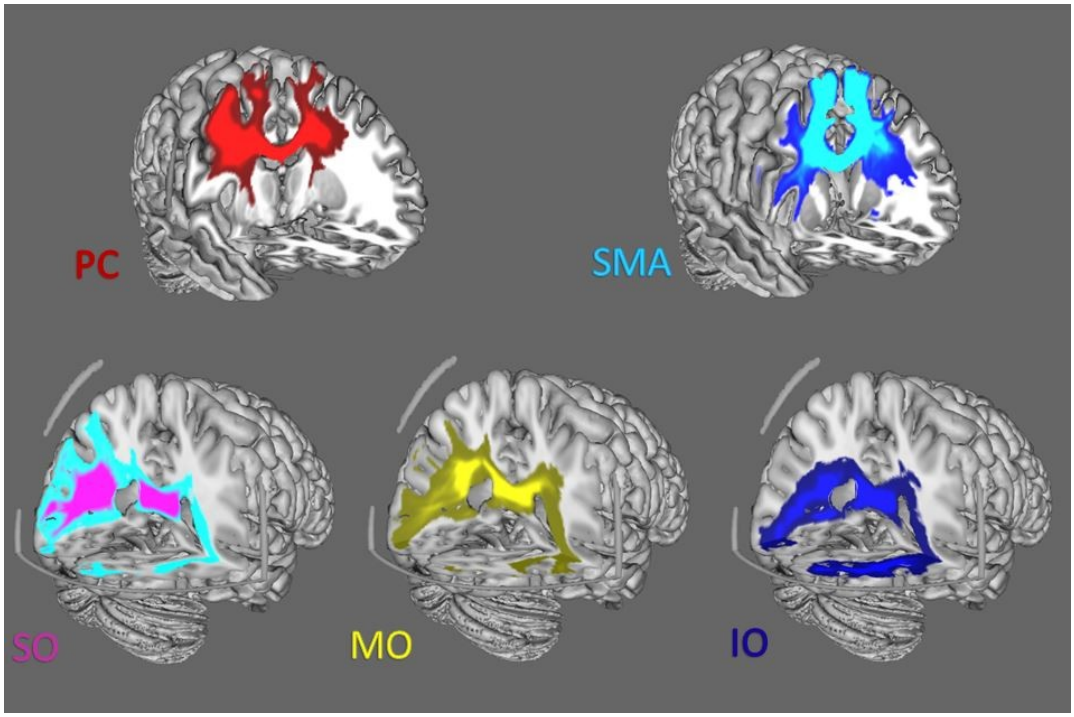

Figure 3. Probabilistic tractography maps from 93 subjects in the ICBM dataset for the five ROIs: Precentral gyrus (PC), Supplementary motor area (SMA), Superior occipital gyrus (SO), Middle occipital gyrus (MO) and Inferior occipital gyrus (IO).

Statistical analysis

The values of relative corpus callosum (RelCC) areas and the DTI measures superior or inferior to 2 SD above or below the group mean were removed (an average of 4.8% of data were removed in the autistic group and 3.6% in the non-autistic group). Multivariate analyses of variance (MANOVA) were conducted to investigate whether the CC measures differed between groups. There was no significant effect of age or intelligence measures when entered as covariates, and thus they were not included in the final model.

fMRI Image analysis

Preprocessing

SPM8 was used for preprocessing and statistical modeling. During preprocessing, images were realigned and unwarped, corrected for slice timing, coregistered to anatomical scans, segmented into gray matter, white matter and CSF, and then spatially normalized into the ICBM152 MNI space. Normalized images were finally smoothed with a 3-D Gaussian filtering kernel of 8mm FWHM.

Statistical modeling

First-level analyses for each subject were conducted with a design matrix for each of the four blocks including the two visual field conditions (left/right) as conditions of interest. Missed trials were entered as a condition of non-interest to exclude any effects related to them. A high-pass temporal filter with a cutoff of 128 seconds was used to remove low-frequency noise. The hemodynamic response was modeled with the canonical hemodynamic function implemented as boxcar basis functions in SPM8.

In the first-level analysis, contrasts were computed for the four conditions**:** Left hand-left visual field (LH-LVF), Left hand-right visual field (LH-RVF), Right hand-left visual field (RH-LVF) and Right hand-right visual field (RH-RVF) vs. the fixation cross baseline. Second-level analyses were then performed to allow inferences about the population by entering the first-level contrasts for each condition in a flexible factorial model with Subject (41 levels), Group (two levels, unequal variance) and Condition (four levels, equal variance) as factors.

Contrasts were computed to isolate the activity specific to each responding hand (LH minus RH: LH-LVF and LH-RVH vs. RH-LVF and RH-RVF, RH minus LH: RH-LVF and RH-RVF vs. LH-LVF and LH-RVH) to examine within-group voxel-wise estimates of task-related activity. A critical threshold of $p < .05$, FWE-corrected and extent threshold of 50 voxels were used. Cortical activity peaks were located with SPM8 Anatomy toolbox.

Laterality index

The LI Toolbox [Wilke et al., 2007] was used to compute laterality indexes (LI) with measures of voxel count and voxel value in each hemisphere to investigate whether the groups differed in terms of the magnitude of lateralization of motor and visual brain activity. LIs were computed for two motor (BA4 and BA6) and two visual (BA17 and BA18-19) masks defined anatomically with the WFU Pickatlas [Maldjian et al., 2003] using contrasts (hand or visual field conditions) and subject-specific adaptive threshold. The outcome values range from -1 (right lateralization) to +1 (left lateralization). The LI measures were transformed to absolute values to measure the magnitude of the lateralization (and not its direction), with a score of 0 corresponding to no lateralization (equal in both hemispheres), and a score of 1 corresponding to complete lateralization.

Structure-performance relationship

Exploratory regression analysis was conducted to investigate the existence of a relationship between behavioral IH transfer time and Purdue measures and the properties of the corpus callosum and to determine whether this relationship differed between groups. A complete model was used to test the relationship between "behavioral measure", GROUP and their interactions for the various dependent variables (CC measures). Residual normality was tested with the Shapiro-Wilk test and for each model, assumptions (normality, linearity, homoscedasticity) were checked by residual analysis. Assumptions of normality, linearity and homoscedasticity were met.

RESULTS

Behavioral tasks

Poffenberger

The Poffenberger paradigm was used to investigate the speed of IH transfer of information through the corpus callosum. Repeated measures ANOVA revealed a Hand X Field interaction ($F(1,61) = 19.17$, $p<.001$), in which response times (RTs) in the uncrossed trials were faster than in the crossed trials. An independent samples t-test showed that the autistic and non-autistic group did not differ in terms of IH transfer time (IHTT) measured by the Crossed-Uncrossed Difference (CUD) (AUT: M=2.4 ms, SD=5.2, TYP: M=2.9, SD=4.2, CUD group difference: $t(61)$ =-.380 p=.705). These measures are in the normal range [1-10

ms; Marzi et al., 1991]. The median RT was also similar in each group (AUT: *M*=276.8 ms, *SD*=47.1, TYP: *M*=268.2 ms, *SD*=27.9, group difference: *t*(61)=.877, *p*=.381). When FSIQ was included in the model as a covariate, it had a significant effect on the CUD measure. However, there were still no significant differences between groups following correction for the FSIQ. The exclusion of participants with an IQ < 85 (three autistic individuals) to match FSIQ between the groups did not affect the results.

The same Hand X Field interaction was obtained in the scanner: RTs in crossed trials were slower than in the uncrossed trials (*F*(1,37)=20.13, *p*<.001). There was no Group effect but autistic individuals tended to have slower CUDs than non-autistic individuals (AUT: *M*=6.38 ms, *SD*=7.77, TYP: *M*=2.73 ms, *SD*=4.58, t-test: *t*(37)=1.802, *p*=.080). The median RT was comparable in the autistic and non-autistic group (AUT: *M*=408.9 ms, *SD*=95.4, TYP: *M*=421.85 ms, *SD*=73.3, t-test: *t*(37)=-0.478, *p*=.635). Results of the Poffenberger task performed outside the scanner are presented in Figure 4 and those performed in the scanner are shown in supplementary material (Supplementary Figure 2).

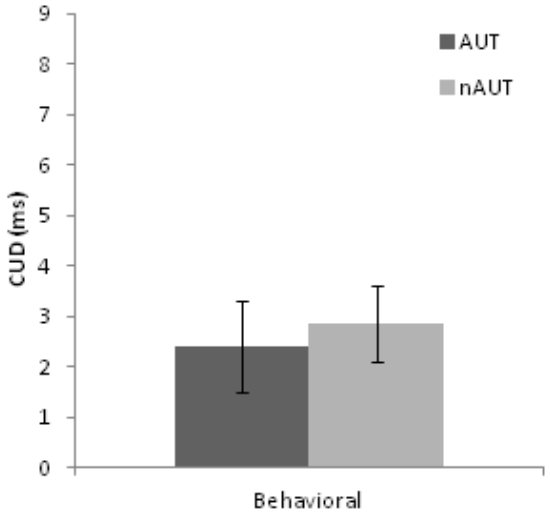

Figure 4. Results of the Crossed-Uncrossed Difference (CUD) in milliseconds (ms) for the autistic (AUT) and non-autistic (nAUT) groups measured with the Poffenberger task outside (Behavioral) the scanner.

Purdue

For the both hand and assembly conditions, autistic participants did not significantly differ from non-autistic participants. A detailed report of the performance is presented in Barbeau et al (in press).

Structural

Total brain volume did not differ between groups (p=.455). CC size differed significantly between groups (F(1,33)=3.33, p=.015). The relative CC areas (RelCC) connecting frontal (CC4-9; F(1,37)=13.11, p=.001) and parietal (CC17-21; F(1,37)=4.71, p=.036) cortical regions were significantly smaller in the autistic group than in the non-autistic group. Structural results are presented in Figure 5.

We also performed the analysis on the RelCC measures before removal of outliers to account for the large variability in CC size in the population. The results remained unchanged (F(1,40)=2.80, p=.029), and the CC in RelCC 4_9 (p=.002) and RelCC 17_21 (p=.026) regions was still larger in non-autistic than in autistic individuals.

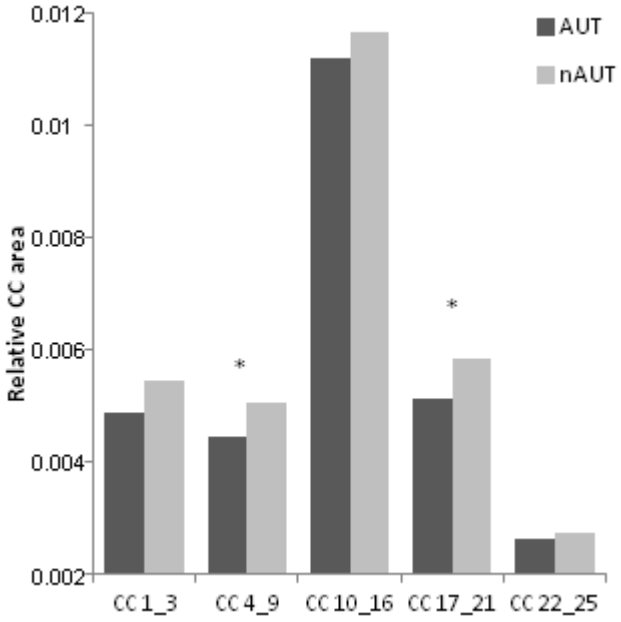

Figure 5. Relative corpus callosum area measures for the subregions 1 to 3, 4 to 9, 10 to 16, 17 to 21 and 22 to 25 displayed for the autistic (AUT) and non-autistic (TYP) group. * Group difference p<.05.

DTI

No group differences were observed for any of the diffusion metrics (FA, MD, RD, AD). See Supplementary Figure 3.

fMRI

Main effects of Hand and Visual field

In order to investigate whether the autistic individuals differed from the non-autistic individuals in terms of the brain regions associated to the visuo-motor transfer of information, they performed an fMRI version of the Poffenberger paradigm. The regions activated during the Poffenberger task were similar between the two groups and included the left and right motor, premotor and visual cortices contralateral to the corresponding hand and visual field (Table 2, Figure 6). This pattern of activation is consistent with other fMRI studies of the Poffenberger paradigm [e.g.: Martuzzi et al., 2006; Tettamanti et al., 2002] and confirm that the visual stimuli were successfully presented to either the right or left hemisphere, and that the motor response was related to the contralateral motor areas. These findings also confirm that the participants of both groups fixated adequately the center of the screen and that they carried out the requested motor response. There was no specific activation within or between groups for the Crossed conditions compared to the Uncrossed conditions. Patterns of activation were similar in both groups for the crossed conditions and the uncrossed conditions.

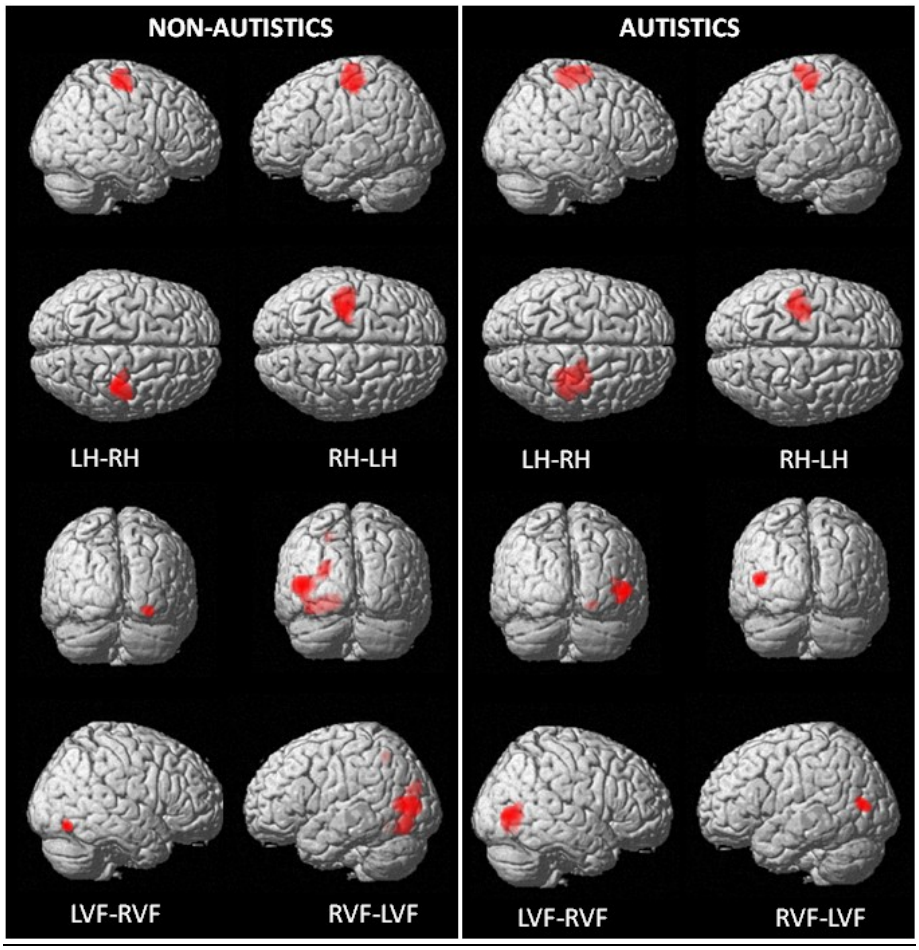

Figure 6. Within-group task-related activity patterns are displayed for the non-autistic and the autistic group computed with the following contrasts: Main effect of hands (left hand minus right hand (LH-RH), right hand minus left hand (RH-LH)), and visual field (left visual field minus right visual field (LVF-RVF), right visual field minus left visual field (RVF-LVF)). Threshold: $t = 4.96$, $p<.05$, FWE, k=50.

Group differences in task-related brain activity

The second level group analyses revealed a between-group difference: the visual and motor-related areas were more active in the non-autistic than in the autistic group (Table 2, Figure 7). No areas were more active in autistic than in non-autistic individuals. For the RH-baseline contrast, the right supplementary motor area and left precentral gyrus were less active in autistic than in non-autistic individuals. For the LH-baseline contrast, the right precentral gyrus was less active in the autistic than in non-autistic group. Overall, for both visual

contrasts (LVF and RVF), the left and right visual areas were less active in autistic than in non-autistic individuals. This group difference was mainly driven by high activity in left occipital areas related to RVF stimulation, mostly for the RH_RVF condition, which is an uncrossed condition.

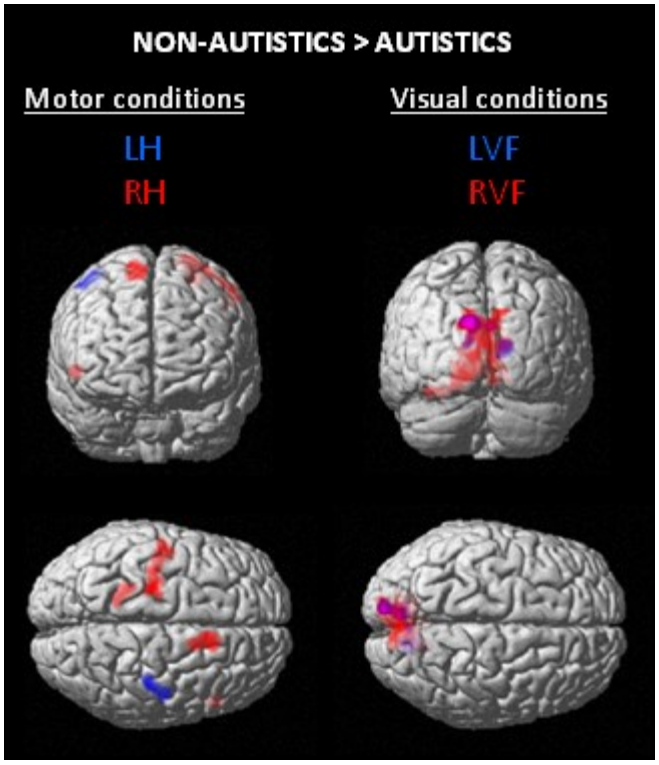

Figure 7. Group difference in task-related activity for the motor (left hand (LH) in blue, right hand (RH) in red (LVF and RVF pooled)) and visual (left visual field (LVF) in blue, right visual field (RVF) in red (LH and RH pooled)) contrasts. Areas of stronger activation in non-autistic than in autistic individuals are displayed. Threshold: $p<.05$, FWE, cluster correction k=50.

Table 2. Activity associated with the visuo-motor Poffenberger task. Main effect of hands and visual fields are displayed for each group as well as group differences.

		Left						Right					
	BA	x	y	z	*t*	*d*	*k*	x	y	z	*t*	*d*	*k*
NON-AUTISTICS													
Motor contrasts													
LH-RH													
Post and Precentral gyrus	6, 4, 3, 1							**40**	**-24**	**64**	**8.27**	**2.00**	**330**
RH-LH													
Post and precentral gyrus	6, 4, 1	**-36**	**-22**	**66**	**10.32**	**2.83**	**699**						
Visual contrasts													
LVF-RVF													
Fusiform, lingual gyrus	18							**26**	**-70**	**-12**	**6.07**	**0.53**	**82**
RVF-LVF													
Middle occipital gyrus	19	**-46**	**-74**	**8**	**9.05**	**5.30**	**1647**						
Lingual gyrus	18	-20	-76	-8	7.64	0.62							
Cuneus	19	-26	-80	20	7.44	0.81							
Superior parietal lobule	7	**-20**	**-58**	**50**	**5.81**	**0.37**	**50**						
AUTISTICS													
Motor contrasts													
LH-RH													
Post and precentral gyrus	6, 1, 4							**34**	**-24**	**70**	**8.29**	**2.39**	**643**
RH-LH													
Post and precentral gyrus	6, 4, 1, 3	**-38**	**-28**	**64**	**7.92**	**1.39**	**459**						
Visual contrasts													
LVF-RVF													
Middle occipital gyrus	19							**50**	**-66**	**2**	**7.01**	**0.63**	**460**
Middle temporal gyrus	39							42	-66	12	5.97	0.41	
Lingual gyrus	18, 19							**18**	**-76**	**12**	**5.50**	**0.08**	**73**
RVF-LVF													
Middle occipital gyrus	19	**-42**	**-74**	**10**	**6.66**	**0.57**	**144**						
NON-AUTISTICS>AUTISTICS													
RH													
Precentral gyrus	4,6	**-38**	**-22**	**64**	**7.62**	**1.55**	**328**						
Supplementary motor area	6							**10**	**18**	**64**	**7.23**	**1.22**	**152**
Inferior frontal gyrus	45							**52**	**20**	**-2**	**6.58**	**1.70**	**71**
Postcentral gyrus	5	**-18**	**-44**	**70**	**6.32**	**1.01**	**102**						
LH													
Precentral gyrus	4,6							**40**	**-26**	**62**	**7.19**	**1.03**	**123**
LVF													
Superior occipital gyrus	18,19	**-12**	**-92**	**30**	**6.48**	**1.09**	**181**						
Calcarine gyrus	17	-12	-78	14	6.20	0.52							
Calcarine gyrus	17							**16**	**-76**	**12**	**7.80**	**0.79**	**196**
Cuneus	18							14	-66	14	6.20	0.63	
RVF													
Cuneus	18,19	**-6**	**-80**	**26**	**7.68**	**0.96**	**2672**						
Cuneus	18							6	-74	24	6.96	0.92	
Lingual gyrus	18							8	-60	-2	7.00	0.63	

Group differences in the lateralization of activation

Because more bilateral activity in homologous brain areas could be indicative of a more important IH communication, the magnitude of lateralization of bilateral activations was investigated. We conducted repeated measure ANOVAs separately for the voxel count and the voxel value measures of laterality index (LI), with Group as a between factor and modality (motor: BA4, BA6, visual: BA17, BA18_19) as a within factor. There was a modality X LI X Group interaction for the voxel count measure ($F(3,30)=3.05$, $p=.043$). Task-related brain activity was more bilateral in the motor areas (mainly for the LH condition) in non-autistic participants, whereas it was more bilateral in the visual areas in the autistic participants. There was a group effect in the visual areas ($F(4,30)=2.92$, $p=.037$), mainly in the primary visual areas, where bilateral activity was higher in autistic than in non-autistic individuals.

Structure-performance relationship

We used exploratory regression analyses to investigate the existence of a relationship between the corpus callosum measurements (size and DTI properties) and the behavioral tasks and to examine whether this relationship (if any) differed between groups.

Poffenberger

Relative CC size

There was a Group X Relative CC size interaction for area 22-25 connecting the visual areas ($p=.018$). The size of the CC in these regions was associated with IHTT in the autistic group ($p=.014$), but not in the non-autistic ($p=.541$) group. IHTT and CC size in the other four regions were not significantly correlated in either group. When all RelCC data (before the removal of outliers) were included in the model, the IHTT correlated moderately with RelCC 4_9 (r=.387, $p=.083$) and RelCC 22_25 (r=.385, $p=.085$) in autistic individuals. In non-autistic individuals, the IHTT was strongly correlated with RelCC 4_9 (r=.602, $p=.004$) and moderately with RelCC 17_21 (r=.385, $p=.085$).

DTI measures

There was a Group X DTI measure interaction in the CC areas connecting the superior and middle occipital areas (FA_SO, FA_MO, RD_SO). The diffusion metrics (FA and RD) of the CC were associated with IHTT in autistic participants (a high FA was associated with a low RD and a fast IHTT) but not in non-autistic participants. No other regional CC property

was associated with IHTT. Structure-performance relationships for the Poffenberger task are presented in Table 3.

Table 3. Regression results showing the relationship between the Poffenberger CUD measure and properties of the corpus callosum. Group X CC measure interactions and within-group effects are displayed for relative corpus callosum area for subregion 22 to 25 (Rel CC 22_25) as well as for fractional anisotropy (FA) in the corpus callosum connecting the superior occipital areas (FA_SO), the middle occipitals areas (FA_MO) and the radial diffusivity for the superior occipital regions (RD_SO). There was no group effect or interaction for any other corpus callosum measure or subregion.

			Within-group effects	
	CC measure	Group X CC measure interaction	Non-autistic	Autistic
Visual	RD_SO	*R*=.373, *t*(1,35)=1.973, *p*=.056	*R*=-.035, *p*=.885	***R*=-.480, *p*=.038**
	FA_SO	*R*=.426, *t*(1,37)=1.971, *p*=.056	*R*=-.082, *p*=.725	***R*=-.543, *p*=.013**
	FA_MO	*R*=.454, *t*(1,37)=2.683, *p*=.011	*R*=.077, *p*=.739	***R*=-.580, *p*=.007**
	Rel CC 22_25	*R*=.451, *t*(1,36)=-2.475, *p*=.018	*R*=-.145, *p*=.541	***R*=.540, *p*=.014**

Purdue pegboard

There were significant Group X CC measure interactions; performance in the Purdue pegboard task was associated with the relative CC area of the posterior corpus callosum (Rel CC 22_25) in autistic participants, but was associated with the more anterior (motor) corpus callosum properties (Rel CC 4_9, AD_SMA) in non-autistic participants. The size of the CC in frontal regions was positively correlated with performance in non-autistic individuals, whereas in autistic individuals, the size of the CC in posterior areas was negatively correlated with performance. No significant associations were observed for the other regions. Structure-performance relationships for the Purdue pegboard_task are presented in Table 4. When all RelCC data were included in the model (before the removal of outliers), performance in the Purdue BH task was negatively correlated with CC size in both parietal (*p*=.035) and occipital

(p=.008) regions in autistic individuals. Performance in the Purdue As task was moderately correlated with RelCC 17_21 in non-autistic individuals (r=.399, p=.066).

Table 4. Regression results showing the relationship between the Purdue pegboard "Both hands" (BH) and "Assembly" (As) bimanual conditions and properties of the corpus callosum. Group X CC measure Interactions and within-group effects are displayed for relative corpus callosum area for subregion 4 to 9 (Rel CC 4_9), 17 to 21 (Rel CC 17_21) and 22 to 25 (Rel CC 22_25) as well as for axial diffusivity in the corpus callosum connecting the supplementary motor areas (AD_SMA). There was no group effect or interaction for any other corpus callosum measure or sub-region.

				Within-group effects	
	CC measure	Purdue	Group X CC measure Interaction	Non-autistic	Autistic
Motor	Rel CC 4_9	BH	R=.388, t(1,35)=2.09, p=.044	***R*=.405, *p*=.076**	R=.292, p=.224
		As	R=.322, t(1,35)=1.59, p=.122	***R*=.429, *p*=.059**	R=.140, p=.569
	AD_SMA	BH	R=.395, t(1,36)=1.95, p=.059	***R*=.459, *p*=.042**	R=.012, p=.960
		As	R=.451, t(1,36)=-1.38, p=.177	***R*=.558, *p*=.011**	R=.313, p=.179
Parietal	Rel CC 17_21	BH	R=.487, t(1,37)=3.09, p=.004	***R*=.381, *p*=.088**	***R*=.553, *p*=.011**
		As	R=.341, t(1,37)=1.87, p=.069	***R*=.444, *p*=.044**	R=.197, p=.405
Visual	Rel CC 22_25	BH	R=.176, t(1,37)=2.23, p=.032	R=.185, p=.423	***R*=.549, *p*=.012**
		As	R=.333, t(1,37)=1.95, p=.059	R=.170, p=.460	***R*=.433, *p*=.057**

Summary of findings

We found that behavioral IHTT and performance in bimanual tasks was similar between autistic and non-autistic people, despite the fact that the corpus callosum (CC) in subregions connecting frontal and parietal cortical areas was smaller in the autistic group. The size of the CC in subregions connecting posterior cortical regions. The primary motor areas contralateral to the hand used and the right supplementary motor area during tasks involving the right hand were less active in the autistic group than in the non-autistic group. The activity of visual areas was lower in autistic participants than in non-autistic participants during the

presentation of stimuli in either the right or left visual field. Bilateral activity was highest in the motor areas in non-autistic individuals whereas in autistic individuals, it was highest in the visual areas. Behavioral IH performance was mainly correlated with the properties of CC subregions connecting bilateral motor areas in non-autistic individuals, whereas it was associated with the properties of posterior CC regions in the autistic group. We will now discuss the implication of these findings for the understanding of interhemispheric integration in autistic people.

DISCUSSION

Behavioral performance

Contrary to our prediction, neither the CUD computed from the Poffenberger task, nor bimanual performance in the Purdue task differed between autistic and non-autistic individuals. This suggests that the basic transfer of visuo-motor information is intact in adult autistic individuals of typical intelligence. This is consistent with the conclusion of Clawson et al. [2013], who used behavioral tasks and electrophysiological recordings in motor areas to investigate interhemispheric transfer in autistic children. According to Barbeau et al. [in press], bimanual and coordination motor skills function normally in autistic individuals and motor deficits associated with autism may instead involve the speed of the execution of simple movements and response anticipation.

Structural and DTI corpus callosum measures

The CC in regions connecting the frontal and parieto-temporal areas was smaller in autistic than in non-autistic individuals, but the size of the CC in sections connecting posterior regions was normal. Consistent with our findings, a meta-analysis of MRI studies of the corpus callosum in autism [Frazier & Hardan, 2009] concluded that the CC subregions connecting the premotor and supplementary motor areas are the most affected in autism, whereas those connecting visual areas display the smallest group differences. Similarly, Lazar and colleagues [2014] found no differences in any of the DTI metrics (FA, MD, RD or AD) of the corpus callosum between adult autistic individuals of typical intelligence and a matched group of non-autistic controls. The wide age range of the participants in our study (14-38) and that of Lazar et al. (18-25), more specifically the inclusion of adults, may account for the lack

of difference between autistic and non-autistic individuals. Indeed, most studies examining the corpus callosum in autism have included younger participants [Travers et al., 2012]. According to Kleinhans et al. [2012], differences in diffusion properties of white matter between autistic and non-autistic individuals, are still present in adolescence and normalize in adulthood. This also occurs for brain volume [Amaral et al., 2008], and the symptoms of autism [Fecteau et al., 2003]. The inclusion of autistic participants of typical intelligence could thus also minimize the discrepancies between groups.

Task-related activation

There were no differences in cortical activation related to crossed or uncrossed conditions of the Poffenberger task within or between groups. A first generation of Poffenberger/fMRI studies in non-autistic populations reported a correlation between CUD and the difference of signal intensity between the crossed and the uncrossed circuits [Iacoboni & Zaidel, 2004], or superior cortical activations in the crossed condition compared to the uncrossed condition [Tettamanti et al., 2002; Weber et al., 2005]. However, four recent fMRI investigations of the Poffenberger paradigm reported that the crossed condition is not associated with specific patterns of activation [Gawryluk et al., 2009; Gawryluk et al., 2011; Martuzzi et al., 2006; Omura et al., 2004], other than the activation of white matter in the corpus callosum. However, the validity of the fMRI signal in white matter is questionable, because the low energy consumption of neurons and low blood volume and flow in white matter give rise to a weak signal [Gawryluk et al., 2009; Gawryluk et al., 2011]. Differences in signal intensity between homologous cortical regions are informative as they may reflect deficits in IH information integration [Fornari et al., 2007]. It is possible that all trials recruit a common network with bilateral activations occurring even in the uncrossed conditions [Gawryluk et al., 2009; Martuzzi et al., 2006]. This may explain the lack of significant difference in cortical BOLD signal between the crossed and uncrossed trials. Martuzzi et al [2006] also suggested that the difference in lateralization of signal strength (e.g. a stronger signal in right than in the left visual areas) could mask subtle differences specific to the crossed conditions, which include trials of both left and right VF stimulation.

We observed activation related to the main effect of the task (motor response, visual stimulation) in the left and right motor, premotor and visual cortices contralateral to the

corresponding hand and visual field in both groups. There were few group differences. The activity during the right hand movement condition in the right BA6, the area opposite to the brain area controlling the right hand, was lower in autistic than in non-autistic individuals. The activity in the left and right BA6 areas was more bilateral in non-autistic individuals whereas it was more bilateral in visual areas in autistic individuals, which may be indicative of better integration between bilateral homologous regions in non-autistic than in autistic individuals [Fornari et al., 2007].

We also observed less task-related activity in visual areas in autistic individuals. We expected the opposite result because most cognitive tasks involving visual input lead to high task-related activity in visual associative regions [Samson et al., 2012]. Autistic individuals outperform non-autistic individuals in visual tasks involving pattern manipulation but not in low-level detection tasks [Meilleur et al., 2014; Rivest et al., 2013], which may require shallower processing for detection. The comparatively low visual activity seen in autistic individuals may also be due to highly efficient perceptual processing, as observed in reasoning tasks in autistic individuals [Soulieres et al., 2009] in visuo-spatial tasks in non-autistic individuals [Ruff et al., 2003], and in highly skilled non-autistic individuals [Bernardi et al., 2013].

Modification of the typical visual motor balance contribution in visuo-motor tasks in autism

The results of the present study suggest that the balance between the visual and motor contribution to the IH transfer of visuo-motor information is modified in autism. IH transfer time was correlated with the relative corpus callosum size and diffusion properties of posterior regions in the autistic group but not in the non-autistic group. Similarly, in autistic individuals, there was a relationship between the properties of the posterior corpus callosum and performance in a visuo-motor bimanual behavioral task, the Purdue pegboard, measured outside of the scanner, whereas performance in this task was related to the properties of the corpus callosum in motor-related areas in non-autistic individuals. This suggests that the transfer of visuomotor information in non-autistic individuals involves the anterior, motor-dedicated corpus callosum, whereas in autism, its visual sections play a predominant role. In support of this interpretation, Lazar et al [2014] reported that intra-axonal diffusivity, the

volume of intra axonal water across the corpus callosum and extra-axonal diffusivity localized in the anterior corpus callosum were all lower in autistic than in non-autistic individuals. Moreover, performance in the Digit Symbol Coding test, a task that involves motor and visual functions as well as interhemispheric integration (Zaidel et Iacoboni, 2003), was correlated with the microstructural properties of the visual and temporal tracts in autistic individuals whereas it was related to the properties of the motor tracts in non-autistic individuals.

Several studies have used variations of the Poffenberger paradigm, e.g. manipulation of visual (luminance, eccentricity) and motor (position of hand/arm) parameters to identify components affecting CUD and examine whether visuo-motor information crosses the corpus callosum at the motor (anterior) or visual (posterior) level. These studies, as well as partial lesions studies, have indicated that normal transfer takes place at the pre-motor level [Berlucchi et al., 1971; Clarke et al., 1989; Corballis et al., 2002; Tettamanti et al., 2002; Zaidel et al., 2003]. Lesions of the anterior corpus callosum sparing the splenium (posterior) cause abnormally long CUDs [Iacoboni et al., 1995; Marzi et al., 2003]. However, long CUDs are also associated with posterior lesions [Marzi et al., 2003], and individuals with lesions of the corpus callosum (either anterior or posterior) may have normal CUDs [Berlucchi et al., 1995]. These observations support the horse race model [Bisiacchi et al., 1994], in which visuo-motor information is transferred at both the pre-motor *and* visual level. The CUD would reflect the "winning", quickest, trans-callosal transfer which triggers the motor response. The fiber composition of the corpus callosum may support faster transfer through the motor fibers than through the visual fibers. The subregion connecting the sensori-motor cortical regions is composed of axons that are more myelinated and have a larger diameter [Aboitiz et al., 2003] than the axons connecting the visual cortices, which are longer [Lewis et al., 2009]. Thus, conduction should be faster along motor fibers than along visual fibers. Moreover, in non-autistic individuals, microstructural properties [diffusivity and FA; Schulte et al., 2005] and size [Schulte et al., 2004] of the anterior corpus callosum (genu) correlates with the CUD.

The relationship between the properties of the anterior corpus callosum and bimanual performance in non-autistic individuals is consistent with previous reports of (1) the relationship between the coordination of bimanual skills and corpus callosum integrity in the regions connecting the supplementary motor areas [Johansen-Berg et al., 2007]; and (2) the

relationship between corpus callosum size and fMRI activation of the cortical motor areas during a bimanual coordination task [Stancak et al., 2003].

Plastic reorganization in autism

Autistic individuals performed well in tasks relying on IH transfer, despite the presence of a below average corpus callosum area and atypical task-related activation. This indicates that the association of structure and activation with performance may be atypical, at least in the absence of a demonstrated correlation between the two series of variables. Clawson et al [2013] proposed that the performance of autistic individuals is normal in tasks involving IH transfer, despite anatomical alterations in the corpus callosum, due to the use of alternative neuronal pathways. Consistent with this view, we found that visual interhemispheric transfer plays an important role in visuo-motor tasks in autistic individuals. This observation also provides another example of the now well established enhanced role of perception in autistic cognitive architecture [see Mottron et al., 2014; Mottron et al., 2013 for recent reviews].

The modification of typical structure-function relationships in individuals showing a normal level of performance in several visuo-spatial, intelligence and language tasks is consistent with the reallocation and extension of the role played by associative perceptual regions in such tasks. Cortical allocation in visual and motor regions displays high variability in autistic individuals [Poulin-Lord et al., 2014]. A recent activation likelihood estimation (ALE) meta-analysis revealed topographical extension and reallocation of activity in visual associative regions during the completion of complex tasks involving visually presented material, [Samson et al., 2012]. For instance, a greater role of visual brain areas was observed in various cognitive tasks of non-perceptual nature such as reasoning [Soulieres et al., 2009] and language processing [Shen et al., 2012] tasks. Structural alterations of corpus callosum, as well as of typical-task related brain activity do not affect simple behavioral interhemispheric visuo-motor performance, because performance may be dependent on alternative regions in autistic people, mainly perceptive regions.

Acknowledgments

This work was supported by an operating grant from the Canadian Institutes of Health Research (CIHR, No. MOP-84243) to L. Mottron, and scholarship from the CIHR to E.B. Barbeau. The authors want to thank the participants for their invaluable contribution to this project. The authors report no potential conflicts of interest.

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SUPPLEMENTARY MATERIAL

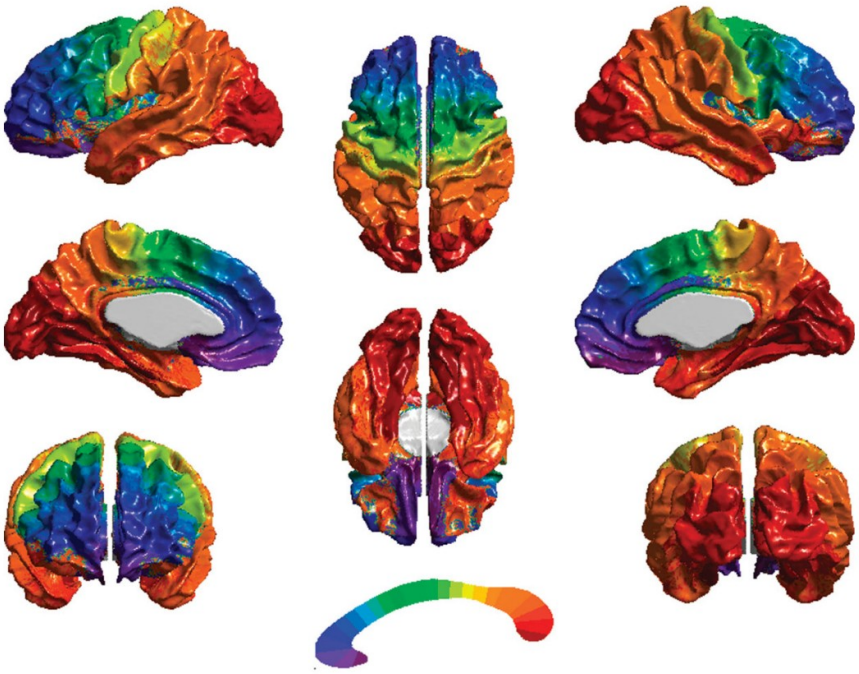

Figure Supp 1. Mapping of surface vertices to the 25 CC subregions with colors corresponding to the CC subregion at which tracts originating from each vertex most often terminated across all subjects. From Lewis et al. 2013 with permission.

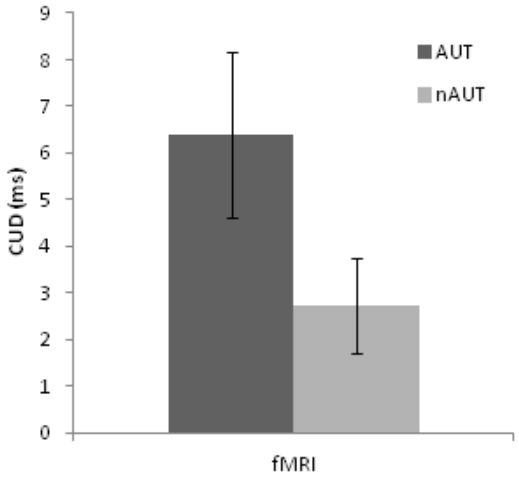

Figure Supp 2. Results of the Crossed-Uncrossed Difference (CUD) in milliseconds (ms) for the Autistic (AUT) and non-autistic (nAUT) groups measured with the Poffenberger task inside (fMRI) the scanner.

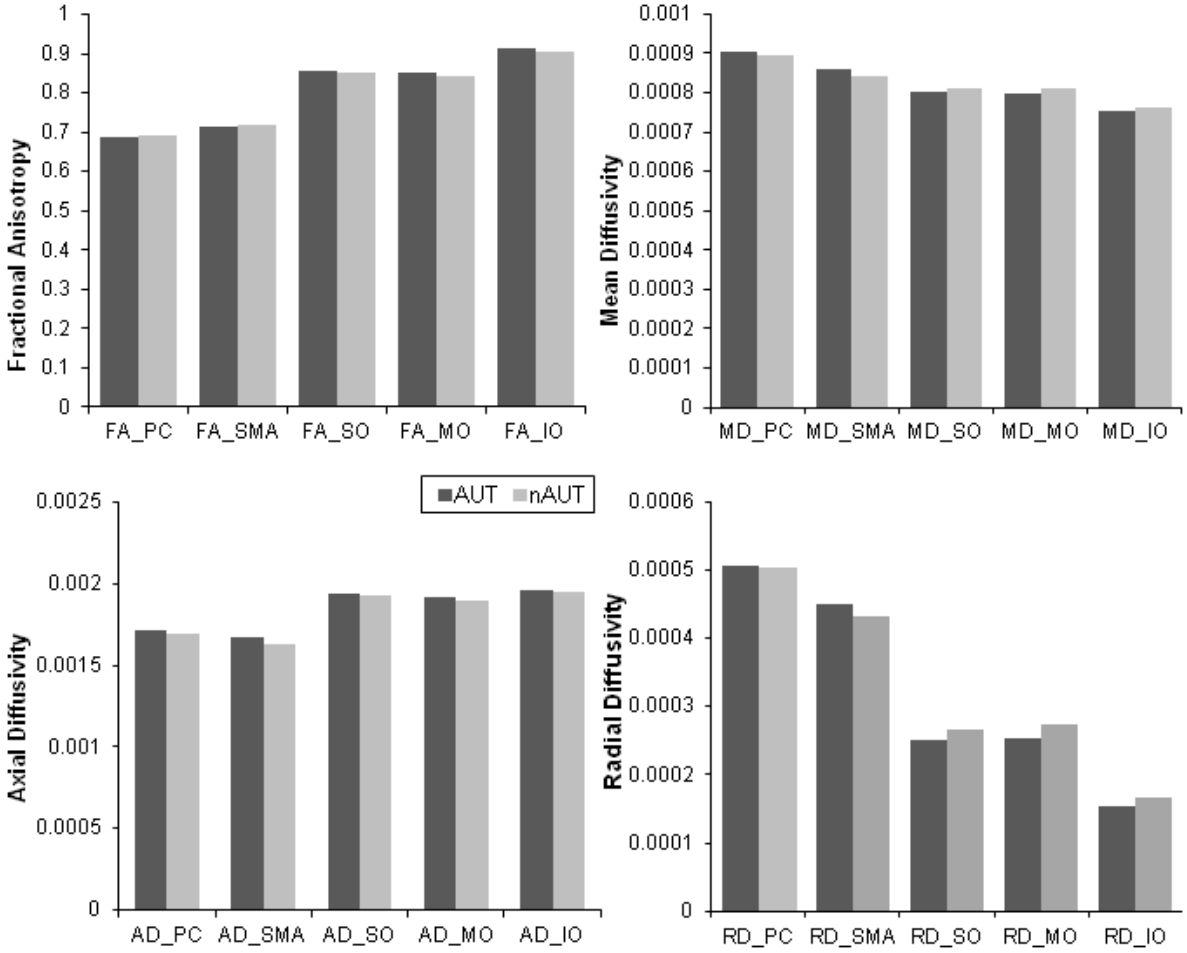

Figure Supp 3. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) for the regions of interest of the corpus callosum connecting the bilateral pre-central (PC), supplementary motor (SMA), superior occipital (SO), middle occipital (MO) and inferior occipital (IO) cortical areas. Values are displayed for the autistic (AUT) and non-autistic (nAUT) groups.

Chapitre 3. Article 2: The level and nature of autistic intelligence III: Inspection time

The level and nature of autistic intelligence III: Inspection time

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Author Note

This work was supported by a Canadian Institutes for Health Research grant to L.M. and a doctoral award to E.B.B.

Abstract

Across the autism spectrum, level of intelligence is highly dependent on the psychometric instrument used for assessment, and there are conflicting views concerning which measures best estimate autistic cognitive abilities. Inspection time is a processing speed measure associated with general intelligence in typical individuals. We therefore investigated autism spectrum performance on inspection time in relation to two different general intelligence tests. Autism spectrum individuals were divided into autistic and Asperger subgroups according to speech development history. Compared to a typical control group, mean inspection time for the autistic but not the Asperger subgroup was significantly shorter (by 31 %). However, the shorter mean autistic inspection time was evident only when groups were matched on Wechsler IQ, and disappeared when they were matched using Raven's Progressive Matrices. When autism spectrum abilities are compared to typical abilities, results may be influenced by speech development history as well as by the instrument used for intelligence matching.

Keywords: Autism, Asperger syndrome, Perception, processing speed, Raven Progressive Matrices

The observation that intelligence in autism is atypical dates back to its earliest descriptions (Asperger, 1944/1991; Kanner, 1943), with early empirical studies reporting uneven autistic performance both within (Rutter, 1966) and across (Bartak, Rutter, & Cox, 1975) commonly used intelligence tests. It is now well-established that intelligence estimates in autism vary with the instrument used for assessment (e.g., Magiati & Howlin, 2001; Mottron, 2004), but opinions conflict concerning which measurement tool is most accurate. Moreover, general intelligence estimates based on constructs established using typical samples may not be wholly appropriate for autism spectrum individuals, whose neurodevelopmental histories and cognitive architecture are markedly atypical. These issues have obvious implications for determining both the prevalence of intellectual disability in autism and the detailed nature of the autistic cognitive phenotype. As autistic abilities are routinely assessed using comparisons with intelligence-matched controls, the choice of an appropriate intelligence measure is a crucial procedural decision.

General intelligence in autism is commonly estimated with Wechsler intelligence scales, which combine scores from an evolving battery of subtests to estimate full-scale IQ (FSIQ). The third versions of the test (WISC-III, WAIS-III; Wechsler, 1991, 1997) include a verbal IQ (VIQ) estimate derived from subtests requiring both verbal comprehension and production, as well as a performance IQ (PIQ) derived from largely non-verbal subtests that nonetheless depend on verbal instructions. Wechsler tests are normed such that typical individuals will tend to achieve similar scores, and thus an even cognitive profile, for FSIQ, PIQ, and VIQ estimates. However, autism spectrum individuals exhibit large variations among the Wechsler subtests, which produce different uneven profiles in subgroups divided according to speech development history (Soulieres, Dawson, Gernsbacher, & Mottron, 2011). Asperger individuals, whose diagnostic definition requires non-delayed speech development, show strengths in verbal subtests such as Vocabulary and Information. Autistics, who present with delays and anomalies in speech development, are characterized by good perceptual and visuospatial skills and show a relative peak in the performance subtest Block Design. Overall it remains unclear which Wechsler subtest scores, or combinations thereof, best estimate intelligence in autism spectrum individuals.

An alternative strategy for estimating general intelligence employs Raven's Progressive Matrices (RPM; Raven, Raven, & Court, 1998), a widely used test of reasoning ability which requires no verbal responses and minimizes the need for verbal instructions. RPM presents novel problems in a uniform visual format consisting of a matrix of visual patterns which must be solved by locating the missing piece from among several provided choices. Items progress from relatively easy perceptual problems to very difficult analytic problems that necessitate rule inference and integration, management of goal hierarchies, and high-level abstraction (Carpenter, Just, & Shell, 1990). In typical individuals, RPM and Wechsler provide comparable intelligence estimates. However, in autism spectrum individuals, RPM performance may be significantly or sometimes dramatically superior, and at a group level may also reflect their highest, rather than their mean or worst, Wechsler subtest scores (Bolte, Dziobek, & Poustka, 2009; Charman et al., 2011; Dawson, Soulieres, Gernsbacher, & Mottron, 2007; Hayashi, Kato, Igarashi, & Kashima, 2008; Soulieres et al., 2011). The high correlation between autism spectrum and typical individuals' item-by-item RPM performance (Dawson et al., 2007; Morsanyi & Holyoak, 2010; Soulieres et al., 2011) implies that inasmuch as RPM measures general intelligence in the typical population (Neisser, 1998), it also does so in autism spectrum individuals.

Another potential avenue for investigating autism spectrum intelligence is the use of elementary cognitive tasks known to be associated with general intelligence in the typical population. One candidate is Inspection time (IT), a task providing estimates of perceptual processing speed or information processing efficiency (Deary et al., 2004; Waiter et al., 2008). Visual IT tasks use a psychophysical staircase procedure to measure the minimum stimulus exposure required to accurately perceive which of two vertical lines, presented in a Pi-like configuration (Figure 1), is longer. Shorter IT is associated with higher intelligence in typical individuals (Sheppard & Vernon, 2008). Two meta-analyses (Grudnik & Kranzler, 2001; Kranzler & Jensen, 1989) support the finding that general intelligence measures and IT are negatively correlated ($r \approx -.50$ after corrections for sampling error, attenuation, and range restriction; but see Mackintosh, 2011 for a critical review).

IT-intelligence associations have been observed in typical samples using various instruments, including RPM (Hill et al., 2011) and Wechsler. Evidence suggests that within Wechsler, the correlation may be stronger with PIQ (Deary, 1996; Nettelbeck & Lally, 1976),

which may result from mandatory involvement of perceptual processing speed in PIQ subtests, or from processing speed and PIQ being modulated by variations of the same underlying source. This source could be at any level from focused attention, response selection, or response monitoring (Hill et al., 2011; Nettelbeck, 2001); to ion channel density, or speed of synaptic transmission; to similar gene ensemble influences (Luciano et al., 2005; Sheppard & Vernon, 2008); to combinations of these. In common with RPM, IT does not require verbal comprehension or expression. However, IT is an elementary task, free of the type of problem-solving associated with the complex high-level demands of RPM. Thus, with its link to typical general intelligence, IT represents an additional and independent avenue for investigating approaches to measuring general intelligence in the autism spectrum.

Two prior studies have investigated IT in autism spectrum participants. Scheuffgen et al. (2000) found that autism spectrum IT performance was significantly better than predicted by Wechsler scores: IT performance did not differ in 29 typical (mean FSIQ = 118.1) and 18 autism spectrum (15 autistic, three Asperger; mean FSIQ=82.8) children, as well as in a subgroup of ten low-FSIQ (mean = 68.0) autistic children. In a related study, IT did not differ between autism spectrum (autistic and Asperger individuals) and non-spectrum children matched on FSIQ. As expected, IT was negatively correlated with FSIQ in the controls, but not in autism spectrum children. However, an autism spectrum subgroup with FSIQ under 100 exhibited 11% shorter IT compared to FSIQ-matched controls (Wallace, Anderson, & Happe, 2009). These two studies, and a case study of an Asperger savant (Wallace, Happe, & Giedd, 2009), failed to support the notion that lower Wechsler IQ scores in autism spectrum individuals can be explained by differences in information processing speed or efficiency. Two other case studies of autistic savants (Anderson, O'Connor, & Hermelin, 1998; Young & Nettelbeck, 1995) found both IT and RPM results superior to what would be predicted from performance on Wechsler or other instruments, including the Columbia Mental Maturity Scale.

In this study, we tested typical and autism spectrum groups using Wechsler IQ, RPM, and IT. Our goal was to compare IT between autism spectrum and typical groups, but also to examine how IT relates to intelligence in the subgroups, and to determine whether earliness of speech development is related to intelligence and IT. From previous findings, we expected the

autistic subgroup to outperform Wechsler IQ-matched controls on RPM and IT. If speech delays, perceptual strengths, and an enhanced role for perception in solving RPM (Soulieres et al., 2009) aggregate in autistics, the strongest association between IT and RPM should be found in this subgroup. Conversely, if non-delayed speech, verbal strengths, and an enhanced role for verbal abilities in RPM performance aggregate in Asperger individuals, their early speech development, rather than their IT, should be related to their RPM performance.

Methods

Participants

Participants were randomly recruited from the research database of the Autism Specialized Clinic at Rivière-des-Prairies Hospital (Montreal, Canada). Inclusion criteria were minimum age 14 and Wechsler FSIQ over 75, while exclusion criteria were uncorrected visual impairment and use of illegal drugs or of alcohol exceeding two drinks per day. The final sample included 42 autism spectrum and 30 typical individuals. Two Asperger participants took antidepressants (paroxetine and venlaflaxine), one a sleep medication (fluorazepam), and three a stimulant (methylphenidate). None of the autism spectrum participants had known brain lesions or co-occurring genetic, neurological or DSM-IV Axis 1 psychiatric conditions other than hyperactivity and language disorders. Typical comparison participants were screened through a questionnaire for personal or familial neurological, psychiatric or medical conditions known to affect brain function. All participants gave written informed consent and were compensated for their participation.

Diagnostic procedures. Most autism spectrum participants were characterized using the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule modules 3 or 4 (ADOS-G; Lord et al., 2000), combined with expert interdisciplinary clinical assessment. However, some participants were characterized using expert interdisciplinary judgment only (one participant) or combined with ADOS-G (four participants) or ADI-R (six participants).

Subgrouping. To test the hypothesis that autism spectrum cognitive profile differences vary with speech development history, the autism spectrum participants were divided into Asperger and autistic subgroups, based on ADI-R questions: (1) age of first words (#9), (2) age of first phrases (#10), with both measures also available for participants diagnosed without

the ADI-R, (3) stereotyped phrases (#33), (4) pronoun reversal (#37), and (5) immediate echolalia (question #17 from the previous ADI version, added here to the ADI-R). We use the term *Asperger* for individuals without speech onset delay for words (<24 months) or phrases (<33 months). The term *autistic* refers to participants with speech onset delay and/or any speech atypicalities including immediate echolalia, stereotyped phrases, or pronoun reversal. Seven participants were excluded because they could not be subgrouped unambiguously, because their clinical diagnosis was inconsistent with our speech atypicality classification criteria, or because we did not have a speech onset history. The final subgroups included 18 autistic and 17 Asperger participants, all of whom met the strict ADI-R threshold for autism diagnosis. Autistic, Asperger and typical groups did not differ significantly in Wechsler FSIQ (p=.720), VIQ (p=.245), and PIQ (p=.263; Table 1). At the subtest level, a Block Design peak (1.5 standard deviation above the average of all subtests; Caron, Mottron, Berthiaume, & Dawson, 2006) was observed in the autistic group. In the Asperger group, the highest scores were observed for Information, Similarities, and Vocabulary subtests.

Matching strategies. Group matching on Wechsler FSIQ resulted in a significant between-group difference in RPM raw scores (p=.042, d=.64; the same result was found with RPM percentiles, p=.037, d= .66, and percentile-derived standard scores, p=.013, d= .70). Both autistic and Asperger subgroups had higher RPM scores compared to the typical group (p respectively .050 (d=.59) and .028 (d=.70)). To explore the effect of using RPM score as an alternative matching variable, a subsample of the initial Wechsler-matched comparison group was selected by removing typical individuals with lower RPM scores, producing an RPM-matched comparison group. The two autism spectrum subgroups and the RPM-matched comparison group did not differ in FSIQ (p=.448), PIQ (p=.188), VIQ (p=.187), or RPM raw scores(p=.685).

Table 1. Participant characteristics

	Autism Spectrum			Typical		*p*		
						Autism Spectrum	Autistic, Asperger	
	Total	Autistic	Asperger	Total	RPM matched	vs. TYP_T	vs. TYP_T	vs. TYP_{RPM}
n	42 (38M:4F)	18 (16M:2F)	17 (15M:2F)	30 (26M:4F)	21 (18M:3F)			
Age (*SD*)	22.8 (5.9)	23.4 (5.8)	20.4 (5.0)	20.3 (4.6)	20.8 (5.0)	.059	.116	.243
Range	14-37	15-34	14-30	14-35	14-35			
FSIQ (*SD*)	102.9 (13.3)	102.4 (14.4)	102.6 (11.9)	105.0 (10.9)	106.8 (10.0)	.769	.720	.448
Range	78-129	78-126	86-129	80-121	87-121			
PIQ (*SD*)	100.9 (11.8)	103.5 (10.8)	97.0 (11.9)	101.8 (13.2)	103.0 (11.9)	.488	.263	.188
Range	75-126	77-118	75-126	72-122	82-122			
VIQ (*SD*)	104.8 (14.7)	102.2 (17.4)	107.6 (11.5)	108.6 (10.4)	110.0 (10.0)	.231	.245	.187
Range	72-134	72-128	94-134	91-127	92-127			
RPM raw (*SD*)	50.3 (6.2)	50.2 (6.7)	50.8 (6.3)	46.5 (5.9)	49.2 (3.9)	.011	.042	.685
Range	36-60	37-60	36-58	31-57	41-57			
Laterality	31R:4L	17R:1L	14R:3L	21R:9L	14R:7L			

Note. Significance level of between-group differences displayed for three different ANOVASs: autism spectrum versus total typical group; autistic versus Asperger versus total typical group; autistic versus Asperger versus RPM-matched typical group. TYP_T: total typical group. TYP_{RPM}: RPM-matched typical group.

Stimuli and procedure

The participants were seated in a quiet, dimly-lit room, surrounded by black wooden panels, with an opening for the screen. A chin-rest 73 cm from the screen minimized head movement. The stimuli were presented with *E-prime* on a 19" monitor using a 120Hz refresh rate. Monitor luminance was checked with a photometer using a gray image before each session to minimize luminance differences across participants (M=17.7 cd/m^2, SD=1.3).

Together with stimulus examples, the following instructions were read to the participants: "Two vertical lines of different length will be briefly presented on the screen; the lines will immediately be masked so that you can't see the difference in length anymore and then will disappear. Your task is to indicate which of the two lines was the longest before the appearance of the mask by pressing the left or right button on the response box." Accuracy was stressed rather than response speed. Each trial began with a central fixation cross presented for 1 s, followed by a blank screen lasting 100 ms. The inspection time stimulus was then displayed for a variable duration of 10-200 ms and immediately masked for 300 ms by two lines shaped as lightning bolts (48mm long or 3.76 degrees of visual angle). The two stimulus vertical lines were 2.35 (30mm) and 2.75 (35mm) degrees in length. The inter-trial interval was 750ms (Figure 1).

Stimulus duration was varied using a staircase procedure, with exposure time decreasing following four consecutive correct responses, and increasing after each incorrect response. The first two reversals were 32ms, the following two reversals were 16ms steps, and the remaining reversals were 8ms steps. The run ended after 15 reversals or a maximum of 96 trials. After 12 practice trials, three runs were collected for each participant.

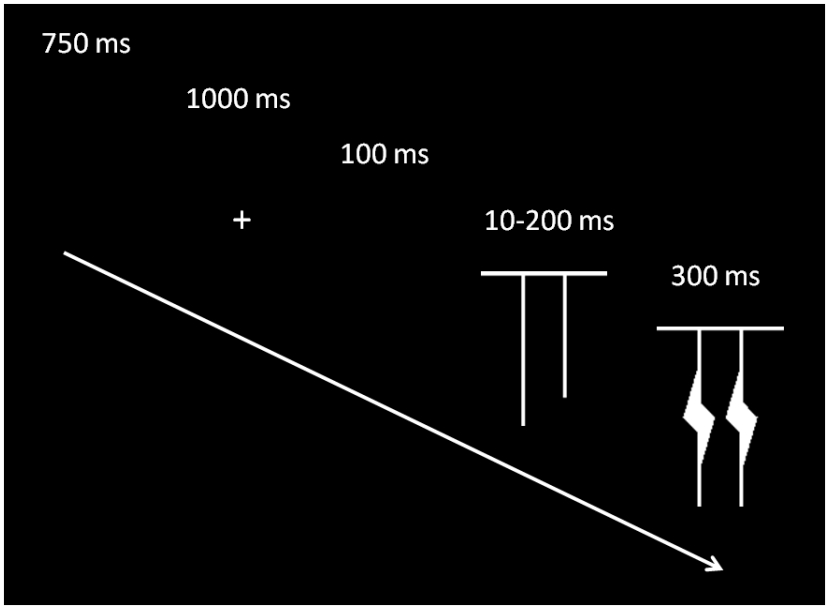

Figure 1. One trial in the Inspection Time task. A fixation cross is presented followed by a blank interval and by the stimulus which is replaced by a visual mask after 10-200 ms.

Statistical Analysis

43 autism spectrum and 32 typical participants were tested. All three runs from one autism spectrum and two typical participants were excluded from further analysis because they exhibited extremely long stimulus durations (250 ms and over, corresponding to 2 *SD* or more from the mean), likely resulting from inattention and response key errors affecting the staircase procedure. Eight additional runs in the autism spectrum and five in the typical group were excluded for the same reason.

We employed a mixed effects model with GROUP as a between-subjects factor and SUBJECT as a random factor, using the *lme* module of R, version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria). For each run, detection threshold was determined by averaging the last three stimulus durations obtained with the psychometric staircase. We compared the autism spectrum group (n=42) to the Wechsler-matched typical group (n=30). Then we investigated subgrouping effects by comparing the autistic (n=18), Asperger (n=17), and typical (n=30) groups. Lastly we compared the autistic and Asperger subgroups to the RPM-matched typical subgroup (n=21).

To investigate the association between IT and other intelligence measures, we conducted regression analyses using RPM percentiles, PIQ, VIQ and FSIQ as dependent variables, exploring effects of IT, GROUP and the IT x GROUP interaction. Interactions clearly not significant (p>.25) were removed from the model. Residual normality was tested with the Shapiro-Wilk Test. We also used regression analyses to investigate whether age of first phrases predicted IT, RPM or Wechsler performance. Since RPM percentile scores are not normally distributed, RPM regressions were also run using Z-transformed percentile scores, yielding similar results.

Results

Inspection Time

Inspection time, the minimal stimulus presentation time allowing detection of the line length difference, did not differ between the autism spectrum (M=100.5ms, SD=38.7) and the FSIQ-matched typical groups (M=114.4ms, SD=45.7; t=1.36, p=.177, Figure 2a). However, the autistic subgroup exhibited a 31.3% shorter IT (M=87.1 ms, SD=31.9) compared to the FSIQ-matched typical group (M=114.4ms, SD=45.7; t=2.25 p=.028, Figure 2b). In contrast, the Asperger subgroup (M=109.7ms, SD=40.0) did not differ from the typical group (p=.73), and had ITs 25.9% longer than the autistic subgroup's (t=1.69; p=.097). Finally, the autistic subgroup's advantage over the typical group disappeared when groups were matched on RPM (typical M=104.0 ms, SD=35.2; group difference t=1.53, p=0.132) and the Asperger subgroup versus typical group difference remained non-significant (p=.635).

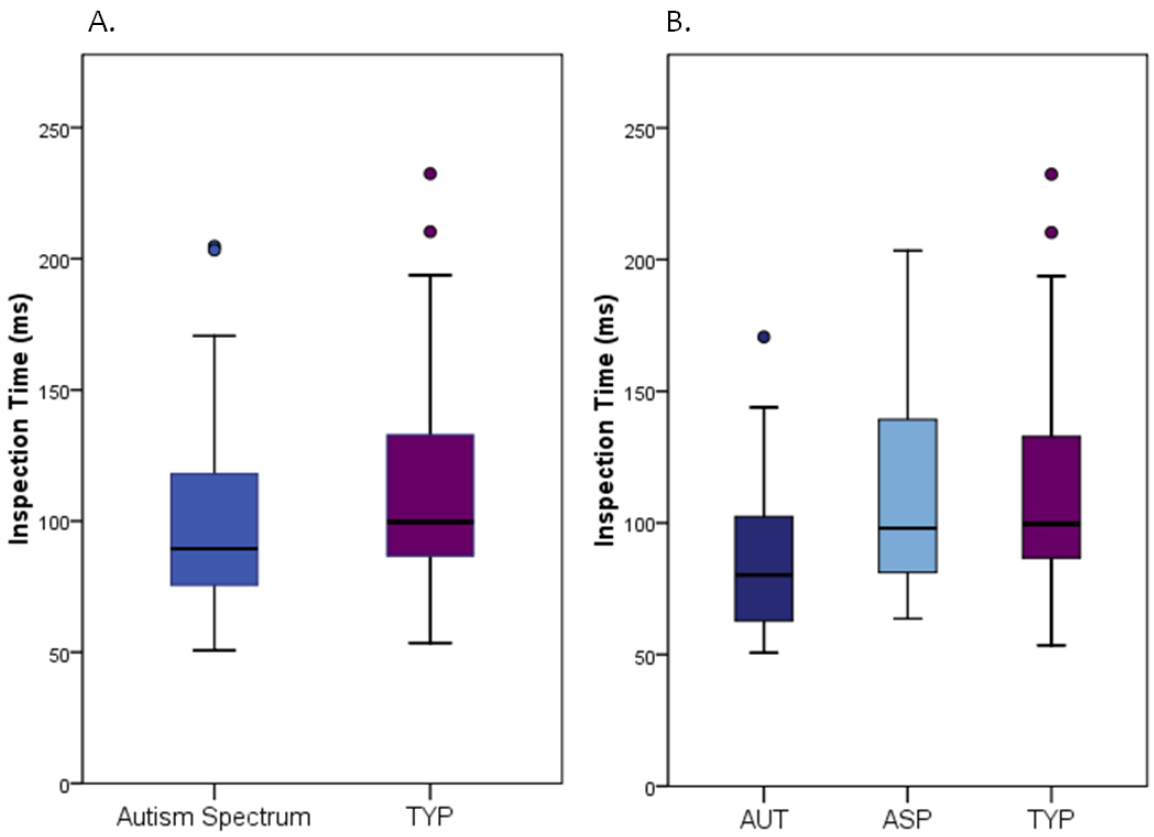

Figure 2. Inspection time distribution for A) autism spectrum (n = 42) and typical (n = 30) groups; B) autistic (n = 18), Asperger (n = 17) and typical (n = 30) groups. Error bars represent 1.5 standard deviation.

Exploratory regression analyses

Using FSIQ-matched groups, IT predicted RPM for the autism spectrum group (Percentiles: R^2=.300, t(1,32)=-3.707, p=.001; standard scores: R^2=.272, t(1,32)=-3.455, p=.002) and the IT x GROUP interaction was not significant (R^2=.381, ΔR^2=.080, t(1,34)=2.005, p=.054). Examining simple main effects, we observed that IT predicted RPM in the autistic subgroup (R^2=.647, p<.001) but not in the Asperger subgroup (R^2=.117, p=.178). IT also predicted 28% of the RPM variance in the controls (p=.003).

While IT did not predict FSIQ or VIQ in any group, IT did predict PIQ for the autism spectrum group (R^2=.229, t(1,32)=-2.487, p=.018) but the between-group effects were not significant (R^2=.231, ΔR^2= .002, t(1,34)=.271, p=.789).

We also examined whether, within the autism spectrum subgroups, Age of First Phrases predicted RPM or IT. For RPM, we found a between-group effect (R^2=.158,

ΔR^2=.151, t(1,34)=-2.357, p=.025). Earlier Age of First Phrases predicted better RPM in the Asperger (R^2=.310, p=.020) but not in the autism subgroup (R^2=.003, p=.818). Earlier Age of First Phrases also predicted better PIQ in the Asperger group only (Interaction: R^2=.229, ΔR^2=.155, t(1,31)=-2.432, p=.021; Asperger: R^2=.295, p=.024; autism: R^2=.013, p=.655. Age of First Phrases did not significantly predict VIQ or IT.

Discussion

Compared with a Wechsler IQ-matched typical group, the autistic group's visual IT was significantly shorter, a processing speed advantage which vanished when RPM was used for group matching. In contrast, Asperger and typical groups did not significantly differ in IT performance, whatever matching instrument was used. For autistics, shorter IT was associated with higher RPM scores, which was not the case for Asperger individuals. Conversely, earlier phrase speech onset was associated with higher RPM and PIQ scores in Asperger individuals but not in autistics. Our results, from adolescents and adults with Wechsler FSIQ over 75, add to existing findings of autism spectrum strengths in RPM (e.g., Charman et al., 2011) and again suggest that Wechsler IQ underestimates general intelligence in this population. Indeed, only when their general intelligence was underestimated using Wechsler IQ did the autistic subgroup show a significant IT advantage.

Our results confirm previous autism spectrum IT findings (e.g., Scheuffgen et al., 2000; Wallace, Anderson, et al., 2009) but allow a more nuanced interpretation. Groups consisting primarily of autistics should perform better on IT than their Wechsler FSIQ scores predict, an effect which may be obscured when autistic and Asperger groups are combined. Thus, in interpreting autism spectrum IT results, subgrouping according to speech development history is important, with differential effects depending on the general intelligence measure used to form comparison groups.

Autistics display atypical visual behavior starting very early in development (Ozonoff et al., 2008), including a preference for complex dynamic patterns (Pierce, Conant, Hazin, Stoner, & Desmond, 2011) and atypically short fixations in visual search (Kaldy, Kraper, Carter, & Blaser, 2011). These behaviors may represent early overt manifestations of IT-related perceptual strengths, phenomena of interest with respect to assessing intelligence in autistic infants, toddlers, and preschool children who have no speech. An early ecological

equivalent of short inspection time in the form of fast information capture, perhaps reflected in the frequently observed fast lateral gazes to objects and faces (Kaldy et al., 2011; Mottron et al., 2007), could be a more useful predictor of autistic cognitive abilities than commonly used developmental measures. IT is only a predictor and not a measure of general intelligence, and thus cannot directly substitute for RPM. However, the simplicity of the IT protocol could give it an important role in early estimation of autistic cognitive potential, in situations where no version of RPM can be used.

Collectively, our findings also further the notion of cognitive versatility across the autism spectrum, as reflected in RPM performance with respect to task (each item can be solved in multiple ways), processing approach (local or global or both, strategic or non-strategic; Caron et al., 2006), and use of perceptual or verbal information (autistic or Asperger). An atypical autonomy among levels and scales of processing in autism spectrum individuals could produce disadvantages in tasks which rigidly require typical processing hierarchies and therefore depend on cognitive similarity to the typical population. Such tasks are characterized by relatively inflexible alternatives with respect to *how* they must be performed. In contrast, RPM problems can be solved via a multiplicity of approaches, with no requirement that solutions be reached in a typical way (Plaisted, Bell, & Mackintosh, 2011). This fact strongly suggests the kinds of contexts in which autism spectrum individuals may best use their atypical abilities.

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Chapitre 4. Article 3: Comparing motor skills in autism spectrum individuals with and without speech delay

Comparing Motor Skills in Autism Spectrum Individuals with and without Speech Delay

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Scientific Abstract

Movement atypicalities in speed, coordination, posture, and gait have been observed in persons across the autism spectrum (AS) and atypicalities in coordination are more commonly observed in AS individuals without delayed speech (DSM-IV Asperger syndrome) than in those with atypical or delayed speech. However, few studies have provided quantitative data to support these mostly clinical observations. Here, we compared perceptual and motor performance between 30 typically developing, 21 AS with speech delay and 18 AS individuals without speech delay to examine the associations between limb movement control and atypical speech development. Groups were matched for age, intelligence and sex. The experimental tasks included: Inspection Time, which measures visual processing speed; the Purdue Pegboard, which measures finger dexterity, bimanual performance and hand-eye coordination; the Annett Peg Moving Task, which measures unimanual goal-directed arm movement; and simple reaction time.

We used analysis of covariance to investigate group differences in task performance and linear regression models to explore potential associations between intelligence, language skills, simple reaction time, and visually-guided movement performance. AS participants without speech delay performed slower than typical participants in the Purdue Pegboard subtests. AS participants without speech delay showed poorer bimanual coordination than those with speech delay. Visual processing speed was slightly faster in both AS groups than in the typical group. Altogether, these results suggest that AS individuals with and without speech delay differ in visually-guided and visually triggered behavior, and show that early language skills are associated with slower movement in simple and complex motor skills tasks.

Keywords: Asperger syndrome, motor skills, motor control, coordination, language delay

Introduction

Movement atypicalities are commonly observed in individuals across the autism spectrum (AS). Although they are not included in the DSM-IV [APA, 1994] diagnostic criteria, the Autism Diagnostic Interview [ADI; Lord et al., 1994], includes questions about motor skills, such as gait, posture, and coordination. DSM-5 [APA, 2013] lists developmental motor or coordination disorders as possibly associated but independent, conditions.

AS has been associated with a range of movement difficulties, including atypical coordination, posture, and voluntary movement speed [Dziuk et al., 2007; Mostofsky et al., 2007; Rinehart et al., 2001]. Mechanisms accounting for these difficulties may include problems with movement planning [Forti et al., 2011; Hughes, 1996], movement anticipation [Brisson et al., 2012], movement preparation and initiation [Glazebrook et al., 2006; Rinehart et al., 2006; Rinehart et al., 2001] and feed-forward control mechanisms [Stoit et al., 2013]. Atypical perceptual processing is a frequently suggested cause for the movement atypicalities associated with autism [Fournier et al., 2010; Whyatt et al., 2012], because it can affect perceptual input and visual-motor integration [Dowd et al., 2011; Linkenauger et al., 2012; Mayes et al., 2007]. When describing altered motor behavior in autism, Gowen and Hamilton [2013] concluded that the "basic motor machinery", including motor learning and motor adaptation, was intact in autism. Instead, they propose that motor problems in AS involve perceptual inputs, and are related to poor higher order sensorimotor integration, resulting in the slow planning of movements.

Moreover, it is unclear whether movement atypicalities are uniformly distributed across the entire autism spectrum, and how the recently introduced clinical DSM-5 specifiers of intelligence, associated conditions, language level, and severity, are related to motor performance. One of the most frequently reported factors influencing the presence and nature of motor atypicalities in AS is language, in particular the time of speech onset. For instance, DSM-IV [APA, 1994] includes "motor delays or motor clumsiness" in the Asperger syndrome (with typical speech onset) diagnostic criteria, and only "abnormalities of posture" in autism with delayed speech onset. The European mental health classification system, ICD-10, also includes motor "clumsiness" as a diagnostic criterion for Asperger syndrome, but not for

autism [WHO, 1992]. Similarly, Macintosh and Dissanayake [2004] concluded in their review that Asperger syndrome individuals displayed more motor difficulties than autistic individuals.

However, studies examining the differential occurrence of motor atypicalities in autistic individuals with or without speech delay have produced inconsistent results. Behere and colleagues [2012] argued that motor performance could be used to classify AS subgroups; although movement deficits are present in both autism and Asperger syndrome, different neural mechanisms may be responsible for atypical movements observed in each condition. Gross motor skills [Gillberg, 1998], fine and gross motor abilities [Klin et al., 1995], and the speed and dexterity of non-dominant hand movements [Szatmari et al., 1990] may be more impaired in individuals with Asperger syndrome than in autism. If both autism and Asperger syndrome are associated with anomalies in movement preparation, autistic individuals may specifically lack anticipation before initiating actions, whereas individuals with Asperger syndrome may exhibit more general deficits in movement preparation [Rinehart et al., 2001]. Furthermore, autistic individuals may have more problems in saccade adaptation than individuals with Asperger syndrome, which could affect visually guided hand movement [Johnson et al., 2013], voluntary saccade control [Stanley-Cary et al., 2011] and gait [Nayate et al., 2012]. However, other evidence suggests that individuals with autism or Asperger syndrome show a similar level of clumsiness, including abilities such as manual dexterity, static and dynamic balance, ball skills and repetitive timed movements [Jansiewicz et al., 2006; Manjiviona et al., 1995; Noterdaeme et al., 2010].

Atypicalities in motor performance are associated with other DSM-5 diagnostic specifiers besides language. For example, IQ is linked with variations in motor abilities [Green et al., 2009; Papadopoulos et al., 2012]. Individuals with intellectual disabilities often show motor skill impairments [Hartman et al., 2010; Westendorp et al., 2011], and intellectual functioning predicts visuomotor integration skills in autism (e.g., the ability to copy simple and complicated designs) [Memisevic et al., 2012]. Even for autistic individuals in the normal intelligence range, motor atypicalities are related to intelligence [Smits-Engelsman et al., 2012]. Fluid and quantitative reasoning, but not verbal abilities, are typically associated with visuomotor integration abilities [Decker et al., 2011]. This observation is relevant when studying AS subgroups, because verbal and non-verbal intelligence relate differently to other cognitive competencies such as processing speed in both autism and Asperger syndrome

[Barbeau et al., 2013]. This difference possibly results from the discrepancy observed in autistic individuals between performance on the Raven's Progressive Matrices (RPM) and Wechsler IQ measures [Dawson et al., 2007], which is less pronounced in individuals with Asperger syndrome [Soulieres et al., 2011], and typically developing individuals. The authors of these studies suggest that the RPM IQ estimate is a more appropriate measure than the Wechsler IQ to control for intelligence when studying differences in non-verbal abilities between and within AS subgroups. We sought to understand better the interactions between speech development, limb motor control and intelligence in autism, in particular because atypical motor control can be an early sign of AS [Landa et al., 2006; Teitelbaum et al., 2004]; therefore, we investigated perceptual and motor behavior in AS individuals differing in time of speech acquisition during development.

In this study we used quantitative psychophysical and kinematic techniques (1) to explore further the association between motor control mechanisms and speech onset in AS, and (2) to examine the relationships between motor performance, visual processing speed and intelligence measures. AS participants were characterized by presence or absence of developmental speech delay and their motor performance was assessed. Our experimental approach involved behavioral analysis of tasks assessing visual perception, visually guided movements and visually-triggered movements to identify the locus of processing atypicalities. The visually-guided tasks used were the Annett Peg Moving Task [Annett, 2002], a unimanual task assessing goal-directed movement, and the Purdue Pegboard, a task assessing fine motor abilities, dexterity, and bimanual coordination. We also used the Inspection Time Task, which measures visual processing speed. Last, visually-triggered movements were examined with a simple reaction time (SRT) task measuring the time required to press a button following the presentation of a brief visual stimulus.

Methods

Participants

All participants were randomly recruited from the research database of the Specialized Autism Clinic at the Rivière-des-Prairies Hospital (Montreal, Canada). The experimental group included 39 AS participants and 30 typically developing individuals (Table 1). Exclusion criteria included: uncorrectable visual impairment, use of drugs or alcohol

exceeding two drinks per day, and FSIQ less than 75. Two AS participants took antidepressants (paroxetine and venlaflaxine), one a sleep medication (fluorazepam), and three a stimulant (methylphenidate). Psychiatric comorbidities were clinically assessed by an experienced psychiatrist in standardized and non-standardized conditions, in addition to an average of two professionals (speech therapist and neuropsychologist). None of the AS participants had any known comorbid genetic, neurological, or DSM-IV Axis I psychiatric conditions, other than hyperactivity (two participants) and language disorders, which occur in a large proportion of AS individuals at some point during development. Additionally, typically developing comparison participants completed a questionnaire to screen for personal or familial neurological, psychiatric or medical conditions known to affect brain function. All participants gave written informed consent and were compensated for their participation.

Diagnostic procedures

Twenty-eight of the 39 AS participants were diagnosed by both the Autism Diagnostic Interview-Revised [ADI-R; Lord et al., 1994] and the Autism Diagnosis Observation Schedule module 3 or 4 [ADOS-G; Lord et al., 2000], combined with an expert interdisciplinary clinical assessment. However, some participants were diagnosed by expert interdisciplinary judgment alone (one participant), or expert judgment combined with either the ADOS-G (four participants) or the ADI-R (six participants). Age of first words and first phrases were available for all participants.

AS subgroups

The 39 AS participants were divided into two groups according to speech onset delay using the ADI-R questions: *age of first words (#9)* and *age of first phrases (#10)*. We used the term *autism* for participants with both a clinical diagnosis of autism and speech onset delay involving first words (≥ 24 months) or first phrases (≥ 33 months), as defined by the ADI. We used the term *Asperger* for individuals with a DSM-IV clinical diagnosis of Asperger syndrome without speech onset delay. Participants with a clinical diagnosis that was not consistent with the corresponding absence or presence of speech onset delay (e.g., clinical diagnosis of autism but no speech delay) were excluded. The final sample consisted of 18 individuals with Asperger syndrome and 21 autistic participants. The autistic, Asperger

syndrome, and typical groups were comparable in terms of age, full scale IQ, performance IQ, and RPM score; however, the autistic group had a lower VIQ than the other two groups, which was expected because developmental speech delay was used in assigning groups.

Table1. Participant characteristics

	Asperger	Autistic	Typical	*p*
n	18 (17M:1F)	21 (19M:2F)	30 (26M:4F)	
Age (SD)	20.7 (4.9)	22.8 (6.2)	20.3 (4.6)	.228
Range	14-30	15-34	14-35	
FSIQ (SD)	103.8 (12.5)	98.3 (13.8)	105.0 (10.8)	.148
Range	86-129	78-120	80-121	
PIQ (SD)	98.0 (12.3)	102.3 (8.2)	101.8 (13.0)	.455
Range	75-126	91-118	72-122	
VIQ (SD)	108.7 (12.1)	97.1 (17.5)	107.9 (10.6)	.010*
Range	94-134	72-124	91-127	
RPM %tile (SD)	78.9 (22.6)	66.6 (28.8)	63.8 (21.0)	.105
Range	25-98	9-98	23-96.5	
Edinburgh	56.5 (70.1)	66.8 (62.7)	32.1 (71.2)	.185
Range	-100-100	-100-100	-100-100	

Procedure

Handedness assessment

Manual preference was estimated by self-report with the ***Edinburgh*** *Handedness Inventory* [Oldfield, 1971] and by observations in the the *Hand Preference Demonstration Test* [Soper et al., 1986]. This test includes 10 items assessing the subject's preferred hand during the performance of a wide range of activities involving miming the 10 actions (e.g. throwing a ball) and performing these actions with real objects (e.g. a ball). Items are presented twice within a session in a pseudorandom order. The two manual preference measures were consistent. The scores were strongly correlated in the whole sample (r=.950, p<.001) and within each group.

Motor skill assessment

The *Annett Peg Moving Task* [Annett, 2002] is a visually-guided movement task that assesses unimanual goal-directed movement by measuring the speed at which a set of 10 pegs can be moved, one after another, from one row of holes to another. The wooden board includes two parallel rows of 10 holes (1.27 cm diameter, 2.22 cm deep, and 3.81 cm apart) 8 inches apart. The pegs are 5.1 cm tall. Six timed trials were completed with each hand in a standing position. A trial was considered valid when no pegs were dropped and no significant distraction interfered. For each participant, the slowest trial of six for each hand was discarded [Annett, 2002]. The remaining five valid trials were then averaged for each hand. The three final measures of the Annett test were: average time (in seconds) taken with the dominant hand (DH), the non-dominant hand (NDH), and the average of all 10 trials (Total).

The *Purdue Pegboard Test* (Model 32020, Lafayette Instrument Co., IL, USA) is a visually-guided movement task that assesses fine goal-directed movements by measuring fingertip dexterity, hand-eye coordination and bimanual coordination. The pieces and holes are much smaller than those of the Annett Peg Moving Task (2.5 mm diameter, 25 mm long)**,** and have to be manipulated between two fingers, requiring greater precision and dexterity. The test measures the ability: 1) to put as many pegs as possible into the pegboard in 30 seconds using the dominant hand (DH), the non-dominant hand (NDH), or both hands simultaneously in a coordinated mirrored fashion (BH), and 2) to assemble washers, collars, and pegs in a specific sequence using both hands in a coordinated and sequential fashion within 60 seconds (Assembly). Trials were completed three times each and averaged. The score for each of the four conditions (DH, NDH, BH, and Assembly) is recorded as the number of pieces placed within 30 seconds. For both tasks, manual preference was controlled by classifying responses according to whether the dominant (DH) or non-dominant hand (NDH) was used.

Simple Reaction Time (SRT)

A visually-triggered simple reaction time measure was obtained to estimate movement speed in the context of simple movements. Participants were seated in a quiet, dimly lit room. Black wooden panels surrounded the participants, with an opening for the computer screen. A chin rest placed at 73 cm from the screen minimized head movements. A grey background

with a centered white fixation cross was present throughout the task and the participants were instructed to maintain fixation. The visual stimulus was a small black square that appeared for 50 ms randomly either to the right or left of the fixation cross, at an eccentricity of 8° of visual angle. The inter-stimulus interval varied randomly from 1000 to 3500 ms to avoid anticipation effects. Participants were instructed to press a button as quickly as possible after detecting the black square. The session consisted of three right and three left hand blocks (about 4 minutes each) of 100 trials each, for a total of 600 trials. The order of blocks varied between participants.

Inspection Time

We used the Inspection Time Task to investigate whether perceptual processing speed contributes to visually-guided movement atypicalities observed in autism [Gepner et al., 2009]. In this task two vertical lines of different lengths were presented for 10-200 ms and then were immediately masked by two irregular vertical shapes. Participants indicated which line was longer. Each stimulus was preceded by a fixation cross prompting the participant to look at the middle of the screen. The duration of each stimulus was individually and adaptively varied in a staircase psychophysical procedure. This procedure determines the minimal exposure time necessary to detect the difference in length [see Barbeau et al., 2013 for a detailed method]. A valid measure of inspection time was available for 18 autistic, 21 Asperger syndrome, and 30 typical participants; three autistic participants did not complete or failed to perform the task correctly.

Statistical analysis

For the Annett Peg Moving Task and the Purdue Pegboard, we removed outlier scores that were two or more standard deviations (SD) above or below the group average. This made the response distributions more Gaussian and therefore more appropriate for the parametric statistical modeling that we used. Outliers were evenly distributed across groups (data points removed for Annett DH condition from 1 Asperger, 1 typical participant; NDH: 1 Asperger, 2 autistics; Purdue DH: 1 Asperger; NDH: 1 Asperger, 1 autistic; BH: 1 Asperger; AS: 1 autistic, 2 typicals). The two participants with hyperactivity (one Asperger and one autistic) were not excluded from most of the analyses because their performance fell within their respective subgroups' range. The statistical analyses were also performed using 3 SD as a

cutoff to account for the possibility that the outliers removed were actually representative of the sample studied. This 3 SD cutoff excluded one Asperger participant for the Annett only. For the SRT task, the response measure was obtained by calculating the median of all trials over 150 ms (shorter RTs were treated as anticipation errors or missed trials and below 800 ms (longer RTs were treated as inattention errors).

Motor tasks. ANCOVAs were conducted for each condition of the Annett Peg Moving test (DH and NDH), the Purdue Pegboard (DH, NDH, BH, and Assembly), and the SRT task with SPSS 17.0.1 software (SPSS Inc., Chicago, IL, USA). The RPM percentile score was used as a covariate in the analysis because of the known relationship between general intelligence and motor skills [Smits-Engelsman & Hill, 2012]. Our ASD groups were formed according to the presence or absence of developmental speech delay; therefore, we additionally examined the effects of Verbal IQ, by treating it as a covariate. The age of participants did not have a significant effect on any of the measures and it was not included in the model. Linear regression analyses were also conducted to investigate the relationship between motor skill measures and the age of first phrases in months and the simple reaction time.

Inspection Time. We used a mixed effects model with group as a between-subjects factor and subject as a random factor and the analysis was conducted in the *lme* module of R, version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria), see Barbeau et al. [2013] for details.

Intelligence. We conducted regression analyses with RPM scores and FSIQ, as independent variables to investigate any residual effects of variations in intelligence on perceptual and motor skills. The effects of intelligence, group, and the intelligence x group interactions were explored. We used a complete model to test the effects of intelligence and group and their interactions for the various dependent variables. If the intelligence x group interaction was not significant ($p>.25$), it was removed from the model. Residual normality was tested with the Shapiro-Wilk test and assumptions (normality, linearity, homoscedasticity) were checked by residual analysis for each model.

Results

Annett Peg Moving Task

When we controlled for intelligence with VIQ, we observed group differences in the dominant hand (DH: $F(2,62)=4.25$, $p=.019$), non-dominant hand (NDH: $F(2,61)=4.52$, $p=.015$), and total average conditions (Total: $F(2,62)=5.56$, $p=.006$). Planned contrasts revealed that autistic participants were 772, 876 and 913 ms slower than typical individuals in the DH ($p=.015$), NDH ($p=.007$) and Total ($p=.003$) conditions, respectively. Asperger participants were slower than typical individuals in the DH condition only (by 664 ms, $p=.026$) (Figure 1). Controlling for intelligence with RPM score did not change the overall pattern of the results.

The use of 3 SD instead of 2 SD as a cutoff for outliers did not affect the overall trend of the results. Indeed, at 3 SD, group differences were still significant for DH, NDH and Total when controlling for VIQ, and the autistic group was significantly slower than the typical group. The Asperger group was also slower than the typical group in the NDH condition. Detailed statistical results are shown in supplementary Table 1.

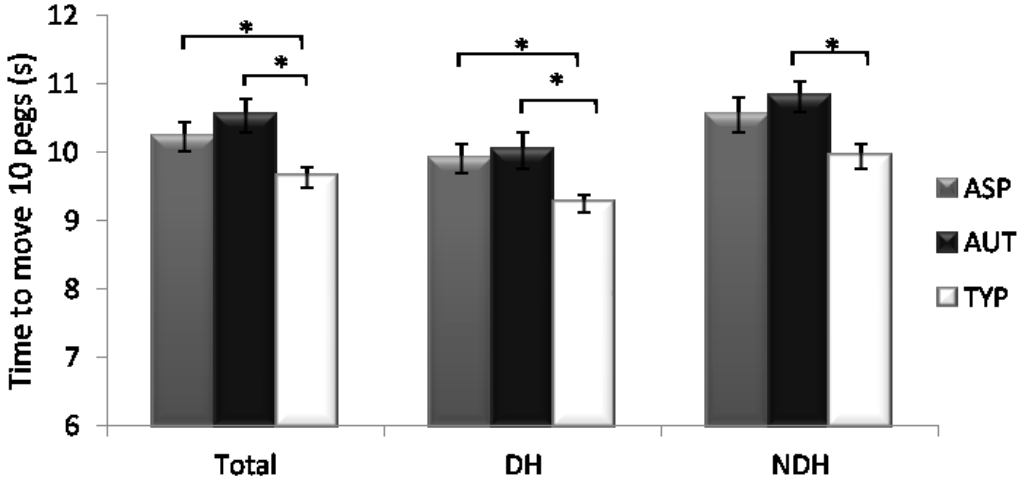

Figure 1. Results of the ANCOVA for the Annett test for the three groups. Average time to move the 10 pegs from 1 row to another with the dominant hand (DH) or the non-dominant hand (NDH) and the total average (Total) of the 2 hands is shown in seconds. *$p<.05$

Purdue Pegboard

When we controlling for VIQ, we found significant differences between groups in the DH ($F(2,63)=6.37$, $p=.003$) and the NDH ($F(2,62)=8.59$, $p=.001$) conditions of the Purdue Pegboard Test. Planned contrasts revealed that Asperger participants placed on average 9.2% fewer pegs in 30 seconds than typical individuals (DH: $p=.001$, NDH: $p<.001$). Autistic individuals tended to be slower than typicals in the unimanual conditions**,** but the difference was not significant (DH: $p=.109$, NDH: $p=.072$). The groups also differed in the bimanual condition (BH: $F(2,63)=5.64$, $p=.006$), and planned contrasts showed that the Asperger group was slower than both the autistic (6% fewer pegs, $p=.006$) and typical groups (7.9% fewer pegs, $p=.003$). There was also a significant difference between groups in the Assembly condition ($F(2,61)=5.52$, $p=.015$), with planned contrasts showing that the slow performance of the Asperger group (7% slower than the autistic group; $p=.004$) mainly accounted for this difference.

When intelligence was controlled for with RPM score, we found significant differences between groups only for the bimanual conditions of the Purdue, namely the Assembly ($F(2,62)=3.45$, $p=.038$) and the BH ($F(2,64)=5.51$, $p=.006$) conditions (Figure 2). Indeed, planned contrasts revealed that Asperger participants were 7% slower in the Assembly task than typical ($p=.015$) and autistic individuals ($p=.041$) and they were also slower than autistic ($p=.023$) and typical individuals ($p=.002$) in the BH condition.

The use of 3 SD as a cutoff for outliers did not affect the overall pattern of the results. When controlling for VIQ, the performance of the groups differed significantly for the unimanual conditions. The Asperger group was slower than the typical group, and the autistic group was also slower than the typical group but for the NDH only. For the bimanual conditions, we observed the same overall trend of group effects: the Asperger group was significantly slower than both the autistic and typical groups. The performance of the autistic and typical group was similar. See supplementary Table 1.

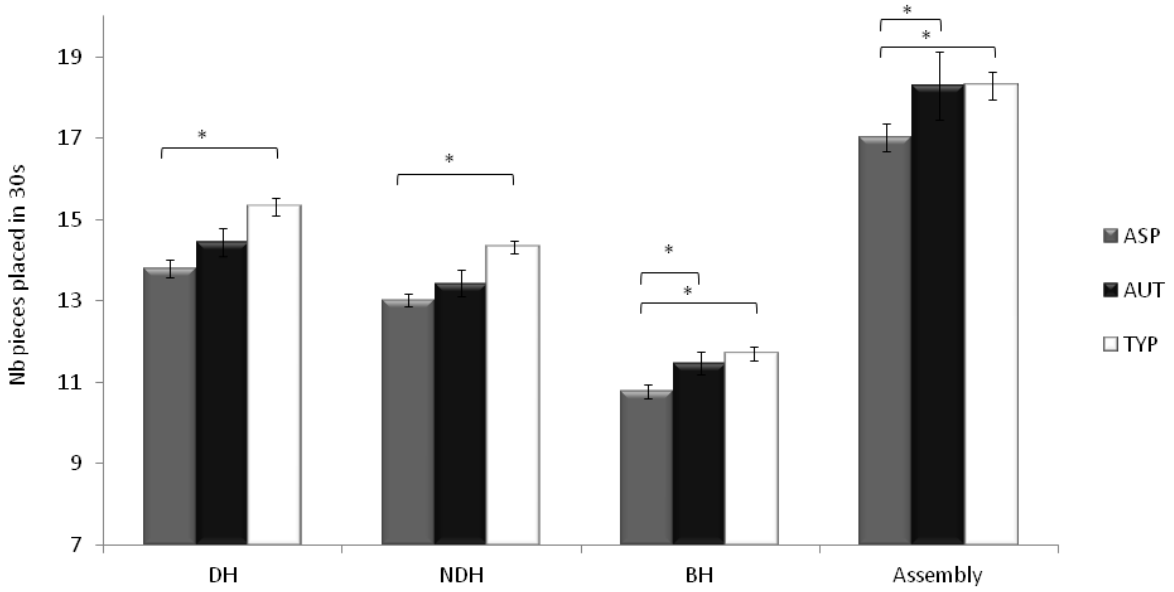

Figure 2. Results of the ANCOVA for the Purdue Pegboard test (DH: dominant Hand, NDH: Non-Dominant hand, BH: both hands) for the three groups, ASP: Asperger, AUT: autistic, TYP: typical individuals. * $p<.05$

Simple Reaction Time

This visually-triggered task is used to isolate movement effects in conditions not requiring visual guidance. We found a difference between groups in performance in this task when controlling for RPM ($F(2,65)=4.119$, $p=.021$). Post-hoc tests revealed that this group effect was primarily accounted for by reaction times in Asperger participants, which were 31.5 ms faster than in autistic participants (RPM: $p=.017$) (Figure 3).

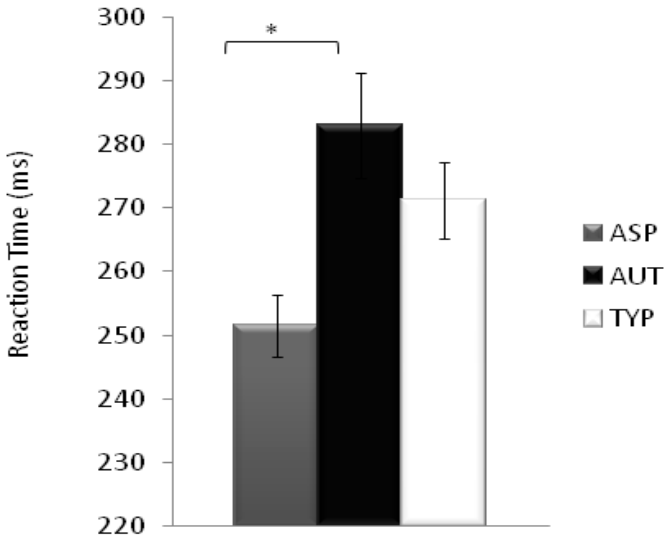

Figure 3. Visually triggered Simple Reaction Time in milliseconds for Aspergers (ASP), autistics (AUT) and typicals (TYP). * $p<.05$

Inspection Time

AS participants, especially those with speech delay, tended to exhibit shorter inspection times than typical participants (ASP vs AUT $t(59)=1.28$, $p=.206$, AUT vs TYP $t(59)=1.743$, $p=.086$) (Figure 4). The sample from this study overlaps with the sample from Barbeau et al. [2013], in which the difference in inspection time reached significance.

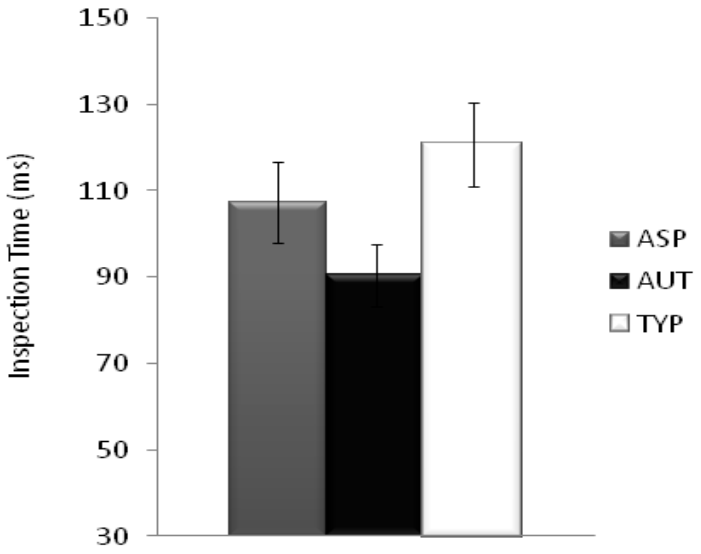

Figure 4. Inspection Time in milliseconds for the autistic (AUT), Asperger (ASP) and typical (TYP) groups.

Exploratory analyses

Relationships between intelligence and motor skills

Typical group. In the typical group, RPM score predicted performance in the Purdue Assembly condition. Simple reaction time did not predict any of the movement scores in the typical group (see Table 2).

AS vs Typical groups. The results of the regression analysis differed between the typical and the AS subgroups (Table 2). The performance of Asperger participants differed most from that of typical individuals in the Assembly condition of the Purdue Pegboard. The intelligence X Group interaction was significant for FSIQ in this task. Wechsler FSIQ predicted the Assembly score in the Asperger group (the higher the IQ, the faster the motor performance), but not in the typical group.

However, the autistic participants differed most from that of the typical group for the bimanual BH condition of the Purdue. The intelligence X Group interaction was significant for

FSIQ in this condition. Intelligence predicted the performance of autistic participants in the BH condition but not that of typical individuals. In addition, a slow SRT predicted a slow Purdue DH score in the autistic group but not in the typical group.

Effects of speech delay. Within the AS group, RPM score did not predict motor performance in any unimanual conditions of the Annett or Purdue tests. However, RPM score did predict performance in the bimanual conditions of the Purdue Pegboard Test. Among AS individuals with equivalent RPM scores, those with speech delay performed the Purdue BH condition faster than those without speech delay. The relationship between RPM score and the Purdue Assembly condition was similar between groups. Nonetheless, we explored within-group effects because this variable differed between groups, which showed that a high RPM score predicted a fast performance in the Purdue Assembly task in the Asperger group, but not in the autism group.

Regarding Wechlser IQ, a high FSIQ predicted a fast performance in the bimanual conditions of the Purdue Pegboard in both groups; however, autistic participants performed significantly faster than Asperger participants with the same FSIQ.

Age of speech onset in AS subgroups

There was an "Age of First Phrases" X group interaction for the unimanual conditions of the Purdue Pegboard. Age of first phrases predicted performance in the unimanual and Assembly conditions in the Asperger group, with late speech onset predicting slow motor performance. This effect was not seen in the autistic group (Table 2).

Simple Reaction Time

In the total AS group, a fast SRT predicted fast motor performance in the Annett DH condition and in the Purdue Pegboard unimanual conditions. Autistic individuals performed the Purdue Pegboard significantly faster than Asperger participants with equivalent reaction times. SRT predicted motor performance in autistic participants, but not in Asperger participants (Table 2). SRT was not significantly associated with performance in the bimanual conditions of the Purdue Pegboard.

Table 2. Significant main effects and group effects or interactions are shown for regression analyses with the Purdue or Annett conditions as dependent variables and Intelligence measures, Simple Reaction Time or Age of first phrases as predictive variables.

						Within-group effects	
			Main effect	Group effect	Interaction	Typicals	Asperger
Purdue	Assembly	FSIQ	R=.451, t(1,43)=2.604, p=.013	t(1,43)=1.966, p=.056	R=.567, t(1,42)=-2.690 p=.010	R=.063 p=.763	***R*=.663, *p*=.003**

						Within-group effects	
			Main effect	Group effect	Interaction	Typicals	Autistics
Purdue	BH	FSIQ			R=.501, t(1,47)=-2.619, p=.012	R=.012, p=.948	***R*=.639, *p*=.002**
	DH	SRT			R=.466, t(1,47)=2.000, p=.051	R=.006, p=.974	***R*=.505, *p*=.020**
Annett	DH	SRT	R=.537, t(1,47)=3.145, p=.003	t(1,47)=-2.509, p=.016		R=.223, p=.244	***R*=.568, *p*=.007**

						Within-group effects	
			Main effect	Group effect	Interaction	Asperger	Autistics
Purdue	BH	RPM	R=.431, t(1,35)=2.174, p=.037	t(1,35)=2.236, p=.032		R=.237, p=.360	R=.404, p=.069
		FSIQ	R=.566, t(1,35)=3.543, p=.001	t(1,35)=2.689, p=.011		R=.565, p=.213	***R*=.639, *p*=.002**
	Assembly	RPM	R=.440, t(1,35)=2.595, p=.014	t(1,35)=1.790, p=.082		***R*=.491, *p*=.039**	R=.356, p=.123
		FSIQ	R=.599, t(1,35)=4.186, p<.001	t(1,35)=2.243, p=.031		***R*=.636, *p*=.003**	***R*=.533, *p*=.016**
		1st phrases			R=.421, t(1,34)= 2.243, p=.032	***R*=.672, *p*=.002**	R=.032, p=.922
	NDH	SRT	R=.476, t(1,34)=-2.952, p=.006	t(1,34)=2.302, p=.028		R=.351, p=.167	***R*=.487, *p*=.029**
	DH	SRT	R=.458, t(1,35)=-2.713, p=.010	t(1,35)=2.458, p=.019		R=.251, p=.325	***R*=.505, *p*=.020**
	DH+NDH	1st phrases			R=.476, t(1,33)=2.759, p=.009	***R*=.703, *p*=.002**	R=.061, p=.799
Annett	DH	SRT	R=.500, t(1,35)=3.397, p=.002	t(1,35)=-1.207, p=.235		R=.277, p=.279	***R*=.568, *p*=.007**

Discussion

Summary of findings

Here, we used several perceptual and motor tasks measuring key aspects of motor behavior, including gross and fine motor skills, visuo-spatial integration, dexterity, coordination and speed, to investigate whether visual processing speed, visually-triggered or visually-guided movement differs between AS individuals with or without speech onset delay. We also investigated the relationship between motor performance, visual processing speed and intelligence in AS. Our results suggest that AS individuals with speech onset delay perform unimanual motor tasks more slowly than typically developing individuals. AS individuals without speech onset delay showed relatively poor fine motor skills, bimanual coordination, and dexterity. The association between motor skills and intelligence also differed between AS subgroups.

Motor impairment in AS: nature and putative mechanisms

Overall, AS individuals showed short visual processing time, normal or short simple reaction time, and normal or prolonged visually-guided movement time. These findings are consistent with a locus for atypical motor performance at an intermediate stage between visual processing and motor execution. Our findings confirm the idea that motor deficits in individuals with Asperger syndrome probably involve complex aspects of movements, such as bimanual coordination and dexterity, which are required for the fast manipulation of small objects [consistent with Klin et al., 1995; and Szatmari et al., 1990]. The notion that individuals with Asperger syndrome have poor complex motor skills may appear contradictory; however, it is consistent with the developmental reorganization of the brain involving region-specific cortical allocation or resource competition in AS individuals with or without speech delay [for a review see Mottron et al., 2014], although direct evidence of motor-speech competition is lacking. Another possible interpretation is that both speech and bimanual tasks require a high degree of interhemispheric coordination. AS is often associated with both a thinner than normal corpus callosum [Frazier et al., 2009] and microstructural abnormalities of white matter [Aoki et al., 2013]; therefore, the differences in performance between AS subgroups may result from competition in interhemispheric functional processing capacity between speech and complex limb movements. A final possibility is that symptoms

of ADHD, which are more frequent in individuals with Asperger syndrome [Ghaziuddin et al., 1998; Tani et al., 2006], are involved in this motor impairment. In the current study, only one autistic and one Asperger syndrome participant were diagnosed as having comorbid hyperactivity. The motor performance of these two participants fell within the range of performance of their respective group. Therefore, clinically significant ADHD cannot explain the impairment in motor skills in the Asperger group, but this does not exclude a potential contribution of undiagnosed ADHD.

The AS subgroup with developmental speech delay performed slowly in tasks involving unimanual hand and arm skills, whereas the manipulation of small objects and bimanual coordination were more typical. According to Rinehart and colleagues [2001], autistic motor deficits may be linked to speed of execution or anticipation. This idea is in line with a recent review by Gowen and Hamilton [2013], suggesting that motor deficits in autism are related to difficulties in sensorimotor integration and not to movement execution mechanisms *per se*. Indeed, difficulties in dynamically incorporating visual information during goal-directed movement may limit the speed at which the movements are carried out in order to maintain their accuracy. Abnormalities of sensory processing, internal representations [Dewey et al., 2007], and formation and transcoding of spatial representations [Dowell et al., 2009] could explain the slow movements we observed in the various tasks; however, the short visual processing time that we observed in both AS groups does not support this interpretation.

Intelligence-language-motor skill relationships

In the group without speech delay, non-verbal intelligence (RPM) predicted the Purdue Assembly score, the task for which these participants showed the poorest performance. By contrast, neither verbal nor non-verbal measures of intelligence were associated with the motor deficits observed in the speech delay subgroup. Similarly, late speech onset (albeit in the normal range), was predictive of poor performance in the Purdue Pegboard task in the Asperger but not the autistic group. Thus, in autistic individuals, motor performance and intelligence are unrelated, and delayed speech onset is not associated with other cognitive abilities or motor performance. By contrast, motor performance appears to be associated with language abilities and intelligence in Asperger individuals. This conclusion is consistent with previous work of our group showing that strong language abilities and high RPM scores

coexist in AS individuals without speech onset delay [Barbeau et al., 2013; Soulieres et al., 2011].

Reaction time and motor skills

AS individuals without speech delay showed significantly faster SRT but significantly slower fine motor skills, and poorer dexterity and bimanual performance than AS individuals with speech delay. Several factors can influence reaction time, including the speed of neural conduction and general neural integrity [MacDonald et al., 2008], the level of arousal and attention [Davranche et al., 2006], and an individual's predisposition to taking care and monitoring their responses. The SRT task does not involve motor response selection or dexterous, agile or coordinated movements of the hand and fingers. This is not the case for the Purdue Pegboard test, which was originally developed to assess manual manipulation abilities in industrial workers, who require both fine finger and goal-directed movements. Thus, AS individuals without speech delay appear to have an intact or highly functioning motor execution system, but may struggle to incorporate perceptual information during the utilization of more complex fine movements.

In the AS with speech delay group, the proficiency of unimanual motor skills was predicted by SRT. This result is consistent with the findings of Rinehart et al. [2001] and suggests that the speed at which movements are executed or anticipated could be a limiting factor in goal-directed movement in autistics. This cannot result from limitations in the speed of processing visual information, because perceptual processing speed is quicker in autistic individuals than in both typically developing individuals and individuals with Asperger syndrome of similar intelligence [Barbeau et al., 2013].

The Autism-Asperger distinction

Our findings suggest that variations in speech onset milestones within autism spectrum disorders are related to limb motor skill development. In AS individuals without speech delay, which broadly coincides with the DSM-IV definition of Asperger syndrome, fine motor skills, hand movement, and in particular, bimanual coordination were all impaired. In individuals of typical intelligence with prototypical autism with speech delay, only unimanual motor abilities were impaired**.** Moreover, a different pattern of relationships between intelligence, language abilities, and motor impairments emerges in the two AS subgroups. Motor abilities vary with

RPM scores, FSIQ and language abilities in Asperger syndrome**,** but are unrelated to intelligence in autism. These observations add to those of cognitive and brain imaging studies [Bonnel et al., 2010; Jones et al., 2009; Sahyoun et al., 2010; Sahyoun et al., 2009; Yu et al., 2011] demonstrating the effects of developmental speech delay on the heterogeneity of AS phenotype. However, speech delay also aggregates with visuospatial abilities [Barbeau et al., 2013], suggesting that phenotypic heterogeneity in the autistic spectrum is at least partly related to the role of perception in the cognitive architecture of autistic individuals [see Mottron et al., 2014 for a model]. It is still unclear whether the diversity of the autism spectrum is best characterized by a combination of the effects of continuous physiological and behavioral dimensions, or by distinct phenotypic groups. Large studies collecting behavioral and physiological data needed to distinguish clinical clusters from continuous dimensional effects are required to address this issue.

Acknowledgments

This work was supported by an operating grant from the Canadian Institutes of Health Research (CIHR, No. MOP-84243) awarded to L. Mottron, and scholarships from the CIHR awarded to E.B. Barbeau and A.-A. S. Meilleur. We thank the anonymous reviewer who provided insightful suggestions about the interpretation of our data. The authors also want to thank the participants for their invaluable contribution to this project. The authors report no potential conflicts of interest.

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Supplementary material

Conditions		Group effects	Planned contrasts		
			ASP - TYP	AUT - TYP	ASP - AUT
Annett	DH	$F(2,63)=3.433$, $p=.038$	$p=.050$	$p=.026$	$p=.795$
	NDH	$F(2,64)=3.628$, $p=.032$	$p=.019$	$p=.050$	$p=.764$
	Total	$F(2,63)=3.836$, $p=.027$	$p=.051$	$p=.015$	$p=.656$
Purdue	DH	$F(2,64)=4.756$, $p=.012$	$p=.003$	$p=.131$	$p=.203$
	NDH	$F(2,64)=4.998$, $p=.010$	$p=.005$	$p=.035$	$p=.531$
	BH	$F(2,64)=2.916$, $p=.061$	$p=.029$	$p=.958$	$p=.050$
	Assembly	$F(2,64)=2.992$, $p=.057$	$p=.045$	$p=.606$	$p=.028$

Supplementary Table 1. ANCOVAs with VIQ as a covariate. Group effects are displayed as well as planned contrasts comparing the Asperger (ASP), autism (AUT) and typical (TYP) groups for the Annett dominant hand (DH), non-dominant hand (NDH) and average (Total) conditions and the Purdue dominant hand (DH), non-dominant hand (NDH), both hands (BH) and Assembly conditions.

Chapitre 5. Discussion

5.1 Résumé des objectifs

La présente thèse avait comme objectif d'investiguer en autisme l'intégrité du traitement de l'information visuomotrice par le cerveau, possiblement affecté par les altérations de la matière blanche. Des différences en autisme, tant au niveau volumétrique qu'au niveau des mesures de diffusion, mènent en effet à prédire des altérations de la communication cérébrale intra et interrégionale. Les réseaux neuronaux impliqués dans le traitement de l'information visuomotrice ont donc été investigués.

Particulièrement, l'effet des réductions anatomiques du corps calleux sur la capacité des fibres de cette structure à transférer l'information d'un hémisphère à l'autre a été étudié en comparant un groupe d'individus autistes à un groupe d'individus au développement typique. Le paradigme de Poffenberger, une tâche visuomotrice, a été utilisé pour estimer le temps de transfert interhémisphérique (TTIH). Ce TTIH est mesuré par la différence entre les essais croisés, nécessitant un transfert par le corps calleux, et les essais non croisés, pour lesquels l'information peut être traitée de façon intrahémisphérique (Crossed-Uncrossed Difference ou CUD).

Les différents aspects du traitement visuomoteur impliqués dans la tâche de Poffenberger ont été investigués plus en profondeur. En raison aussi des particularités perceptives et motrices propres à l'autisme et de leur relation suggérée avec les atypicalités de la matière blanche, les habiletés motrices et la vitesse de traitement visuel ont donc été mesurées séparément chez les mêmes participants. La tâche de temps d'inspection (Inspection Time (IT)) a été utilisée afin de mesurer la vitesse de traitement perceptif. Cette tâche psychophysique mesure le temps minimal de présentation visuelle requis pour traiter correctement l'information. Elle consiste à discriminer la différence de longueur entre deux lignes verticales en indiquant si celle de gauche ou de droite est la plus longue. Contrairement à l'Indice de vitesse de traitement (IVT) inclus dans les échelles de Wechsler, la tâche d'IT ne comprend pas de composante motrice et n'est donc pas contaminée par une performance motrice. De plus les tâches *Annett peg moving* et *Purdue pegboard*, ont été utilisées pour

mesurer les habiletés motrices, plus particulièrement les habiletés motrices nécessitant une guidance visuelle. Les groupes ont donc été comparés afin de déterminer si les autistes montrent des particularités au niveau du traitement de l'information présentée visuellement et de la rapidité de l'exécution motrice guidée visuellement.

Un groupe d'individus Asperger a été inclus dans les études de temps d'inspection et de motricité. Cela a permis de vérifier si la vitesse de traitement visuel et les troubles moteurs peuvent différentier les sous-groupes TSA, et d'ainsi mieux caractériser les profils cognitifs de chaque sous-groupe et l'effet de la présence ou non de retard de langage sur ceux-ci.

5.2 Résumé des résultats

5.2.1 Poffenberger et transfert interhémisphérique

Au niveau comportemental, la tâche de Poffenberger a révélé que les autistes ne montraient pas de ralentissements significatifs de temps de transfert interhémisphérique quantifié à l'aide de la mesure de comportementale de CUD (Barbeau, Lewis, Doyon, Benali, Zeffiro & Mottron, en révision; Chapitre 2). La CUD moyenne se trouvait dans l'intervalle attendu selon une méta-analyse (Marzi et al., 1991), tant dans le groupe d'autistes que dans celui d'individus à développement typique, appariés selon l'âge, la latéralité manuelle et l'intelligence non verbale. Au niveau cérébral anatomique, tel qu'attendu, les autistes présentaient un plus petit corps calleux, particulièrement au niveau des fibres connectant les régions bilatérales frontales et pariétales. Les mesures d'IRM de diffusion, dont l'anisotropie fractionnelle (FA) et la diffusivité, ne différaient pas entre les groupes. L'investigation de la tâche de Poffenberger à l'aide de l'IRMf a révélé que, malgré une performance similaire à la tâche, des différences sont présentes au niveau des activations cérébrales dans les aires motrices et visuelles impliquées. Les autistes ont présenté moins d'activation dans la région motrice primaire controlatérale à la main utilisée pour appuyer sur le bouton et dans l'aire motrice supplémentaire droite pour les essais avec la main droite, donc du côté du cerveau opposé à la région contrôlant cette main. Concernant l'activité reliée à la stimulation visuelle dans les champs visuels gauche et droit, les autistes ont montré moins d'activation dans les aires occipitales bilatérales, surtout pour les essais dans le champ visuel droit. La magnitude

de latéralisation des activations a aussi été investiguée puisqu'une activité plus bilatérale au niveau des régions homologues gauches et droites connectées par le corps calleux pourrait être indicatrice d'une meilleure intégration des informations entre ces régions (Fornari et al., 2007). Les deux groupes ne présentaient pas la même répartition des activations à ce niveau; les sujets typiques avaient une activation plus bilatérale au niveau des aires motrices, alors que les activations étaient plus bilatérales au niveau des régions visuelles dans le groupe d'autistes. Les analyses de régression ont aussi révélé des différences intéressantes entre les groupes en ce qui concerne la relation entre les mesures comportementales d'intégration interhémisphérique (la mesure de TTIH du Poffenberger et les conditions bimanuelles du Purdue) et les propriétés régionales du corps calleux. Le transfert interhémisphérique de tâche de Poffenberger serait principalement relié aux propriétés du corps calleux connectant les régions motrices chez les typiques. Chez les autistes, la performance aux tâches est plutôt associée aux propriétés du corps calleux postérieur, connectant les aires visuelles. Des relations analogues ont été observées pour les mesures de performances bimanuelles du Purdue.

5.2.2 Vitesse de traitement perceptif

Les résultats de l'étude de la tâche de temps d'inspection (Barbeau, Soulieres, Dawson, Zeffiro, & Mottron, 2013; Chapitre 3) ont montré que, les autistes ne présentaient pas de déficits au niveau de la vitesse de traitement perceptif. Ils étaient même significativement meilleurs que les typiques lorsque les groupes étaient appariés au QI global des échelles de Wechsler, la façon la plus courante d'apparier au niveau de l'intelligence. Cette bonne performance des autistes était associée à leur bonne performance aux matrices de Raven. Cette étude appuie la notion selon laquelle le QI Wechsler sous-estime l'intelligence générale des autistes, alors que la mesure de raisonnement du Raven et la vitesse de traitement perceptif sont plus représentatives de leur niveau intellectuel. Les trois mesures se trouvent à des niveaux équivalents chez les typiques. Cette force perceptive pourrait être en lien avec le comportement visuel atypique observable en très jeune âge chez les autistes et être impliquée dans le surfonctionnement perceptif autistique. De plus, ce résultat démontre l'impact du choix des variables d'appariement auxquelles une importance particulière doit être portée. On peut aussi supposer que la vitesse de détection des stimuli lors de la tâche de Poffenberger ne serait

donc pas ralentie. Dans une perspective plus générale, ces résultats suggèrent que la vitesse de traitement perceptif n'est pas affectée négativement par la matière blanche et la connectivité atypique.

5.2.3 Habiletés motrices

Une évaluation des habiletés motrices a aussi été effectuée à l'aide de deux tâches motrices, les tests d'Annett et de Purdue, mesurant la motricité fine et globale unimanuelle, la dextérité, la coordination bimanuelle et la coordination œil-main (Barbeau, Meilleur, Zeffiro, & Mottron, en révision, Chapitre 4). Les autistes étaient plus lents au niveau unimanuel, pour placer les bâtonnets dans les trous un à la fois. Toutefois ils ne montraient pas de ralentissements significatifs au niveau de la coordination bimanuelle. De plus, les déficits moteurs étaient reliés au temps de réaction à la tâche de Poffenberger, ce qui est compatible avec la suggestion que les déficits moteurs des autistes résident dans la rapidité de l'exécution du mouvement ou dans son anticipation (Rinehart et al., 2001). Les résultats de cette étude suggèrent que si les troubles moteurs sont possiblement liés aux différences de matière blanche intrahémisphérique (Mostofsky et al., 2007), cela n'est pas le cas pour ce qui est des différences de matière blanche interhémisphérique.

5.2.4 Récapitulatif

Ces trois études ont permis d'investiguer l'intégrité du traitement de l'information visuomotrice et montrent que chez les autistes, la rapidité traitement de l'information visuelle simple est intacte ou supérieure, mais ils montreraient des ralentissements au niveau de mouvements nécessitant une guidance visuelle. Au niveau de l'intégration de l'information entre les régions homologues bilatérales, la communication entre les régions visuelles serait plus efficace qu'entre les régions motrices sans pour autant affecter significativement les performances bimanuelles motrices, et ce, malgré diminutions de corps calleux. Les atypicalités de matière blanche affecteraient donc certains aspects moteurs, mais garderaient intact ou favoriseraient le traitement perceptif. Cela suggère des mécanismes compensatoires ou adaptatifs au développement atypique du cerveau menant à un cerveau connecté différemment.

5.2.5 Les sous-groupes du spectre autistique

Un autre aspect investigué dans la présente thèse est la distinction entre deux sous-groupes du spectre autistique : les autistes, avec retard de langage et les Asperger, sans retard de langage. En effet, les deux sous-groupes différeraient au niveau des habiletés perceptives visuelles, plus caractéristiques des autistes, mais aussi au niveau des déficits moteurs (Behere et al., 2012; Gillberg, 1998; Klin et al., 1995; Rinehart et al., 2001; Szatmari et al., 1990). Au niveau des habiletés motrices, nos résultats suggèrent en effet que les deux groupes diffèrent dans la nature de leurs déficits moteurs, les Aspergers étant plus atteints que les autistes au niveau de la dextérité fine et de la coordination bimanuelle. Chez les individus Asperger, le temps de réaction de la tâche de Poffenberger était significativement plus rapide que celui des autistes, suggérant que le problème ne réside pas au niveau de la rapidité de l'exécution motrice (ce qui semble être le cas pour les autistes), mais qu'ils présentent plutôt des difficultés lorsque la dextérité et la coordination sont impliquées. De plus, dans ce sous-groupe, les déficits moteurs étaient reliés à l'âge d'acquisition du langage ainsi qu'au niveau intellectuel (RPM, Wechsler). Sur le plan visuel, l'étude de temps d'inspection confirme que la supériorité de vitesse de traitement perceptif des autistes ne se retrouve pas dans le sous-groupe des Asperger. Ces derniers réussissent à un niveau similaire à celui des typiques, la vitesse de traitement perceptif est donc caractéristique du profil cognitif des autistes, avec retard de langage. Les deux sous-groupes présentent donc des profils cognitifs différents, ce qui souligne l'hétérogénéité phénotypique des troubles du spectre autistique et l'importance d'en tenir compte.

5.3 Discussion générale

5.3.1 Effet des réductions anatomiques du corps calleux sur sa fonction

Le fait que nous ayons observé chez les autistes, comparativement aux individus typiques, des réductions de grosseur du corps calleux au niveau frontal et pariéto-temporal, mais pas dans les sections plus postérieures, est cohérent avec la littérature. Une méta-analyse des études IRM en autisme a d'ailleurs conclu que les régions du corps calleux montrant le plus de réductions sont les régions connectant les aires prémotrices et motrices

supplémentaires et que les régions connectant les aires postérieures du cerveau montraient des réductions moindres (Frazier & Hardan, 2009). Un plus petit corps calleux est associé à une réduction du nombre d'axones, de leur diamètre et/ou à une myélinisation moins importante (Witelson, 1985) et ces variables affectent la vitesse de transfert des fibres. Des effets en autisme sur l'efficacité du transfert interhémisphérique étaient donc attendus. Plusieurs études ont déjà mis en relation les diminutions du corps calleux avec certaines fonctions cérébrales. En l'absence de lien causal direct, ces études n'ont pu que conclure aux réductions de corps calleux en tant qu'index d'une diminution globale de la matière blanche. Une étude a tenté d'investiguer directement le transfert d'information d'un hémisphère à l'autre n'a observé aucune différence entre un groupe d'autistes et un groupe de typiques au niveau comportemental malgré les atypicalités du corps calleux (Clawson et al., 2013). Ces auteurs ont aussi tenté d'associer leur mesure de TTIH à l'activité cérébrale (EEG) dans les régions motrices sans trouver de relation. On peut toutefois se demander si une relation aurait été trouvée s'ils avaient regardé aussi l'activité électrique dans les zones visuelles. En effet, notre investigation à l'aide de l'IRMf a permis d'observer une plus grande association entre le TTIH et les propriétés du corps calleux au niveau visuel chez les autistes comparativement au groupe d'individus typiques. De plus, les activations moins bilatérales dans les régions motrices, mais plus bilatérales dans les régions visuelles en autisme supportent aussi ce résultat. Il est donc possible que les réductions observées au niveau du corps calleux connectant les régions motrices chez les autistes n'affectent pas le temps de transfert. L'utilisation de trajectoires alternatives pourrait résulter en un transfert plus rapide au niveau plus postérieur visuel. Toutefois, cela n'exclut pas que le transfert existe aussi au niveau moteur. En effet, selon le modèle *horse race* du transfert interhémisphérique (Bisiacchi et al., 1994), il ne s'agit pas d'un trajet unique et rigide. Il est probable que dans le cas de la tâche de Poffenberger, le transfert se fasse tant au niveau des régions motrices que visuelles, du moins chez des individus typiques. Par contre, vu entre autres, la composition du corps calleux, le transfert le plus rapide ou « gagnant », soit celui qui déclenche la réponse motrice, aurait plutôt lieu au niveau des fibres connectant les régions motrices. Les axones composant le corps calleux connectant les régions motrices ont de plus grands diamètres et sont plus myélinisés (Aboitiz et al., 2003), ce qui les rend plus rapides à conduire l'information. Ils sont aussi plus courts comparativement aux axones connectant les régions visuelles ce qui se traduit aussi en des

délais de transmission plus courts (Caminiti et al., 2009; Lewis, Theilmann, Sereno, & Townsend, 2009). Chez les autistes par contre, les fibres visuelles pourraient être les plus rapides, ou plus souvent « gagnantes » que les fibres motrices pour transférer l'information et donc associées à la mesure de TTIH. Effectivement, des réductions dans le corps calleux des autistes au niveau moteur appuient cette hypothèse. Ces réductions ont été attribuées à un sous-développement sélectif des fibres de plus gros diamètre et un surdéveloppement des fibres de plus petit diamètre (Zikopoulos & Barbas, 2010; Lazar et al., 2014). De plus Lazar et al. (2014) ont utilisé une méthode alternative à la DTI, soit la Diffusional Kurtosis Imaging (DKI) décrivant séparément les propriétés intra et extra axonales de la matière blanche. Leurs résultats suggèrent une densité diminuée des axones dans le genu du corps calleux, ce qui affecte directement son efficacité à transférer l'information.

Pour finir, rappelons la pertinence de la tâche de Poffenberger pour mesurer le temps de transfert « gagnant » par sa capacité de refléter particulièrement le temps de transfert le plus rapide par le cerveau, étant donné les instructions d'appuyer le plus rapidement possible dès la détection du stimulus. Un plus grand rôle des fonctions visuelles dans le transfert interhémisphérique impliqué dans la tâche visuomotrice de Poffenberger, est consistant avec l'étude de Lazar et ses collègues (2014). Ils ont étudié le test du Code, une composante de l'IVT du Wechsler requérant une communication interhémisphérique (Alexander et al., 2007; Zaidel & Iacoboni, 2003). La performance à la tâche, qui comprend des composantes visuelles et motrices, était plus fortement corrélée aux propriétés du corps calleux connectant les régions visuelles et temporales chez les autistes, mais à celles connectant les régions motrices chez les typiques.

5.3.2 Nature des réductions de corps calleux en autisme

L'hypothèse d'un moins bon transfert interhémisphérique chez les autistes, formée considérant les propriétés altérées du corps calleux, était en partie basée sur l'extrapolation de l'effet sur le transfert interhémisphérique des réductions, des lésions et même de l'absence de corps calleux chez des individus non autistes. Toutefois, les résultats de notre étude portent à croire que les diminutions du corps calleux autistique ne soient possiblement pas de même nature que les variations de grosseur normale de corps calleux dans la population typique. Par

exemple, les femmes, qui sont en général moins latéralisées que les hommes dans leurs fonctions cérébrales, ont en moyenne un plus gros corps calleux (Steinmetz, Staiger, Schlaug, Huang, & Jancke, 1995). De plus, l'observation que les gauchers ont en général un corps calleux plus gros que celui des droitiers (Witelson, 1985, 1989) est expliqué par le fait qu'un cerveau plus symétrique, donc ayant des fonctions moins latéralisées, nécessite plus d'intégration interhémisphérique, et donc un plus grand nombre de fibres (Dorion et al., 2000). Une fonction plus latéralisée serait plus indépendante de l'hémisphère opposé. Un plus gros corps calleux est en général effectivement associé à un plus grand nombre de fibres et donc à un niveau de connexion interhémisphérique plus fort (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). Or, en autisme, on observe un corps calleux plus petit, mais des fonctions cérébrales *moins* latéralisées. De plus, ces différences en matière de latéralisation sont associées à une plus grande proportion de gauchers dans la population autiste (15-20 %; Hauck & Dewey, 2001) que dans la population typique (~ 9%).

Toutefois, en autisme, les diminutions de volume du corps calleux ne seraient pas nécessairement, ou du moins pas uniquement, dues à une diminution du nombre de fibres. Les études de DTI en autisme permettent d'investiguer la nature des atypicalités des fibres de matière blanches et montrent principalement des diminutions de FA dans le corps calleux des autistes (méta-analyse: Aoki et al., 2013). Or, la FA n'est pas particulièrement liée au nombre de fibres, mais plutôt à l'intégrité de la membrane, à la myélinisation, au diamètre des fibres et à la directionnalité ou cohérence des fibres. De plus, des augmentations de diffusivité moyenne et radiale dans le corps calleux des autistes ont été suggérées comme indiquant des altérations au niveau de la myélinisation des axones (revue de littérature: Travers et al., 2012). Lazar et ses collaborateurs (2014) ont quant à eux démontré des altérations dans le ratio de fibres de gros diamètre par rapport aux fibres de petit diamètre, un ratio favorisant un plus grand nombre d'axones de petit diamètre en autisme.

Certaines études ont investigué la relation entre les propriétés du corps calleux des autistes et les différences de latéralisation cérébrales. Lo et al. (2011) ont observé que les diminutions de FA dans les sections du corps calleux connectant les régions frontales et temporales, associées à une connectivité interhémisphérique réduite, étaient reliées à des diminutions d'asymétrie dans l'intégrité des fibres de matière blanche intrahémisphériques.

Cela n'est pas conforme avec la notion que moins de latéralisation nécessite plus de connectivité interhémisphérique. Floris et collègues (2013) ont investigué directement l'asymétrie du corps calleux en mesurant son volume, bilatéralement, dans des tranches para-sagittales droites et gauches. Ils suggèrent que la latéralisation atypique de la partie centrale du corps calleux pourrait être impliquée dans les symptômes moteurs de l'autisme. Ils ont aussi montré que, contrairement aux typiques, les autistes ne montraient pas de relation entre l'index d'asymétrie du corps calleux et la latéralité manuelle. Les variations dans les propriétés du corps calleux en autisme n'auraient donc effectivement pas le même effet que dans la population non autiste, ce qui est possiblement explicable par des différences dans leur nature ou leur origine.

Le développement atypique du cerveau autistique, soit la croissance rapide précoce suivie d'un ralentissement et menant à des cerveaux plus gros, joue un rôle dans les différences de relation entre le corps calleux et la latéralisation des fonctions cérébrales. Des fibres de corps calleux plus longues associées à un cerveau plus gros causeraient une réduction dans le nombre de fibres, la quantité de myéline ou le diamètre des fibres. Ces réductions structurales seraient dues au coût (en terme de consommation des ressources) associé aux projections de longue distance, favorisant le développement des fibres de courte distance (Lewis et al., 2013). Des différences au niveau de l'organisation cellulaire ont aussi un effet sur le développement des connexions. Le plus grand nombre de neurones dans certaines régions de matière grise qui comprendraient aussi un plus grand nombre mini-colonnes plus étroites (Casanova et al., 2006) créerait une plus grande compétition entre les neurones pour les ressources d'énergie nécessaires à leur fonctionnement, soit les facteurs neurotrophiques (Piven et al., 1997). Cela favoriserait aussi les connexions de courte distance ipsilatérales demandant moins de ressources et d'énergie que les connexions de longue distance et défavoriserait la connectivité interhémisphérique (Vidal et al., 2006).

Le rôle du corps calleux dans le développement de la spécialisation hémisphérique est important (Westerhausen et al., 2004). Les particularités du cerveau autistique et l'impact des mutations génétiques y étant associées sur la formation et l'élimination des connexions neuronales, modifient aussi le développement du corps calleux et affectent la latéralisation des fonctions. Ces modifications interhémisphériques chez les autistes ont d'ailleurs un effet sur

l'organisation globale du cerveau et affecteraient les fonctions langagières et motrices dont les déficits seraient en partie causés par leur latéralisation atypique (Kleinhans, Muller, Cohen, & Courchesne, 2008; Wittling, Schweiger, Rizhova, Vershinina, & Starup, 2009). Cela supporte la nature possiblement différente des réductions du corps calleux comparativement à celles observables dans la population non autiste. De plus, vu le développement atypique du cerveau autistique, ces réductions n'auraient pas les mêmes effets sur la latéralisation ni sur la vitesse de transfert de l'information simple qui est intacte (Barbeau et al., en révision; Clawson et al., 2013). Cette réorganisation cérébrale lors du développement du cerveau ne serait pas uniquement à l'origine de différences de connectivité interhémisphérique, mais d'atypicalités de connectivité générale menant à une description de l'autisme en tant que trouble de la connectivité. Cette connectivité, parfois accrue, parfois diminuée, dépendamment de la distance des connexions et des régions impliquées, mais définitivement atypique, serait aussi associée à une plus grande indépendance des régions corticales menant à des sous ou des surfonctionnements régionaux (Mottron et al., 2006), notamment de nature perceptive.

5.3.3 Surfonctionnement visuel et activation cérébrale occipitale

Le modèle de surfonctionnements perceptif (Mottron et al., 2006), caractéristiques de la cognition autistique, est supporté par un ensemble de résultats comportementaux, mais aussi par les études d'imagerie cérébrale montrant une plus grande implication des régions cérébrales reliées au traitement visuel, un résultat largement répliqué. Au niveau cérébral fonctionnel, des activations supérieures dans les régions occipitales lors du traitement du matériel présenté visuellement ont été mises en évidence dans une méta-analyse des études IRMf en autisme (Samson et al., 2012). Un plus grand rôle des régions visuelles a aussi été observé dans des tâches cognitives complexes, soit de raisonnement (Soulieres et al., 2009, Annexe II) et de langage (Shen et al., 2012) par exemple. De plus, nous avons montré une connectivité accrue, dans une étude de cohérence EEG en sommeil, à l'intérieur des zones visuelles ainsi qu'entre les régions visuelles et le reste du cerveau (Léveillé et al., 2010, Annexe III), un résultat répliqué depuis à plusieurs reprises (Di Martino et al., 2011; Dominguez et al., 2013; Keown et al., 2013; Shen et al., 2012; Supekar et al., 2013). Cela appuie aussi notre résultat d'une plus grande implication postérieure dans le transfert interhémisphérique de la tâche de Poffenberger.

Au niveau des activations cérébrales IRMf reliées à la tâche de Poffenberger, notre résultat d'une moins grande activité visuelle chez les autistes parait donc contradictoire avec la littérature. Une interprétation possible de ce résultat réside dans la nature de la tâche qui consiste en une simple détection, ne nécessitant pas plus de traitement visuel des stimuli, par ailleurs toujours identiques. De plus, le temps de présentation très court (100 ms) laisse peu de place à une analyse visuelle poussée. L'implication supérieure de la perception visuelle en autisme a été principalement observée dans des tâches demandant plus de traitement de l'information visuelle (Samson et al., 2012). Dans un même ordre d'idées, une performance supérieure a été montrée chez les autistes pour des tâches de discrimination et manipulation de patrons visuels, mais pas pour des tâches de détection de bas niveau (Meilleur, Berthiaume, Bertone, & Mottron, 2014; Rivest, Jemel, Bertone, McKerral, & Mottron, 2013). Remington et collègues (2012) ont investigué une tâche de recherche visuelle, pour laquelle les autistes montrent des avantages. Ils ont manipulé la quantité d'information à traiter et ont montré que la supériorité de performance des autistes était surtout évidente quand la tâche était plus difficile et impliquait de traiter un plus grand nombre d'information, donc lorsque la tâche demandait plus aux capacités perceptives. Il est possible que la nature très facile à la tâche de détection de Poffenberger ne laisse pas de place à une supériorité de traitement ou d'accomplissement.

L'hypothèse de l' « efficacité neuronale », postulant que des fonctions cérébrales plus efficaces soient possiblement associées à une utilisation moindre des ressources, est aussi une explication possible à la moins grande activation visuelle observée chez les autistes. Bien que la présente étude ne permette pas de confirmer cette théorie, elle est supportée par des observations de diminutions d'activité liée à une meilleure performance à une tâche visuomotrice et associée à une meilleure expertise suite à un apprentissage (Haier et al., 1992). Des diminutions d'activation cérébrale dans des tâches cognitives ont aussi été associées à une plus grande intelligence et donc une meilleure efficacité des régions cérébrales impliquées, mais uniquement pour des tâches simples et modérément faciles (Neubauer & Fink, 2009). Une moins grande activation des régions impliquées dans une tâche visuomotrice a aussi été observée chez des individus considérés « experts » comparativement à des individus sans expertise, dans une tâche simple et demandant peu cognitivement, et ce, pour une performance

égale à la tâche (Bernardi et al., 2013). Si l'on considère les autistes comme des experts en perception visuelle, les diminutions d'activation pour cette tâche requérant un traitement visuel simple, sans différence de performance entre les groupes, pourraient donc être le reflet d'une meilleure efficacité neuronale.

Le fait d'activer les aires visuelles de façon moins importante dans cette tâche de détection peut aussi être le reflet d'un mode cognitif particulier aux autistes les menant à résoudre une tâche au niveau cognitif le plus bas possible (Kana et al., 2013; Mottron, Burack, Stauder, & Robaey, 1999; Mottron et al., 2006, principe 5). Il est possible que par défaut, le système visuel des typiques traite les stimuli visuels de façon plus extensive (ex, analyse des contrastes, de la luminance) alors que le cerveau des autistes s'en tient à la simple détection de présence du stimulus; la nature, position ou les caractéristiques du stimulus étant non pertinents à la tâche. Cette hypothèse est aussi cohérente avec l'observation des suractivations visuelles en autisme pour des tâches plus complexes. Les suractivations visuelles souvent associées à des diminutions de l'activité frontale comparativement aux typiques pour différentes tâches, ont été interprétées comme une façon de résoudre des tâches cognitives complexes avec un traitement plutôt de type bas niveau, soit en utilisant la perception visuelle (Kana et al., 2013). Ce résultat est en accord avec celui de Soulières et al. (2009), observant, même dans une tâche complexe de raisonnement, que les autistes utilisent la perception de façon plus importante pour résoudre les problèmes alors que les typiques utilisent des stratégies relevant plutôt des fonctions frontales. Cela suggère aussi la plus grande implication du traitement visuel comme conséquence du traitement frontal déficitaire, mais, possiblement aussi, résultant d'une plus grande autonomie de fonctionnement des régions postérieures en autisme, liée à la connectivité cérébrale atypique (Just et al., 2012). Notre résultat d'un plus petit corps calleux en frontal associé au transfert de l'information plus visuel va aussi en ce sens.

Ces mécanismes compensatoires ou reliés à un effet de plasticité suite à l'expertise ont pour effet un maintien de la performance aux tâches étudiées ou parfois une meilleure performance. Dans la tâche de raisonnement des matrices de Raven (Soulieres et al., 2009), la plus grande activité visuelle et la moins grande activité frontale n'étaient en effet pas associées à un meilleur résultat au test, mesuré par l'exactitude des réponses. Toutefois, les autistes

avaient des temps de réponse significativement plus rapides, ce qui a mené à suggérer un avantage dans le traitement de l'information comparativement aux individus typiques. Cet avantage au niveau de la rapidité de réponse a aussi été observé dans diverses autres tâches telles que le sous-test Blocs du Wechsler, les figures cachées et la recherche visuelle (ex.: Caron et al., 2006; de Jonge, Kemner, & van Engeland, 2006; Edgin & Pennington, 2005; Falter, Plaisted, & Davis, 2008; O'Riordan M, 2004; O'Riordan & Plaisted, 2001; O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001).

Le rôle de la vitesse de traitement perceptif dans la cognition autistique a été investigué spécifiquement grâce à la tâche de temps d'inspection. Nous avons montré en effet que la meilleure performance des autistes à la tâche d'IT était reliée à leur performance supérieure au Raven. Cela est donc compatible avec un rôle plus important des processus visuels dans l'intelligence et le raisonnement autistique, plus particulièrement, une plus grande efficacité ou rapidité de traitement de l'information visuelle par le cerveau.

5.3.4 Vitesse de traitement perceptif : l'impact des déficits moteurs

En autisme, vu les atypicalités de la matière blanche et son rôle important dans la vitesse de conduction de l'information dans le cerveau, la vitesse de traitement a été investiguée à plusieurs reprises. Les échelles de Wechsler comprennent les sous-tests Code et Recherche de symbole qui, ensemble, forment un indice utilisé comme mesure de vitesse de traitement. Outre les pics au sous-test Blocs et le plus bas QIV différenciant les autistes des individus typiques au profil cognitif mesuré avec le Wechsler, on observe aussi des scores plus bas chez les autistes au niveau de l'IVT. Toutefois, comme la mesure de cet indice comprend des aspects perceptifs et moteurs, elle ne peut être considérée comme mesurant la vitesse de traitement à proprement dite. En effet, l'IVT implique de recopier au crayon des petits symboles présentés et de biffer rapidement des symboles avec un crayon. La vitesse de traitement perceptif intacte, voire supérieure (Barbeau et al., 2013) des autistes (appariés aux typiques avec le Wechsler), combinée à leurs déficits de rapidité motrice (Barbeau et al., en révision) et aux déficits graphomoteurs observés dans cette population (Mayes & Calhoun, 2007), suggèrent que les déficits rapportés à l'IVT sont probablement liés davantage à la composante motrice qu'à la vitesse de traitement de l'information présentée.

L'IVT nécessite une intégration entre les hémisphères et requiert donc l'implication du corps calleux (Zaidel & Iacoboni, 2003). Des liens ont d'ailleurs été observés entre la performance à l'IVT des autistes et les atypicalités du corps calleux (Alexander et al., 2007). Lazar et ses collègues (2014) ont étudié plus spécifiquement le sous-test du Code et ont observé des différences entre la performance à la tâche et les régions du corps calleux auxquelles elle est associée. Chez les typiques la performance était reliée aux propriétés du corps calleux connectant les régions motrices, alors que chez les autistes, la performance était reliée aux propriétés microstructurales des régions du corps calleux connectant les aires visuelles et temporales. Les auteurs ont donc suggéré que les groupes diffèrent dans les mécanismes sous-tendant la performance au Code. Suivant la logique de notre interprétation des résultats de la tâche de Poffenberger, il se pourrait que chez les autistes, les atypicalités de matière blanche inter et intrahémisphériques dans les régions associées à la motricité (Mostofsky et al., 2007), mènent à une surimplication des fonctions visuelles dans ces tâches. Par contre, vu la nature chronométrée du test, le rôle trop important de la motricité (plus particulièrement de l'orthographie) dans l'IVT ne leur permettrait pas d'atteindre une performance au niveau de celle des typiques malgré leur surfonctionnement visuel.

La présente thèse et les liens qui ont été montrés entre le rôle de la perception et la balance d'activité entre les régions postérieures et frontales mènent aussi à se pencher, après l'impact des déficits frontaux sur le fonctionnement occipital, sur l'inverse, soit le rôle de la perception dans les fonctions frontales, plus spécifiquement, les fonctions motrices.

5.3.5 Intégration sensorimotrice et le lobe pariétal

Malgré une perception intacte ou supérieure, il n'est pas exclut que les fonctions visuelles puissent avoir un rôle à jouer dans les déficits moteurs en autisme. Les tâches motrices étudiées dans la présente thèse sont des tâches guidées visuellement nécessitant la coordination œil-main, une analyse visuospatiale de l'espace, et pour lesquelles la rétroaction visuelle est essentielle afin de guider et d'ajuster le mouvement. L'intégration visuomotrice est requise dès les étapes précoces de l'exécution motrice, par exemple lors de la préparation du mouvement, un aspect ayant été pointé comme étant déficitaire en autisme (Dowd et al., 2011). Des déficits ont aussi été observés spécifiquement au niveau de l'intégration

visuomotrice (Linkenauger, Lerner, Ramenzoni, & Proffitt, 2012; Mayes & Calhoun, 2007), ainsi qu'au niveau de la formation et l'utilisation de la représentation spatiale et de l'intégration sensori-motrice pour planifier les mouvements efficacement et de façon juste (Dowell, Mahone, & Mostofsky, 2009; Gowen & Hamilton, 2013). Dowell et ses collaborateurs suggèrent que l'intégration de l'information visuelle servant à la planification et à l'exécution du mouvement serait affectée. De façon intéressante, chez les autistes, un input proprioceptif et une rétroaction visuelle atypiques durant une action motrice pourraient être liés à des différences de connectivité anatomique et fonctionnelle dans les régions sensorimotrices et visuelles du cerveau (Izawa et al., 2012).

Just et collègues (2012) ont d'ailleurs montré, dans une tâche de traitement exécutif visuospatial (Tour de Londres), des réductions de la connectivité entre les régions pariétales et frontales, et donc, une plus grande autonomie pariétale. Les régions pariétales supérieures du cerveau, situées entre le lobe occipital et le lobe frontal, sont responsables de l'intégration visuomotrice, et jouent un rôle dans les actions dirigées et l'imitation et dans la planification et le contrôle des actions (Iacoboni, 2006). Dans une tâche d'apprentissage visuomoteur, les autistes ont démontré moins d'activité cérébrale reliée à la tâche dans les régions pariétales supérieures (Muller, Kleinhans, Kemmotsu, Pierce, & Courchesne, 2003). Donc, en autisme, l'analyse visuelle serait intacte, mais des atypicalités pourraient être présentes pour ce qui est de transcoder l'information visuelle afin d'être appliquée pour guider l'action motrice, conséquemment à une moins bonne communication entre les régions pariétales et les régions motrices frontales. Une récente revue de littérature sur les habiletés motrices en autisme (Gowen & Hamilton, 2013) suggère que l'input sensoriel de bas niveau serait intact, voire supérieur, mais le traitement sensori-moteur de plus haut niveau serait anormal. Par exemple, des différences dans la balance entre l'input proprioceptif et visuel dans l'apprentissage moteur pourraient être source d'atypicalités motrices telles qu'observées en autisme.

5.3.5 Génétique, plasticité et variabilité

La relation entre les origines génétiques de ce trouble neurodéveloppemental qu'est l'autisme et les altérations cérébrales anatomiques et fonctionnelles réside en des modifications au niveau de l'équilibre fonctionnel des neurones. En effet les gènes impliqués

dans l'autisme sont en grande partie reliés à l'homéostasie des neurones et des synapses (Huguet et al. 2013). Cela affecterait entre autres la plasticité synaptique, un mécanisme favorisant les effets de l'expérience sur l'anatomie et la fonction des régions cérébrales, augmentant leur variabilité. En effet, l'activité neuronale induit des modifications au niveau de la synapse permettant aux circuits neuronaux une réponse dynamique à l'expérience. Les mécanismes de plasticité synaptique en lien avec l'activité des neurones seraient d'ailleurs une cible importante des mutations génétiques observées (Ebert & Greenberg, 2013).

Les mécanismes de formation et d'élimination de connections dans le cerveau ont aussi été impliqués dans les anomalies de développent du cerveau des jeunes autistes. Les facteurs neurotrophiques jouent un rôle important dans ces mécanismes et régulent la prolifération, la migration, la différentiation et l'intégrité cellulaires qui sont aussi affectées en autisme (Nickl-Jockschat & Michel, 2011). Des niveaux altérés de facteurs neurotrophiques sont aussi observés (Nickl-Jockschat & Michel, 2011 pour une revue de littérature) et auraient donc un impact sur la connectivité cérébrale atypique ainsi que sur les différences structurales observées. Les facteurs neurotrophiques sont aussi impliqués dans les processus de neuroplasticité et la formation des synapses permettant la communication entre les neurones. En plus d'être liée aux altérations microstructurales cérébrales, une plus grande plasticité pourrait avoir un lien causal avec les mécanismes de réallocation corticale observés dans le cerveau autiste (Markram & Markram, 2010). En effet, une plus grande plasticité fonctionnelle prédirait plus de variabilité au niveau de l'allocation régionale des fonctions cérébrales.

Pierce et collègues (2001) ont été parmi les premiers à montrer une réallocation corticale en autisme, soit le fait d'activer une région pour une fonction qui n'implique normalement pas celle-ci. Ce phénomène pourrait être largement représenté en autisme (Mottron et al., 2014). Dans l'étude de Pierce, les autistes ne présentaient pas les activations cérébrales reliées au traitement des visages typiquement observées dans le gyrus fusiforme. Deux autres études ont aussi montré une localisation des activations en réponse au traitement de visages qui divergeait des celle des sujets typiques et se trouvaient dans des régions cérébrales normalement pas associées au traitement de visages (Humphreys, Hasson, Avidan, Minshew, & Behrmann, 2008; Scherf, Luna, Minshew, & Behrmann, 2010). Les

démonstrations de suractivations visuelles lors de tâches de langage (Shen et al., 2012) ou de raisonnement (Soulieres et al., 2009) peuvent aussi être considérées, selon le modèle Trigger-Threshold-Target de l'autisme (TTT; Mottron et al., 2014, présenté plus loin), comme des exemples de modifications des allocations fonctionnelles régionales. De plus, non seulement les régions cérébrales impliquées pour une même tâche différeraient entre les autistes et les typiques, mais les régions activées seraient plus variables à l'intérieur même du groupe autiste.

Une plus grande variabilité intragroupe dans la localisation des régions activées a été observée lors d'une tâche d'apprentissage visuomoteur (Muller, Cauich, Rubio, Mizuno, & Courchesne, 2004; Muller et al., 2003). Dans cette tâche, les autistes présentaient une plus grande variabilité interindividuelle au niveau de la localisation des activations reliées à la tâche dans les régions pariétales supérieures et prémotrices. Une plus grande variabilité spatiale interindividuelle a aussi été observée dans les régions visuelles, lors des tâches de traitement de visages (Pierce et al., 2001; Scherf et al., 2010).

Les études sur le cerveau typique suggèrent que la variabilité spatiale dans l'allocation des fonctions du cerveau ne soit pas distribuée de façon égale dans l'ensemble des régions corticales. En effet, dans une étude de connectivité fonctionnelle, plus de variabilité a été observée dans les régions associatives hétéromodales que dans les régions motrices et perceptives unimodales (Mueller et al., 2013). Ce résultat est supporté par le fait que ces mêmes régions montrent aussi une plus grande variabilité en termes de gyrification (Braun, 2009). En autisme, il semblerait que les mécanismes de plasticité favoriseraient aussi ces régions non primaires qui présenteraient une gyrification augmentée (Wallace et al., 2013) ainsi que de plus importantes altérations structurales (Nickl-Jockschat et al., 2012) comparativement aux individus typiques. Afin de tester cette plus grande variabilité de localisation en autisme, en plus de voir si elle est spécifique aux régions secondaires par rapport aux régions primaires, nous avons effectué une analyse de la variabilité interindividuelle de localisation des activations IRMf reliées à la performance d'une tâche visuomotrice d'imitation (Poulin-Lord et al., 2014, voir Annexe IV). La nature de la tâche a aussi permis d'observer comment la variabilité se répartit entre les régions visuelles et motrices. Une plus grande variabilité dans la localisation des activations a été observée dans

le groupe d'autistes, plus particulièrement dans les aires motrices et visuelles associatives et du côté gauche.

La même analyse de variabilité a été effectuée avec les données IRMf de la tâche de Poffenberger (Annexe I) et nous avons aussi observé une plus grande variabilité de localisation des activations dans les aires motrices et visuelles associatives que primaires. De plus, la localisation des activations dans les régions motrices gauches (BA4 et 6) était plus variable chez les autistes que chez les typiques, une différence principalement causée par plus de variabilité dans le cortex moteur primaire (BA4). Nous n'observons pas la plus grande variabilité dans les aires associatives reliées à la motricité (BA7). Toutefois, comme le mouvement à effectuer lors de la tâche de Poffenberger est extrêmement simple comparativement à la tâche d'imitation, un moins grand nombre de participants présentaient de l'activation dans l'aire BA7, diminuant ainsi le pouvoir statistique de la comparaison. De la même façon, la présence de pics d'activations dans les aires visuelles primaires (BA17) seulement dans la moitié des sujets autistes a rendu la comparaison statistique entre les régions primaires et associatives visuelles difficile dans cette analyse.

Par ailleurs, l'analyse de variabilité ne suggère pas que les différences de groupes au niveau des activations visuelles l'étude de Poffenberger soient affectées par une localisation intragroupe plus variable. Toutefois, de façon générale, la plus grande variabilité interindividuelle soulève des questionnements quant à l'interprétation des résultats en IRMf, puisqu'elle pourrait être à l'origine de différences de groupe en termes de localisation et d'intensité des activations. La variabilité et la réallocation corticale sont donc d'importantes variables à considérer. La plus grande variabilité interindividuelle suggère aussi des mécanismes de plasticité atypiques et possiblement plus importants en autisme pouvant être mis en relation avec des aspects comportementaux. Par exemple, en plus de l'utilisation de stratégies cognitives différentes comparativement aux individus typiques, chaque individu autiste pourrait utiliser des stratégies uniques pour arriver à une même fin. Nous présenterons maintenant l'impact de ce résultat sur l'hétérogénéité du phénotype autistique, représenté dans la nosographie par la distinction autisme-Asperger.

5.3.7 Implications pour la distinction autisme-Asperger

La publication récente du DSM-5 (APA, 2013) a apporté des changements importants quant au diagnostic de trouble envahissant du développement. On parle maintenant de Trouble du spectre autistique (TSA) en utilisant une approche dimensionnelle selon des niveaux de sévérité, faisant ainsi disparaitre les catégories d'autisme, de syndrome d'Asperger et de TED-NS du DSM-IV (APA, 1994). Des spécificateurs de niveau d'intelligence, de langage et autres conditions associées, telles que le trouble développemental de motricité et de coordination, permettent ensuite une meilleure caractérisation du diagnostic. La logique de cette approche dimensionnelle est appuyée par le fait que les traits autistiques ne sont effectivement pas considérés comme catégoriels, mais comme faisant partie d'un continuum de traits et de sévérités s'étendant au spectre élargi (ex.: famille des autistes), et même à la population typique (voir Barbeau, Mendrek, & Mottron, 2009, Annexe V), pour une discussion sur les traits autistiques). Toutefois, les observations cliniques et les études empiriques supportent l'existence de différents sous-groupes du TSA caractérisés par différents traits ou combinaison de traits. Les études empiriques, tant au niveau cérébral fonctionnel et anatomique qu'au niveau cognitif, langagier, perceptif et moteur, soulèvent la question à savoir si autisme et syndrome d'Asperger devraient toujours être considérés comme deux conditions distinctes ou non. Les résultats de la présente thèse représentent un pas en avant dans la distinction et la caractérisation des deux sous-groupes. L'étude avec la tâche de temps d'inspection montre que les individus autistes et Asperger peuvent en effet être distingués par leurs styles cognitifs. La plus grande vitesse de traitement perceptif étant spécifique aux individus autistes (TSA avec retards de langage) et associée à leur performance de raisonnement aux matrices de Raven, alors que les Asperger (TSA sans retard de langage) présentent des résultats similaires à ceux des typiques. De plus, spécifiquement chez les Asperger, ce sont les habiletés langagières précoces (âge des premières phrases) qui sont associées au meilleur raisonnement non verbal. De façon similaire, on a précédemment rapporté des corrélations entre les scores au Raven et la performance visuospatiale au sous-test des Blocs (échelle non verbale du Wechsler) chez les autistes, mais avec le sous-test Similitudes (échelle verbale) chez les Asperger (Soulieres et al., 2011).

Au niveau clinique, il est souvent suggéré que les déficits moteurs seraient plus communs chez les individus avec syndrome d'Asperger, mais peu d'études expérimentales l'ont confirmé. Les résultats de l'étude « Comparing motor skills in autism spectrum individuals with and without speech delay » (Barbeau et al., en révision; chapitre 4) démontre que les autistes présentent aussi des troubles de motricité, mais que les deux groupes peuvent être distingués par des déficits moteurs de nature différente. En effet, les déficits des individus Asperger seraient plus remarquables lors de tâches plus complexes impliquant dextérité et coordination bimanuelle. Les autistes quant à eux, seraient plus affectés au niveau de la rapidité d'exécution simple. De plus, les déficits moteurs respectifs des deux sous-groupes s'inscrivent différemment dans leur profil cognitif. Nous avons montré qu'effectivement, les déficits moteurs étaient en lien avec l'intelligence et les habiletés langagières chez les individus Asperger, mais chez les autistes, les déficits moteurs n'étaient aucunement en lien avec l'intelligence ou les atypicalités de langage. Ensemble, les investigations des aptitudes visuomotrices à l'aide des tâches motrices et de temps d'inspection prédisent la présentation de l'hétérogénéité cognitive dans le TSA. Le retard de langage coexiste avec les bonnes habiletés visuospatiales, alors que les bonnes aptitudes langagières sont associées aux déficits de coordination motrice.

5.3.8 Relation avec les modèles récents de l'autisme

L'hétérogénéité observée dans le profil cognitif des différents sous-groupes du spectre autistique appuie le récent modèle Trigger-Threshold-Target (TTT) de l'autisme (Mottron et al., 2014). Selon ce modèle, les mutations génétiques à l'origine du phénotype autistique, bien qu'étant très diverses et de nature polygénique, ont en commun qu'elles entrainent ou déclenchent (*trigger*) des réactions de plasticité neuronale tant au niveau de la synapse, lieu de communication entre les neurones, que de l'organisation corticale. Toutefois, ces mutations ne sont pas suffisantes pour causer en soi le phénotype autistique, mais sont plutôt des facteurs prédisposant à l'autisme. Certains autres facteurs, tels que des polymorphismes de gènes particuliers jouent un rôle déterminant et modifient le seuil (*threshold*) au-delà duquel la réaction plastique peu survenir. Une certaine vulnérabilité génétique pourrait aussi diminuer les seuils de sensibilité à des facteurs environnementaux déclencheurs (Herbert, 2010). La nécessité d'un élément déclencheur explique aussi pourquoi l'autisme se manifeste durant le

développement malgré la présence de prédispositions génétiques (Markram & Markram, 2010). De plus, les différentes combinaisons possibles d'éléments génétiques déclencheurs et de seuils cibleraient (*target*) différentes régions cérébrales. Selon le modèle TTT, les régions impliquées dans la perception et le langage seraient plus particulièrement touchées, et ce, vu leurs similarités au niveau évolutif, neuronal et développemental. En effet, ces régions ont évolué relativement récemment et se développent sur une période de temps plus prolongée ce qui les rend plus susceptibles à la plasticité et à la variabilité. La cible de ces réactions de plasticité variable expliquerait donc l'hétérogénéité des forces et faiblesses cognitives observées dans le spectre autistique, soit les forces en perception pour les autistes et les forces langagières pour les individus Asperger.

Le modèle TTT stipule que la plasticité favoriserait les fonctions langagières chez les Asperger, mais elles utiliseraient des ressources cérébrales nuisant aux habiletés motrices. Le développement « négligé » (*neglect*) de la motricité cause ainsi les déficits moteurs caractérisant ce sous-groupe et les différentiant des autistes. Cela est conforme avec le résultat montrant que des déficits moteurs sont corrélés et s'agrègent avec les habiletés en langage dans le sous-groupe Asperger. Considérant les atypicalités de la matière blanche, la compétition pour les ressources cérébrales pourrait, dans ce cas, venir du fait que le langage et la motricité bimanuelle requièrent tous deux un haut degré de coordination interhémisphérique. Le développement précoce du langage utiliserait les allocations régionales disponibles et/ou la capacité de traitement interhémisphérique, laissant peu de place au développement des habiletés motrices bimanuelles. À l'opposé, un manque ou un retard de développement du langage, rendraient disponible au développement moteur complexe plus de ressources.

Dans l'étude de la vitesse de traitement perceptif, nous avons montré que l'implication des forces perceptives était spécifique aux autistes avec retard de langage. Selon le modèle TTT, ce traitement perceptif accru serait un obstacle au développement des fonctions langagières en entrainant une négligence (*neglect*) des aspects non perceptifs impliqués dans le langage, le déficit le plus important les distinguant des Asperger. Outre ces différences entre les sous-groupes pour ce qui est des aspects cognitifs « négligés », les sous-groupes auraient

en commun les déficiences dans le domaine social. Voir figure 1 pour une schématisation des aspects *trigger*, *threshold*, *target* et *neglect* du modèle.

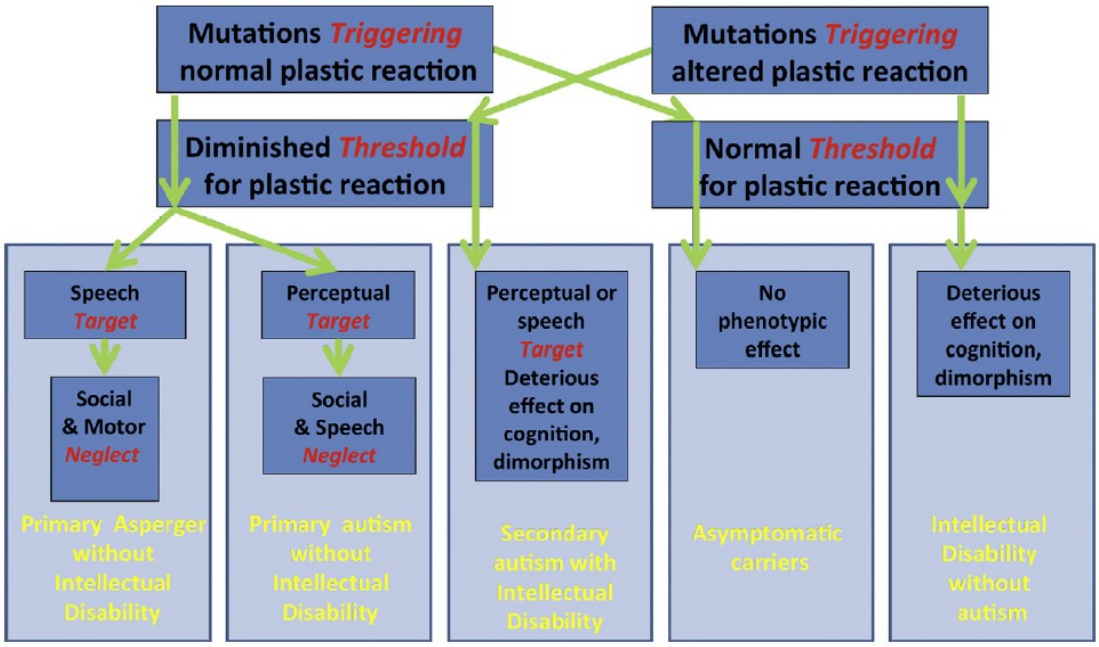

Figure 1. Schématisation du modèle Trigger-Threshold-Target (TTT) de l'autisme. Tiré de Mottron et al. (2014).

Les liens établis précédemment entre la plasticité cérébrale, la connectivité atypique et les surfonctionnements perceptifs sont aussi compatibles avec une autre théorie récente de l'autisme. Cette théorie, développée pour expliquer de façon cohérente et unifiée l'hétérogénéité de l'autisme, est celle de l'Intense World (Markram & Markram, 2010). Selon ce modèle, l'autisme serait un « syndrome moléculaire » qui, si activé, fait en sorte que l'expression de gènes devient plus sensible à des stimulations environnementales et cause une accélération et un surdéveloppement du cerveau. Plus spécifiquement, les microcircuits neuronaux seraient affectés de façon à provoquer leur hyperfonctionnement, leur hyperréactivité et leur hyperplasticité, causant les traits autistiques. Selon ce modèle, l'ensemble des traits autistiques serait donc expliqué par une hyperperception, une hyperattention, une hypermémoire et une hyperémotivité. Chacun de ces aspects serait affecté à des degrés différents selon les individus, leur génétique, leurs expériences et des facteurs épigénétiques, expliquant les différentes sévérités du spectre autistique. De plus, les

microcircuits seraient plus ou moins affectés selon la région cérébrale dans laquelle ils se trouvent. Les régions liées aux processus cognitifs, perceptifs et moteurs plus élémentaires seraient plus touchées au détriment du fonctionnement des processus cognitifs de plus haut niveau ou plus intégratifs. Toujours selon le modèle Intense World, durant le développement du cerveau, un apport de l'information plus important provenant des aires sensorielles vers les aires intégratives de plus haut niveau, comme les aires associatives et frontales, pourrait causer la croissance excessive observée dans ces régions. Ce modèle est aussi cohérent avec les théories de connectivité de l'autisme, particulièrement la surconnectivité locale qui serait associée à l'hyperréactivité des mini-colonnes et à leur plus grande autonomie. Les augmentations de matière blanche en jeune âge agiraient de manière compensatoire afin de coordonner cette activité locale intense et à tendance autonome. En résumé, un hyperfonctionnement local et une plasticité augmentée, en réaction à l'environnement, déclenchent un développement accéléré du cerveau et une hyperréactivité sensorielle. De plus, la mémoire intensifiée pour chaque expérience vécue rendrait les autistes plus réticents aux surprises.

Cela nous mène à une autre théorie, celle du cerveau prédictif dysfonctionnel (Gomot & Wicker, 2012; Van de Cruys et al., 2014) basée sur les observations cliniques des particularités de traitement sensoriel et de réticence au changement. Selon ce modèle, de nombreux symptômes de l'autisme viendraient de difficultés de prédiction. Un cerveau prédictif utilise l'information de l'environnement pour prédire une suite, intégrer les informations et comprendre une situation. Les prédictions sont aussi le résultat des expériences vécues et des expériences attendues et le fait de prédire de façon adéquate sert de filtre attentionnel et permet, par exemple, de traiter l'information sociale en triant ce qui est pertinent de ce qui ne l'est pas. Les déficits de prédictions en autisme associés aux biais de traitement local de l'information réduiraient la tendance normale à traiter l'information dans son contexte. Ils expliqueraient aussi les comportements répétitifs et ritualisés en tant que mécanisme compensatoire rassurant. Ce modèle explique aussi les difficultés de perception et de fonctions exécutives telles que la flexibilité et la planification en lien avec une influence top-down altérée des fonctions frontales sur les procédés de traitement sensoriel. Il est concordant avec les théories de sous-connectivité de longue distance et appuie les

informations présentées précédemment concernant le rôle d'une relation atypique entre les mécanismes frontaux et perceptifs, tant dans le raisonnement que dans les performances visuomotrices. Au niveau moteur, cette théorie est aussi compatible avec la présente thèse puisque le cerveau prédictif dysfonctionnel affecterait l'anticipation et la planification des mouvements (Sinha et al., 2014).

5.3.9 Implications

Le profil cognitif distinct des autistes et des individus Asperger, catégorisés selon la présence ou l'absence de retard de langage est important et discriminatoire. Il devrait être pris en compte en recherche, malgré le DSM-5, principalement dans le cas d'études empiriques impliquant la perception, la motricité ou le langage. Un critère d'inclusion de trouble du spectre autistique sans égard à sa composition exacte aura des répercussions au niveau des résultats de groupes et de leur interprétation. De plus, les différences marquées au niveau du profil cognitif pourraient être considérées dans l'élaboration de stratégies d'apprentissage, d'intervention ou d'adaptation spécifiques à chaque individu, dépendamment entre autres, des particularités perceptives, motrices ou langagières qu'il présente. Notre étude de la vitesse de traitement perceptif a aussi permis de mettre en lumière une attention particulière devant être portée aux mesures utilisées en recherche afin d'apparier les groupes au niveau de l'intelligence. Encore une fois, le profil atypique en autisme rend le test de Wechsler peu représentatif de leur niveau d'intelligence réel, niveau qui serait plus adéquatement mesuré à l'aide du test des matrices de Raven, ne nécessitant aucune instruction ou réponse verbale.

La présente thèse suggère aussi une prudence quant à l'interprétation des différences observées en autisme à l'aide de l'imagerie, au niveau cérébral anatomique et fonctionnel. L'effet de différences anatomiques ne devrait pas être assumé automatiquement comme étant celui auquel on s'attendrait d'une même différence liée à une variabilité naturelle ou, par exemple, à une lésion, dans la population non autiste. Vu l'effet de la génétique sur la plasticité cérébrale en autisme et la réorganisation corticale qui en découle, il est possible qu'une différence anatomique soit associée à des mécanismes adaptatifs ou compensatoires de réorganisation ayant un effet sur les fonctions impliquées. Il en est de même pour les activations cérébrales fonctionnelles; l'effet de la variabilité interindividuelle dans la

localisation des activations, la réallocation corticale au niveau de la région impliquée dans une tâche donnée, ainsi que l'effet de l'expertise doivent être considérés.

5.3.10 Limites et avenues de recherche

Nous avons investigué le lien entre la performance au paradigme de Poffenberger et les propriétés de la matière blanche interhémisphérique permettant le transfert de l'information entre les régions bilatérales motrices ou visuelles. Il serait intéressant d'étudier aussi la connectivité *intra*hémisphérique afin de voir comment, chez les autistes, les propriétés de la matière blanche connectant les régions occipitales et frontales d'un même hémisphère peuvent être mises en relation avec les performances au paradigme de Poffenberger. Par exemple, les différences d'efficacité de communication entre les régions visuelles et motrices pourraient expliquer, entre autres, des temps de réponse légèrement plus lents chez les autistes.

Dans un même ordre d'idées, une autre étude pertinente consisterait à investiguer la tâche de temps d'inspection à l'aide de l'IRMf afin de vérifier l'implication des régions visuelles dans cette tâche chez les autistes comparativement aux individus typiques et Asperger. Il serait intéressant de vérifier si la plus grande vitesse de traitement perceptif est liée à une surconnectivité locale, à une plus importante activation dans les aires visuelles ou à une moins grande connectivité avec les régions plus antérieures et donc à une plus grande indépendance des régions visuelles.

De plus, des analyses de connectivité fonctionnelle pour chaque composante de la tâche seraient complémentaires aux analyses déjà effectuées. Notamment, quantifier le niveau de connectivité fonctionnelle ou effective entre les régions homologues motrices et visuelles impliquées dans la tâche de Poffenberger pourrait appuyer les résultats obtenus dans la première étude. Également, étudier la connectivité entre les régions visuelles et motrices ipsilatérales activées durant la tâche de Poffenberger permettrait de contribuer à l'élaboration des modèles de connectivité de l'autisme. La magnétoencéphalographie (MEG), une technique d'imagerie cérébrale ayant une résolution temporelle supérieure à l'IRMf, permettrait une meilleure description du trajet emprunté par l'information lors de la tâche de Poffenberger et de comment celui-ci il diffère chez les autistes. En combinant les résultats obtenus en MEG et en IRMf, il serait possible de mieux cerner le décours temporel et spatial du traitement de

l'information dans les 200 à 400 ms qui séparent le moment où le stimulus est présenté de celui où le sujet fait sa réponse motrice. Ainsi, il serait possible de confirmer si effectivement le transfert de l'information d'un hémisphère à l'autre se fait principalement au niveau visuel chez les autistes plutôt qu'au niveau subséquent, soit moteur.

Afin de pousser plus loin l'investigation du traitement visuomoteur en autisme et vu le rôle suggéré de la communication entre les lobes pariétal et frontal dans les déficits moteurs observés en autisme, il serait intéressant de tenter de faire des liens entre la performance aux tâches motrices et les propriétés de la matière blanche intrahémisphérique. Plus particulièrement, étudier les propriétés des fibres connectant les lobes pariétal et frontal permettrait de savoir si, effectivement, les difficultés aux tâches de Annett et Purdue peuvent être associées à une l'intégration sensorimotrice atypique. Dans la présente thèse l'étude en IRM n'incluait pas de groupe Asperger, toutefois, il serait pertinent de comparer les autistes aux individus Asperger afin de déterminer si les troubles d'intégration sensorimotrice sont spécifiques aux autistes. Il serait aussi intéressant de préciser si les réductions de corps calleux sont spécifiques aux autistes ou non et si on trouve des réductions dans différentes régions du corps calleux chez les individus Asperger. Il serait ainsi possible de vérifier si la plus grande implication du traitement visuel dans le transfert interhémisphérique est spécifique aux autistes, comme on pourrait s'y attendre. Le sous-groupe d'individus Asperger présentant des difficultés comportementales en ce qui a trait à la coordination bimanuelle, l'imagerie permettrait de savoir si ces difficultés peuvent être associées à des réductions des régions motrices du corps calleux. D'autre part, il serait intéressant de faire les analyses de variabilité de localisation des activations en incluant un groupe d'individus Asperger afin de tester le modèle TTT selon lequel on s'attend à une plus grande variabilité, mais dans différentes régions (moins perceptives, mais plus dans les aires associées au langage). De façon générale, la littérature sur les différences cérébrales dans les TSA pourrait bénéficier d'une meilleure caractérisation selon les sous-groupes.

Bien que la présente thèse ne présente pas la réponse finale quand à la nature des différences entre les autistes et les Asperger, elle appuie certaines pistes qui vaudraient la peine d'être explorées. S'il est vrai que les modifications génétiques ne ciblent pas les mêmes régions dans les différents sous-groupes, cela suggère la pertinence pour les recherches futures

de se concentrer sur l'origine des variations phénotypiques et d'investiguer des différences génétiques entre les sous-groupes du TSA qui, de toute évidence, mènent à des trajectoires développementales et une symptomatologie différentes. Haar et ses collègues (2014) insistent sur l'importance de définir différents sous-groupes sur la base de la génétique, des comorbidités cliniques des sensibilités sensorielles qu'ils considèrent comme la prochaine étape la plus urgente pour la recherche sur les TSA.

L'âge des participants étudiés dans la présente thèse constitue aussi une limite importante pour l'interprétation des résultats et leur généralisation. Premièrement, les résultats s'appliquent principalement aux groupes d'âge investigués, soit des adolescents et adultes entre 14 et 35 ans, or, on sait que beaucoup de symptômes et comportements autistiques se normalisent ou se contrôlent avec le développement vers l'âge adulte (APA, 2013), de plus, tel que discuté, les atypicalités au niveau cérébral s'amenuisent aussi vers à l'âge adulte. Aussi, puisqu'entre 14 et 35 ans, le cerveau subit toujours des changements, étudier une étendue d'âge plus restreinte, et donc un échantillon plus uniforme, serait idéal. D'autre part, dans le cas de la première étude de cette thèse, étudier des participants plus jeunes aurait pu faire ressortir des résultats différents, possiblement entre autres, des différences de groupe au niveau des mesures de DTI. Le fait d'étudier des populations plus âgées laisse place à des mécanismes compensatoires et adaptatifs pouvant expliquer un parton de résultats qui diffère de ce qui pourrait être observé avec des populations plus jeunes. Vu le développement atypique du cerveau autiste, plus d'études longitudinales seraient informatives et permettraient entre autres d'investiguer, pour certaines particularités cérébrales ou cognitives, la part qui est compensatoire et la part qui est primaire, ou intrinsèque au fonctionnement du cerveau autiste.

Conclusion

L'autisme est un trouble d'origine neuro-génétique caractérisé par des altérations au niveau de la connectivité cérébrale, incluant des diminutions du corps calleux, causées par un développement atypique du cerveau. Ces différences ont des effets sur le fonctionnement du cerveau causant des atypicalités au niveau de la communication entre les régions et au niveau de la latéralisation des structures et des fonctions. Ces différences développementales ainsi que l'impact de la génétique sur la plasticité synaptique provoqueraient une organisation cérébrale différente. L'absence de déficit direct au niveau de l'intégration interhémisphérique en lien avec les diminutions du corps calleux dans les régions connectant les aires motrices pourrait être le reflet de mécanismes compensatoires. Elle pourrait aussi résulter d'une organisation différente dans la distribution des fibres du corps calleux, organisation qui favoriserait les régions visuelles.

La réorganisation cérébrale implique un plus grand rôle de la perception dans la cognition autistique, tant au niveau de la communication interhémisphérique que du fonctionnement local. Les surfonctionnements visuels se présentent au niveau comportemental par des forces cognitives lorsque la perception est impliquée et incluent une bonne vitesse de traitement perceptif ainsi qu'au niveau cérébral, par la plus grande implication des régions occipitales pour diverses tâches ou fonctions cognitives. De plus, il est probable que la connectivité atypique entre certaines régions du cerveau et le lobe frontal ait un effet sur la motricité en causant des déficits dans l'intégration entre l'information perceptive et la production des mouvements. Cela affecterait leur planification, leur anticipation et leurs ajustements. Ces particularités au niveau perceptif et moteur seraient déterminantes dans la classification des sous-groupes du spectre autistiques selon la présence ou l'absence de retard de langage. Les surfonctionnements perceptifs seraient associés aux individus avec retard de langage (les autistes), mais pas à ceux sans retard de langage (les personnes Asperger). De plus, les deux sous-groupes diffèrent au niveau de la sévérité et de la nature des leurs déficits moteurs. Les Asperger ayant des troubles moteurs plus complexes impliquant la coordination et la dextérité. Ces résultats sont compatibles avec le modèle TTT de l'autisme; la plasticité

accrue et l'organisation cérébrale se présenteraient de façon différente entre les sous-groupes causant la variabilité phénotypique des troubles du spectre autistiques. En plus de cette variabilité entre les sous-groupes, les processus plastiques causeraient une variabilité importante entre les individus, au niveau, entre autres, de la localisation des régions cérébrales impliquées dans une tâche.

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Annexe I. Topographical variability of the Poffenberger task-related activation in visual and motor regions

METHODS

Individual variability was computed in terms of localization of task related activation in Brodmann motor (BA 4, 6 (primary) and 7 (associative) and visual (BA 17 (primary), 18 and 19 (associative)) ROIs. For each participant and each ROI, the coordinate of the strongest activation peak was extracted. The distance from this coordinate and the group's corresponding coordinate was measured.

See Poulin-Lord et al. 2014 (Annexe IV) for detailed methods regarding spatial localization and distance calculations as well as for variability analyses.

Repeated measure ANOVAs were used for the visual and motor modalities with Region (Primary, Associative), Side (Left, Right) and Group as factors. Two-tailed independent-samples *t*-tests were used to further investigate significant main effects and interactions. Levene's tests (homogeneity of variance) were also used.

REULTS

Repeated measures ANOVA

There was an effect of Region: associative regions being more variable than primary regions for motor ($F(1,24)=7,33$, $p=.012$) and visual ($F(1,19)=28,58$, $p<.001$) modalities.

Group comparison (t-tests)

Only significant results are displayed.

<u>BA4-6 Left (Figure 1)</u>

AUT > TYP ($t(34)=2.107$, $p=.046$). Levene's test for equality of variances: $p=.003$.

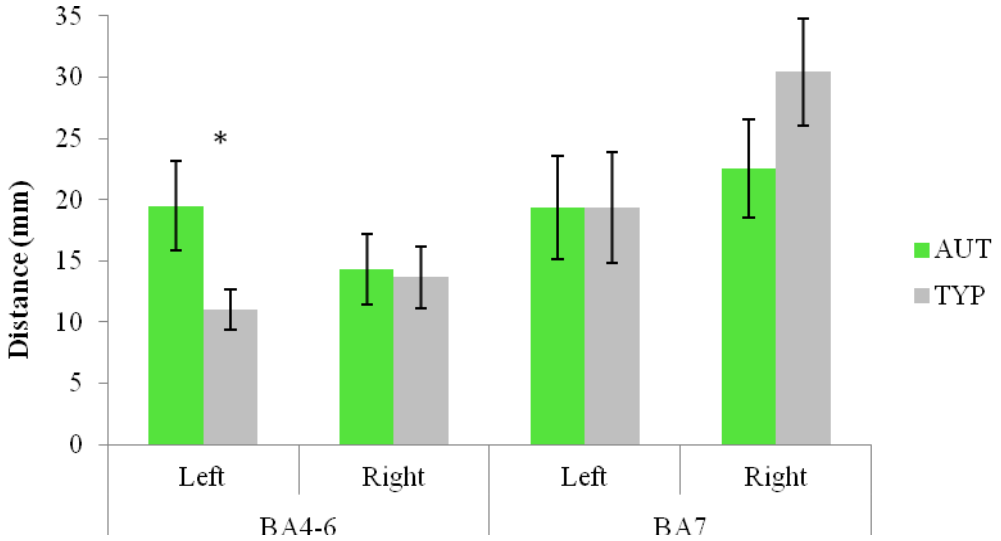

Figure 1. Mean distances in millimeters from the group mean activation peak in the motor ROIs in autistic (AUT) and typical (TYP) groups during the Poffenberger task. * p<.05.

Looking at BA 4 and 6 separately, we observed that the increased variability in autistics was mainly driven by BA4. Also, the same tendency was observed regarding the effect of Region: globally, BA 6 was more variable than BA4 in both groups and less variable than BA7 (figure 2) $F(2,22)=7.27$, p=.004. For BA4 : Levene p=.001 but no group difference with the t-test : p=.114.

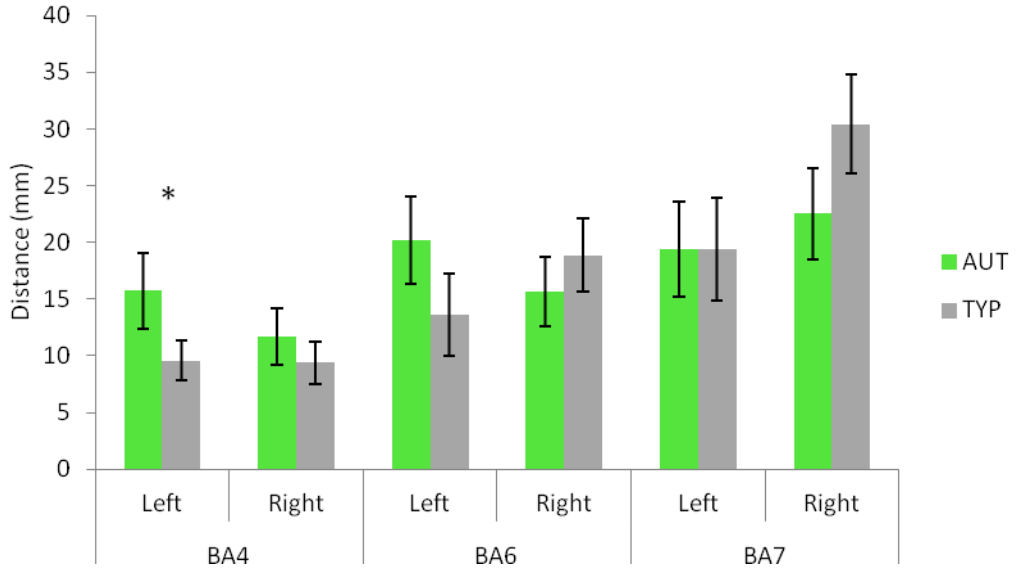

Figure 2. Mean distances in millimeters from the group mean activation peak in the motor ROIs (BA4 and BA6 displayed separately) in autistic (AUT) and typical (TYP) groups during the Poffenberger task. * $p<.05$.

There were no group differences for the visual modality (Figure 3).

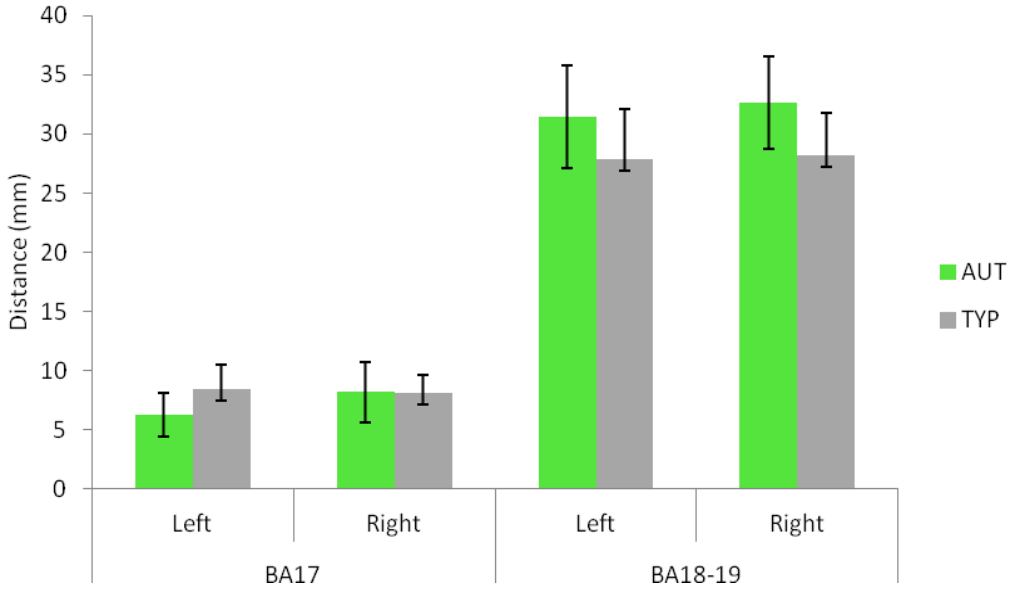

Figure 3. Mean distances in millimeters from the group mean activation peak in the visual ROIs in autistic (AUT) and typical (TYP) groups during the Poffenberger task.

% participants showing peaks of activation

A great majority of participants showed activations in BA 4, 6 and 18-19, however, the statistical results for BA 17 and BA 7 have to be interpreted with caution as the *n* were low for those conditions, a smaller proportion of participants showed activation for those ROIs:

BA17: autistics 55%, typicals 74,5 %

BA7: autistics 75%, typicals 84 %

Annexe II. Enhanced visual processing contributes to matrix reasoning in autism

Enhanced visual processing contributes to matrix reasoning in autism

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ABSTRACT

Recent behavioral investigations have revealed that autistics perform more proficiently on Raven's Standard Progressive Matrices (RSPM) than would be predicted by their Wechsler intelligence scores. A widely-used test of fluid reasoning and intelligence, the RSPM assays abilities to flexibly infer rules, manage goal hierarchies, and perform high-level abstractions. The neural substrates for these abilities are known to encompass a large frontoparietal network, with different processing models placing variable emphasis on the specific roles of the prefrontal or posterior regions. We used functional magnetic resonance imaging to explore the neural bases of autistics' RSPM problem solving. Fifteen autistic and eighteen non-autistic participants, matched on age, sex, manual preference and Wechsler IQ, completed 60 self-paced randomly-ordered RSPM items along with a visually similar 60-item pattern matching comparison task. Accuracy and response times did not differ between groups in the pattern matching task. In the RSPM task, autistics performed with similar accuracy, but with shorter response times, compared to their non-autistic controls. In both the entire sample and a subsample of participants additionally matched on RSPM performance to control for potential response time confounds, neural activity was similar in both groups for the pattern matching task. However, for the RSPM task, autistics displayed relatively increased task-related activity in extrastriate areas (BA18), and decreased activity in the lateral prefrontal cortex (BA9) and the medial posterior parietal cortex (BA7). Visual processing mechanisms may therefore play a more prominent role in reasoning in autistics.

KEYWORDS: fMRI, perception, pattern matching, intelligence.

INTRODUCTION

Raven's Standard Progressive Matrices (RSPM; Raven 1976) is broadly recognized as an effective means to estimate fluid intelligence, that is, the general ability underlying novel problem solving and reasoning (Mackintosh 1998). Consisting of a series of matrix reasoning problems of increasing complexity and difficulty, RSPM assays abilities to infer and integrate rules, to manage goal hierarchies and to form abstractions (Carpenter, et al. 1990). RSPM may be regarded as the most general single test of intelligence, as its measures are highly correlated with a wide range of other intelligence tests (Neisser 1998; Snow, et al. 1984). Recently, we observed that autistics' RSPM performance was better than predicted by their scores on the Wechsler intelligence scales (WISC-III, WAIS-III; Wechsler 1991; Wechsler 1997), the test battery most commonly used to assess autistics' intelligence. For both children and adults, autistics' RSPM scores were on average 30 percentile points higher, and ranged up to 94 percentile points higher, than their Wechsler scores, whereas for non-autistics there was no discrepancy (Dawson, et al. 2007). In related work, Asperger syndrome children were found to have significantly higher RSPM raw scores compared to a group of typically developing children matched on age and Wechsler IQ (Hayashi, et al. 2008). Together, these findings suggest that Wechsler IQ may routinely underestimate intelligence in autism and that autistics' reasoning abilities may be significantly better than reported in much of the existing clinical literature. However, the neural mechanisms responsible for this unexpectedly high level of reasoning skill are not obvious. One way to explore the source of autistics' enhanced RSPM performance is to investigate the brain mechanisms involved in matrix reasoning.

Previous neuroimaging studies exploring fluid reasoning in non-autistics have identified task-related activity in a large, bilateral frontoparietal network, involving multiple regions in lateral prefrontal and posterior parietal cortex (Haier, et al. 1988; Kalbfleisch, et al. 2007; Kroger, et al. 2002; Lee, et al. 2006; Perfetti, et al. 2008; Prabhakaran, et al. 1997). Despite the wide range of cognitive processes involved in complex tasks such as RSPM, the brain regions repeatedly identified across studies are relatively consistent (see Jung and Haier 2007 for a systematic review). Within this network, some authors emphasize the role of dorsolateral and ventrolateral prefrontal cortex in reasoning (Christoff, et al. 2001; Crone, et al. 2009; Duncan,

et al. 2000; Kane and Engle 2002). Evidence supporting the importance of prefrontal cortex in reasoning includes impairments in fluid reasoning reported to occur following prefrontal damage (Duncan, et al. 1995; Duncan, et al. 1996; Waltz, et al. 1999), though this finding is not universal (Villa, et al. 1990). In a PET study, Duncan et al. (2000) used two different tasks, one using verbal and the other non-verbal material, that both involve reasoning in the context of novel problem solving, that is, *fluid* reasoning. The overlap in task-related activity, located in lateral frontal cortex, was thought to reflect the reasoning component common to the two tasks. However, using similar reasoning tasks in an fMRI study, Duncan and colleagues recently reported activity in both frontal and parietal cortex, weakening their claims concerning a predominant role of prefrontal cortex in reasoning (Bishop, et al. 2008).

There are numerous alternative accounts of the functional neuroanatomy of reasoning that emphasize the involvement of a larger, more spatially distributed set of cortical regions (Haier, et al. 2003; Jung and Haier 2007; Lee, et al. 2006). Based on their review of 37 structural and functional neuroimaging studies, Jung and Haier (2007) formulated the Parieto-Frontal Integration Theory (P-FIT) of intelligence, a behavioral and physiological account of the regional functional specialization of fluid intelligence. In this model, occipital and temporal cortical activities (Brodman areas 18, 19, 21, 37) are associated with a collection of recognition, elaboration and imagery processes acting on sensory input received from primary visual cortex. Outputs of these processes influence posterior parietal cortical areas (BA 7, 39, 40) responsible for abstraction and elaboration. Parietal regions then interact with dorsolateral and ventrolateral prefrontal cortex (BA 6, 9, 10, 45, 46, 47), to support the need for varying amounts of hypothesis testing. Finally, primary and premotor regions are engaged to generate appropriate responses. This type of spatially and temporally distributed processing model gives particular emphasis to the contributions of occipital and parietal brain regions to the larger reasoning network.

One experimental strategy for distinguishing among candidate reasoning models involves studying how regional brain activity is differentially modulated according to problem complexity or individual differences in reasoning skill. Activity changes related to problem

complexity have been investigated using a figural vs. analytic characterization of RSPM items. While figural items can be largely solved with perceptual strategies such as gestalt completion, analytic items require progressively more complex rule inference and integration (Carpenter, et al. 1990). As problem complexity increases, so does activity across many parts of the reasoning network (Lee, et al. 2006; Prabhakaran, et al. 1997), including changes in prefrontal cortex (Christoff, et al. 2001; Crone, et al. 2009; Kalbfleisch, et al. 2007; Kroger, et al. 2002). As for individual differences, higher intellectual abilities are associated with relatively increased engagement of occipital and parietal cortex and decreased engagement of frontal cortex in abstract reasoning, as is activity associated with a variety of cognitive tasks (Blair 2007).

Because recent findings show a relative advantage for autistics in RSPM performance as compared to their Wechsler IQ, studying the neural mechanisms responsible for autistics' reasoning skills may provide unique insights into the nature of autistic cognition. The complex character of matrix reasoning, and the existing evidence for regional functional specialization of many perceptual and cognitive processes, raises the possibility that, when reasoning, autistics may differentially engage the some components of the frontoparietal reasoning network. This notion is supported by evidence from previous fMRI studies comparing autistic to non-autistic brain activity during reasoning tasks involving semantic categorization, sentence comprehension and working memory. These studies have all found increased activity in extrastriate areas and decreased activity in prefrontal cortex in autistics (Gaffrey, et al. 2007; Kana, et al. 2006; Koshino, et al. 2005). In addition, in developing the enhanced perceptual functioning (EPF) model of autism, we have compiled a wide array of behavioral and physiological evidence regarding the atypical and enhanced role of perception in autism (Mottron, et al. 2006). The EPF model offers a mechanistic account explaining why a significant proportion of autistics display advantages in visual perceptual tasks, including target detection, visual discrimination and visuospatial construction. Extending this model to more complex cognitive phenomena, it is possible that autistics' skill in fluid reasoning reflects stronger engagement of occipital and parietal neural mechanisms responsible for visual attention, object encoding and abstraction.

To explore the neural bases of autistic reasoning, we used fMRI to measure neural activity during RSPM problem solving, making minimal modifications to the test to maximize the ecological validity of the results. This approach has the potential advantage of allowing more accurate inferences about the particular brain processes engaged when RSPM is administered in clinical settings. The EPF model predicts that the neural systems involved in matrix reasoning will include stronger engagement of visual perceptual mechanisms in autistics.

METHODS

In this study, autistic and non-autistic control participants completed two related self-paced tasks, the 60 RSPM problems in random order, and a comparison pattern matching task designed to be visually similar to RSPM but requiring minimal reasoning. Task-related changes in brain activity were recorded using fMRI.

Participants

The entire experimental sample comprised 15 autistics and 18 non-autistics, 14 to 36 years old (Table 1). While both groups performed the self-paced RSPM fMRI task with equivalent accuracy, the autistic group responded more quickly. To avoid possible confounds associated with this discrepancy in mean response times, our principal analyses were conducted on participant samples additionally matched on mean RSPM task response times. This matching process was achieved by excluding results from the three fastest autistic participants and the five slowest non-autistic participants, resulting in equivalent mean response times in final groups comprising 12 autistic and 13 non-autistic participants.

All participants gave written informed consent and were compensated for their participation in accordance with protocol # 06-07 018 approved by the Regroupement Neuroimagerie/Québec IRB. Exclusion criteria were: uncorrectable visual impairment; current use of psychoactive or vasoactive medications; and use of drugs or alcohol exceeding 2 drinks per day. All structural scans were reviewed by a neurologist to rule out the presence of any anatomical abnormalities. Additionally, non-autistics were screened through a questionnaire for any personal or familial

neurological or medical conditions known to affect brain function. Groups were matched on age, sex, manual preference and full-scale IQ.

Clinical Characterization. The autistic participants were recruited from the research database of the Pervasive Developmental Disorders Specialized Clinic of Rivière-des-Prairies Hospital (Montreal, Canada). A multidisciplinary evaluation based on DSM-IV criteria is performed at the clinic, including the Autism Diagnostic Interview-Revised (ADI-R; Lord, et al. 1994), the Autism Diagnosis Observation Schedule module 3 or 4 (ADOS-G; Lord, et al. 2000), clinical evaluation and psychometric testing. Twelve autistic participants were characterized with both standardized diagnostic instruments, and three were characterized with the ADI and a clinical interview based on an ADOS-G assessment. Individuals with no history of speech delay, echolalia or pronoun reversal, and who therefore also met criteria for Asperger syndrome, were excluded from the sample.

Psychometric Characterization. Full-scale IQ scores were derived from Wechsler Scales of Intelligence (WISC-III or WAIS-III) scores; autistics in the performance matched sample had a mean IQ of 101.5 and non-autistics 105.31. The corresponding scores for the entire sample were 99.73 and 106.22. Manual preference was estimated using the Edinburgh Handedness Inventory. There was no significant difference between the two groups in IQ or manual preference (Table I).

TABLE I Participant Characteristics. Groups were matched on sex, age, full scale IQ and manual preference. These measures are reported for the entire group of participants, as well as for subsamples matched on RT. Age is reported in years. Manual preference is reported as the Edinburgh score (from -100 completely left-handed to +100 completely right-handed). ADI: Autism Diagnostic Interview. Between group differences were examined using ANOVA followed by post-hoc independent sample *t*-tests.

	Entire sample			Performance matched sample		
	AUT	nonAUT	*p*	AUT	nonAUT	*p*
Sample size (sex)	15 (2F, 13M)	18 (3F, 15M)		12 (1F, 11M)	13 (2F, 11M)	
Age						
M (*SD*)	22.40 (5.95)	21.72 (5.20)	.73	22.08 (4.91)	20.15 (3.02)	.26
Range	14 - 35	14 - 36		16 - 32	16 - 25	
Full scale IQ						
M (*SD*)	100.87 (12.05)	106.22 (12.97)	.23	101.50 (12.56)	105.31 (14.49)	.49
Range	85 - 121	81 - 131		87 - 121	81 - 131	
Verbal IQ						
M (*SD*)	99.20 (14.39)	110.17 (11.50)	.02	100.92 (14.63)	109.62 (12.63)	.13
Range	81-121	85-127		81-121	85-127	
Performance IQ						
M (*SD*)	102.80 (11.98)	100.72 (14.39)	.65	101.92 (12.91)	99.62 (15.47)	.69
Range	95-120	79-133		95-120	79-133	
Manual pref						
M (*SD*)	67.93 (45.68)	57.89 (49.15)	.55	67.67 (49.14)	58.46 (51.29)	.65
Range	-75 - +100	-50 - +100		-75 - +100	-50 - +100	
ADI						
M (cut-off)						
Social	23.27 (10)			22.16 (10)		
Comm.	18.47 (8)			17.67 (8)		
Behavior	7.00 (3)			7.08 (3)		

Task descriptions

Pattern matching task. To allow comparison with a task requiring minimal reasoning, we developed a self-paced 60-item pattern matching task that had similar spatial and temporal

properties to the RSPM problems, with a target stimulus displayed above 8 possible answers (Figure 1a). The stimulus was presented until the participant responded. In this self-paced, variable epoch length design, individual problem presentations were separated by periods of fixation whose duration varied from 4 to 7 sec, following an exponential distribution.

RSPM task. We used a slightly modified version of the original, 60-item, untimed, paper version of the RSPM. The RSPM problems are matrices of related geometric designs, from which the final (right-hand bottom) entry is missing and must be chosen from an array of 8 possible answers (Figure 1b and c). In the original version of the test, simple or figural items at the beginning progress to more difficult and complex analytic items. We made modifications to the original RSPM by: (1) horizontally shifting the rows of possible answers, respectively to the left and right, to simplify the mapping of answers made by pressing buttons with the left or right hand; and (2) reducing non-specific temporal effects by presenting the 60 RSPM items in a counterbalanced order, so that difficulty was not confounded with presentation order. The periods of fixation between problem presentations were the same as those used in the pattern matching task.

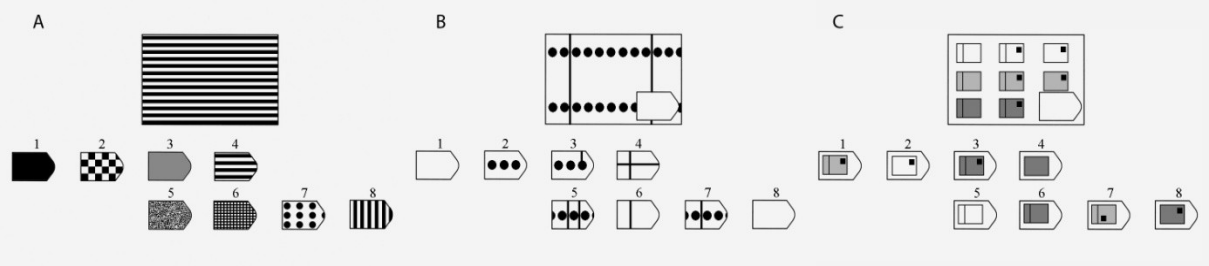

Figure 1. Sample stimuli for the pattern matching and RSPM tasks. (A) Pattern matching problems required matching the global pattern presented at the top of the screen with one of the patterns presented in the 2 rows below. (B) and (C) RSPM task problems were the 60 items of Raven's Standard Progressive Matrices. The task required selecting the correct answer from the alternatives presented at the bottom of the screen. An example of a figural problem is shown in (B) and of an analytic problem in (C).

Procedure

The first practice session, lasting 5 to 10 min, was done with the participant sitting in front of a computer monitor to gain familiarity with the stimuli and use of the response buttons. Pattern matching items used in this session were similar, but not identical, to those used during the fMRI sessions. Participants were instructed to select the response pattern that best matched the target pattern among the 8 possible choices and then press one of a linear button array for answers "1-4" with their left hand or another button array for answers "5-8" with their right hand.

The second practice session took place in a mock MRI scanner, using the same pattern matching task employed in the previous practice session. After practicing in the mock scanner, the participants were instructed to solve the RSPM problems by "finding the best answer to fill in the missing piece in the large rectangle." Participants were also told to study each problem until reasonably certain that they had determined the best answer, with no explicit time limit.

The actual fMRI testing session then followed. The imaging session began with a 10 min EPI session with eyes closed to allow participants to acclimate to the gradient noise and confining environment of the MRI system, a procedure employed to minimize between-group differences in sensitivity to the imaging environment. Then the 60-item pattern matching task was presented, which took approximately 9 to 12 min. Participants then completed the 60-item RSPM task, which took 14 to 35 minutes depending on individual speed. A structural MRI scan was done after the RSPM task. Instructions for the two tasks were repeated before going into the fMRI scanner and immediately before each task.

Image acquisition

We used a Siemens Trio 3T scanner with an 8 channel phased-array head coil. Functional data were acquired using an echo planar imaging pulse sequence (48 slices, 3mm cubic voxels, TR = 2850 ms, TE = 30 ms, flip angle = 90°). The first 2 volumes of each session were discarded to allow for longitudinal magnetization equilibration. T1-weighted structural brain images

were acquired at the end of the experiment (MP-RAGE, 176 slices, 1 mm cubic voxels, TR = 2530 ms, TE = 3.48 ms, flip angle = 7°).

Stimuli were displayed on a rear projection screen at the back of the scanner bore, with a mirror fixed on the head coil allowing participants to see the screen. Tasks were presented using Presentation (www.neurobs.com).

Image analysis

We used SPM5 (www.fil.ion.ucl.ac.uk/spm/) and MRIcron (www.sph.sc.edu/comd/rorden/mricron/index.html) for image preprocessing, statistical analysis and visualization.

Preprocessing. Image preprocessing steps included: (1) correction for slice timing differences by temporally interpolating voxel time courses in each slice to acquisition time of the middle slice of the EPI volume; and (2) two-pass realignment involving initial registration of all images to the first image of the time series, followed by registration of the images to the mean of the images computed after first realignment, followed by resampling using 4^{th} degree b-spline interpolation.

Spatial normalization. Images were directly transformed into MNI305 space by directly determining the non-linear mapping between realigned images and the SPM5 EPI template, using 8mm source imaging smoothing, 16 nonlinear iterations and resampling to 2mm cubic voxels using 5^{th} degree b-spline interpolation. To compensate for residual within and between group anatomical differences, spatially normalized images were smoothed with an isotropic Gaussian spatial filter with a full-width at half maximum (FWHM) of 9 mm.

Statistical modeling. For each participant, volumes acquired during the pattern matching and RSPM task sessions were treated as separate time series. For each session, BOLD-contrast signal variance was decomposed with a set of regressors using a general linear model. For both the pattern matching and RSPM tasks, total variance was decomposed into components

associated with task performance, with intervening fixation periods serving as an implicit inter-trial baseline for comparison. Regressors for pattern matching, figural RSPM items and analytic RSPM items of various difficulty levels were constructed by first generating boxcar functions of variable width with: (1) amplitudes of 1 during the task periods and 0 for the intervening fixation periods; and (2) durations corresponding to time spent considering each problem. These boxcar functions were then convolved with the SPM5 canonical hemodynamic response function resulting in regressors used to obtain parameter estimates proportional to task-related neural activity per unit time. These regressors, together with other regressors modeling residual movement-related signal modulation, the mean signal for the session, and a discrete cosine transform basis set modeling the low-frequency, presumably artifactual, signal modulations below 0.01 Hz, jointly comprised the full model for each participant. Ordinary least-squares parameter estimates for each regressor were then calculated from the fit of the model to the data using classical restricted maximum likelihood algorithms.

To allow inferences at the population level, a summary statistics second-level analysis was performed using a voxel-wise factorial ANOVA, with Group and Task factors, on images representing the activity associated with the task vs. fixation contrasts derived from each participant. The Group factor (2 levels) was assumed to have unequal variance and independence between levels. The Task factor (6 levels: pattern matching, RSPM with 1 figural and 4 analytical difficulty levels) was assumed to have unequal variance and dependence among levels. For our planned contrasts, the critical threshold for within-group voxel-wise estimates of task-related activity (task vs. fixation) was $p < .05$, FWE-corrected, with an extent threshold of 50 contiguous voxels. Because of the expected weaker strength of between-group comparisons or between-tasks comparisons, the critical threshold used for these contrasts was $p < .001$, uncorrected, with an extent threshold of 50 contiguous voxels, jointly providing sufficient protection from Type I error.

We then computed a series of statistical parametric maps to examine a set of focused hypotheses, including: (1) simple effects contrasts examining the form of pattern matching and RSPM task-related activity within each group, (2) conjunction analysis identifying aspects of

the task-related activity common to both groups, (3) between-group contrasts revealing how task-related activity differs between groups, (4) parametric analysis identifying effects of matrix reasoning problem difficulty, (5) prior anatomical specification using small volume correction analysis identifying visual processing areas differentially modulated in the autistic and non-autistic groups, and (6) Group X Task interaction contrasts revealing the regions where matrix reasoning exceeded pattern matching activity in the autistic compared to the non-autistic groups.

The 60 RSPM task items were divided into figural and analytic types, grouping problems of similar type and allowing examination of difficulty effects. Classifications derived from Van der Ven and Ellis (2000) and Lynn (2004) were used to classify 16 of the RSPM items as figural and 44 as analytic. Analytic items were further divided into 4 levels of difficulty, for which the difficulty was estimated from the mean accuracy of a previous sample of 26 non-autistic adults drawn from our research database, who were examined using the original paper version of RSPM. In the image analyses, a parametric analysis was conducted using these 4 levels of difficulty, with the contrast weights for the 4 levels derived from the mean accuracy obtained for that level in the non-autistic 26-adult sample. In addition, contrasting the easiest analytic items with the figural items, matched for accuracy, allowed identification of activity differences related to problem type, while controlling for problem difficulty.

As the EPF model posits that visual processing mechanisms play a central role in autistic cognition, we used it to generate anatomical predictions concerning loci of differential activity between autistic and non-autistic groups engaged in matrix reasoning. Specified regions of interest (ROIs) in occipital and posterior parietal cortex were derived from task vs. fixation contrasts, collected from a separate group of 16 typical adults (21 to 40 years old) performing the same pattern matching task (unpublished results). ROIs centered on the eight most significant local maxima in occipital and parietal cortex, four in each hemisphere, were used to compare task-related activity in autistics and non-autistics in both the pattern matching and RSPM tasks. Critical thresholds were chosen using a small volume correction based on a search radius of 10 mm and a significance level of $p < .05$, FWE-corrected. We hypothesized

that activity related to visual matrix reasoning would be higher in autistics relative to non-autistics in the occipital and parietal regions. This procedure represents a relatively strict test of one of the central predictions of the EPF model, because the ROIs to be used for the RSPM task were derived from an independent sample studied at a different site using a different MRI system.

Eye movement. As growing evidence documents atypical oculomotor behavior in autism, we took steps to estimate the net amount of oculomotor activity during each session. Following methods developed to derive estimates of saccadic (Beauchamp 2003) or pursuit (Tregellas, et al. 2002) eye movement density from brain image time series, we used an approach similar to those used in previous autism studies (Haist, et al. 2005; Mizuno, et al. 2006; Villalobos, et al. 2005), in which the variation of BOLD-contrast signal in the orbits serves as an index of the net amount of ocular movement (or saccade density). Two 12.5 mm spherical ROIs were used to extract the time-course of the BOLD-contrast signal for each eye of each participant. For each participant, the standard deviation of the temporal variability of BOLD-contrast signal was averaged for both eyes to obtain an estimate of net saccade density during problem solving. A Group x Task analysis of variance was used to compare the saccade density between the two groups in the two tasks.

Head movement. Between-group differences in head motion can be a concern in studies with clinical populations. To mitigate these effects, the preprocessing realignment process yields estimates of head translation and rotation that are then treated as covariates in the first-level fMRI model. As the incorporation of head motion estimate covariates in the statistical models used to isolate the task-related effects of interest provides incomplete protection from head motion modulation of the MRI signal, we also tested for between-group differences in the estimated head motion. Head motion time series were used to compute estimates of net head translation and rotation in both groups. Then the mean displacement (mm/sec) and rotation (degrees/sec) along each of the x, y and z axes were computed for both tasks. The peak-to-peak translation (mm) for x, y and z axes and the peak-to-peak rotation (degrees) for the pitch,

roll and yaw axes were also computed for each participant in each task. Those parameters were compared in autistics and non-autistics with Group x Task ANOVA.

RESULTS

Behavioral data

Task accuracy and response time. A Group x Task (pattern matching, figural and analytic task types) ANOVA was conducted on accuracy in the RT-matched sample. This analysis revealed a main effect of Task, F (2, 46) = 101.62, $p < .01$, with highest accuracy for the pattern matching task, then the figural items, then the analytic items (pairwise comparisons, all $p < .01$ after Bonferroni correction for multiple tests). However, there was no main effect of Group and no interaction between Group and Task factors, both $F < 1$. A similar ANOVA on RT in the matched samples revealed a main effect of Task, F (2, 46) = 224.95, $p < .01$, with the pattern matching problems being the fastest, then the figural reasoning problems, with the analytic reasoning problems being the slowest (all $p < .01$). There was no effect of Group and no interaction between the Group and Task factors, both $F < 1$. These results confirm that our matching procedure satisfactorily removed between-group differences in RT, while preserving similar accuracy levels in both groups across task levels (see Table II).

TABLE II Behavioral results for the pattern matching and RSPM tasks. Accuracy and RT performance measures are reported for the entire autistic (AUT) and non-autistic (nonAUT) sample, as well as for subsample matched on RT. There were 60 pattern matching and 60 RSPM problems. Of the 60 RSPM items, 16 are considered figural and 44 are considered analytic. Analytic items were further divided into four levels of difficulty from least (analytic 1) to most (analytic 4) difficult. Between group measure differences were assessed using ANOVA followed by independent sample *t* tests. Values are reported as mean and standard deviation - *M* (*SD*). RTs are reported in seconds.

	Entire sample			Performance matched sample		
	AUT	nonAUT	*p*	AUT	nonAUT	*p*
Pattern matching task						
Percent correct	99.11 (1.88)	98.15 (3.38)	.38	98.89 (2.05)	97.92 (3.75)	.39
RT	2.43 (0.91)	2.90 (1.33)	.37	2.69 (0.82)	2.60 (0.73)	.76
RSPM task						
Total (60 items)						
Percent correct	75.83 (10.39)	73.70 (9.12)	.54	74.72 (10.87)	72.82 (9.99)	.65
RT	13.65 (4.10)	19 (6.75)	.01	14.59 (3.56)	15.74 (3.94)	.45
Figural (16 items)						
Percent correct	93.30 (8.65)	90.63 (7.80)	.37	93.23 (9.02)	89.90 (8.28)	.35
RT	6.55 (1.89)	8.07 (2.24)	.05	7.01 (1.62)	7.10 (1.80)	.89
Analytic 1 (11 items)						
Percent correct	94.16 (7.65)	94.44 (8.33)	.92	93.18 (7.87)	94.41 (9.49)	.73
RT	9.60 (4.30)	11.05 (4.32)	.35	10.25 (4.31)	9.15 (2.53)	.44
Analytic 2 (12 items)						
Percent correct	78.57 (20.86)	81.48 (15.00)	.65	75.69 (21.16)	78.21 (16.51)	.74
RT	14.04 (5.35)	19.10 (6.70)	.03	15.10 (4.93)	16.03 (4.11)	.61
Analytic 3 (10 items)						
Percent correct	72.14 (20.07)	67.22 (18.73)	.48	70.83 (21.51)	66.15 (19.38)	.57
RT	16.85 (4.84)	23.62 (9.47)	.02	17.82 (4.25)	20.03 (7.55)	.38
Analytic 4 (11 items)						
Percent correct	32.47 (16.62)	25.76 (12.18)	.20	31.82 (17.55)	26.57 (13.10)	.40
RT	24.67 (9.23)	38.53 (17.03)	.01	26.46 (8.72)	30.67 (10.35)	.28

In order to verify that both groups had similar performance on an item-per-item basis, mean accuracy of each item was computed for each group. Correlation of item accuracy between groups was very high, $r = .89$, $p < .01$, demonstrating that, regardless of complexity or difficulty, both groups were similar in accuracy across all the RSPM items. We also attempted to assess whether performing RSPM in the scanner, with items presented in a randomized order, influenced item difficulty. We compared the difficulty level of each item in the original RSPM, derived from a 26-adult sample selected from the research database, with the difficulty level of each item for the autistic and non-autistic groups performing the RSPM task in the scanner. The high in vs. out of the scanner item difficulty correlation found in both groups ($r = .60$, $p < .001$, for the autistics and $r = .65$, $p < .01$, for the non-autistics), while not as high as the between-group, in-scanner correlation, suggests that the task modifications made for fMRI compatibility did not significantly modify the relative difficulty associated with solving the RSPM items in the MRI environment.

Eye movement

As between-group differences in saccade frequency can confound the interpretation of activity modulations observed during temporally extended visual tasks that involve significant visual search components, saccade frequency was estimated from orbital ROIs used to extract the BOLD-contrast signal fluctuation time series for each session. The temporal variation of each time series was then computed as a measure of saccade frequency averaged over the session. The net saccade density (standard deviation of the fluctuation of the BOLD-contrast signal) was similar in autistics and non-autistics in the pattern matching task (mean 4.21 vs. 4.72) and in the RSPM task (mean 3.96 vs. 4.44). A Group x Task (pattern matching vs. RSPM) ANOVA on net saccade density revealed no between-group differences, $F(1, 23) = 0.59$, $p = .45$, and no interaction, $F(1, 23) = 0.04$, $p = .95$. These results suggest that between-group differences in saccade frequency are not a major source of variance in our imaging data.

Head movement

The mean 3D translation and rotation rates, as well as peak-to-peak translation and rotation amplitudes along the x, y and z axes for each participant were examined using a repeated

measures ANOVA. In the RSPM task, the mean 3D displacement rate was 0.033 mm/sec in autistics and 0.040 mm/sec in non-autistics, and the mean 3D rotation rate was 0.026 deg/sec in autistics and 0.037 deg/sec in non-autistics. A Group x Task (pattern matching vs. RSPM) x Displacement rate (translation, rotation) ANOVA revealed no significant between-group difference, F (1, 23) = 0.64, p = .43 and no significant Group x Task interaction, F (1, 23) = 1.54, p = .23, or other interactions involving group. Similarly, a Group x Task (pattern matching vs. RSPM) x Peak-to-peak displacement (x, y, z, pitch, roll, yaw) ANOVA revealed no significant effect of Group, F (1, 23) = 0.94, p = .34, and no Group x Task interaction, F (1, 23) = 1.33, p = .26, or other interactions involving group. These results provide no evidence for between-group head motion effects.

Imaging data

Pattern matching task: simple effects contrasts, conjunctions and between-group contrasts. The pattern matching task contrasted with the fixation inter-trial baseline identified broad areas of activity increases in occipital cortex, posterior parietal cortex, prefrontal cortex, brainstem and cerebellum, with both groups having similar patterns (see Tables III and IV, and Figure 2). Between-group contrasts revealed higher activity in autistics in discrete bilateral frontal areas involving BA 4 and 6 ($p < .001$ uncorrected).

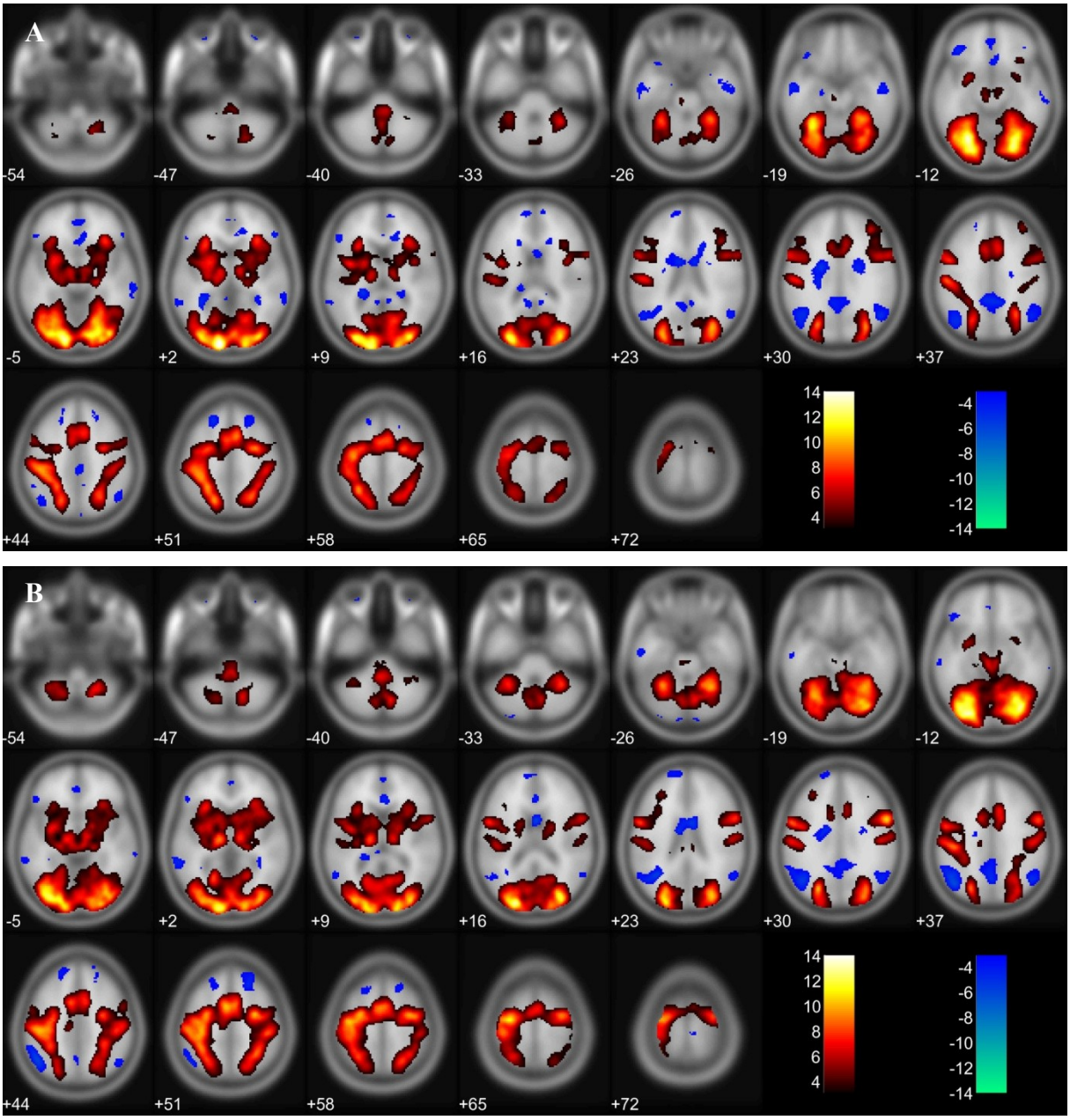

Figure 2. Relative changes in pattern matching task-related activity contrasted with inter-trial fixation-related activity displayed in axial section. Signal increases are shown in red-yellow and signal decreases are shown in blue-green. Regional variations in task-related activity are displayed using an uncorrected critical threshold of $p < .001$ for t-statistic maps overlaid on the SPM5 T1 template. Images are displayed using the neurological convention. Results are shown for (A) the non-autistic and (B) the autistic group.

TABLE III. Activity associated with the pattern matching task. We show t-values for signal increases and decreases for the pattern matching vs. fixation baseline contrast in the non-autistic and autistic groups. Coordinates are in MNI space. Height threshold: $t = 4.88$, $p < .05$, FWE corrected. Extent threshold: k = 50 voxels.

(A) Local maxima of signal change in non-autistics.

		Left					***Right***				
Region label	**BA**	**x**	**y**	**z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
Pattern matching > fixation											
Occipital											
Cuneus	17	-12	-98	4	14.53	2.47					
Lingual gyrus	17	-14	-92	-2	14.49	2.47					
	18						26	-80	-10	12.99	2.21
Middle occipital gyrus	18	-20	-86	-8	13.50	2.30					
Fusiform gyrus	19	-28	-70	-12	13.65	2.32	28	-70	-12	12.59	2.14
Parietal											
Inferior parietal lobule	40	-36	-38	48	10.26	1.75					
		-42	-30	46	9.88	1.68					
Superior parietal lobule	7	-28	-50	54	9.67	1.65	26	-62	50	8.86	1.51
Precuneus	7	-18	-66	50	9.62	1.64	28	-62	38	8.39	1.43
Frontal											
Inferior frontal gyrus	9	-58	8	30	6.91	1.18	58	8	30	6.32	1.08
							60	8	22	5.70	0.97
							46	8	26	6.55	1.12
	47						32	26	-2	8.44	1.44
Precentral gyrus	6	-50	2	36	7.81	1.33					
Insula	13	-38	-2	12	7.62	1.30	38	0	14	5.70	0.97
		-28	20	4	8.37	1.43	32	24	8	7.05	1.20
Subcortical											
Thalamus		-12	-14	6	7.25	1.23	12	-10	2	6.53	1.11
							22	-24	-4	6.53	1.11
Brainstem		-8	-14	-4	6.57	1.12	8	-18	-4	5.59	0.95
							2	-36	-42	6.06	1.03
Putamen		-24	0	2	7.65	1.30	22	4	0	5.46	0.93
							26	-4	0	5.02	0.85
Claustrum							30	6	-8	5.28	0.90
Globus Pallidus		-26	-14	0	6.43	1.09					
Pattern matching < fixation											
No significant loci											

(B) Local maxima of signal change in autistics.

		Left					*Right*				
Region label	**BA**	**x**	**y**	**z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
Pattern matching > fixation											
Occipital											
Inferior occip. Gyrus	18	-32	-84	-10	13.56	2.31					
Middle occip. Gyrus	18	-22	-92	16	13.23	2.25	30	-84	16	12.14	2.07
Fusiform gyrus	19	-36	-76	-10	13.24	2.25	34	-76	-12	13.03	2.22
Cuneus	19	-12	-98	2	12.27	2.09					
Parietal											
Postcentral gyrus	40	-46	-28	46	10.27	1.75					
Inferior parietal lobule	40						32	-42	46	8.17	1.39
Superior parietal lobule	7						32	-52	50	8.83	1.50
							24	-60	56	8.31	1.41
Frontal											
Inferior frontal gyrus	9						56	6	30	10.60	1.80
Superior frontal gyrus							2	4	18	6.26	
Precentral gyrus	6	-56	2	32	8.57	1.46					
	44						54	8	12	6.35	1.08
Insula	13	-38	-4	12	7.07	1.20					
Subcortical											
Claustrum		-28	20	4	7.39	1.26					
Claustrum		-32	-4	-4	7.20	1.23					
Thalamus		-14	-18	6	9.65	1.64	12	-14	0	7.92	1.35
Medulla		-2	-40	-42	6.97	1.19					
Cerebellum Lobule VIII		-20	-58	-54	5.87	1.00					
Cerebellum Lobule VIII		-26	-50	-54	5.50	0.94					
Cererbellum Lobule VIII		-34	-54	-54	5.50	0.94					
Pattern matching < fixation											
Temporal											
Middle temporal gyrus	39	-36	-58	24	5.78	0.98					
Parietal											
Inferior parietal lobule	39	-44	-68	38	6.33	1.08					

TABLE IV. Group differences and similarities in pattern matching activity.

(A) Conjunction analysis of the pattern matching task in non-autistic and autistic groups. Local maxima of signal increases and decreases are given for the conjunction null of the non-autistic and autistic groups on the pattern matching task vs. fixation baseline contrast. Coordinates are in MNI space. Height threshold: $t = 4.88$, $p < .05$, FWE corrected. Extent threshold: k = 50 voxels.

		Left					***Right***				
Region label	**BA**	**x**	**y**	**z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
Pattern matching > fixation											
Occipital											
Middle occipital gyrus	18	-24	-84	-10	12.87	2.19					
		-26	-92	16	12.02	2.05	32	-88	12	11.42	1.94
Fusiform gyrus	19	-30	-76	-10	12.54	2.13	30	-68	-12	12.07	2.05
		-28	-66	-14	11.83	2.01					
Cuneus	17	-12	-98	2	12.27	2.09					
Parietal											
Inferior parietal lobule	40	-44	-30	46	9.78	1.67					
		-36	-34	50	9.63	1.64					
		-32	-44	50	9.09	1.54	34	-48	54	7.04	1.19
Precuneus	7	-28	-58	54	8.46	1.44	28	-56	50	8.05	1.37
Frontal											
Inferior frontal gyrus	9						48	8	28	6.54	1.12
							58	8	30	6.32	1.07
							60	8	22	5.70	0.97
Middle frontal gyrus	6						30	-4	52	9.07	1.55
Precentral gyrus	6	-54	4	34	7.16	1.22					
Insula	13	-38	-4	12	7.07	1.20	32	20	4	6.18	1.05
							28	26	0	6.49	1.11
Subcortical											
Claustrum		-28	20	4	7.39	1.25					
		-34	-2	2	6.22	1.06					
Thalamus		-12	-14	6	7.25	1.24	12	-10	2	6.53	1.11
Putamen		-28	-2	-4	7.14	1.21					
Midbrain		-8	-14	-4	6.57	1.12	8	-18	-4	5.59	0.95
Medulla							2	-36	-42	6.06	1.03
Pattern matching < fixation											
No significant loci											

(B) Between-group differences in the pattern matching task. Local maxima of differential activity for the pattern matching task contrasted with the fixation baseline are shown for the autistic versus non-autistic groups. Coordinates are in MNI space. Height threshold: $t = 3.15$, $p < .001$, uncorrected. Extent threshold: k = 50 voxels.

		Left					***Right***				
Region label	**BA**	**x**	**y**	**z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
Non-autistic > Autistic											
No significant foci											
Autistic > Non-autistic											
Frontal											
Middle frontal gyrus	6	-20	-16	58	3.98	0.68	28	-14	46	3.64	0.62
Precentral gyrus	4	-44	-14	42	3.27	0.56	42	-16	40	3.57	0.61
		-32	-14	42	3.95	0.67	46	-18	32	3.98	0.68
	6	-56	0	20	3.71	0.63	22	-18	50	3.88	0.66
		-50	-6	-34	3.84	0.65	22	-16	64	3.82	0.65
							30	-12	70	3.82	0.65

RSPM task: simple effects contrasts, conjunctions and between-group contrasts. The RSPM task compared to the inter-trial fixation baseline revealed an extended bilateral network of activity in non-autistics (see Table V and Figure 3), encompassing occipital cortex, posterior parietal cortex, lateral premotor cortex, primary motor cortex, insula and cerebellum. This contrast yielded highly similar results in the autistic group, with a similar spatially extended pattern of activity. A between-group conjunction analysis confirmed the impression resulting from visual inspection of the individual group maps that both groups exhibited very similar bilateral activity patterns in occipital cortex, posterior parietal cortex and the inferior and middle frontal gyri ($p < .05$, FWE corrected; see Table VI).

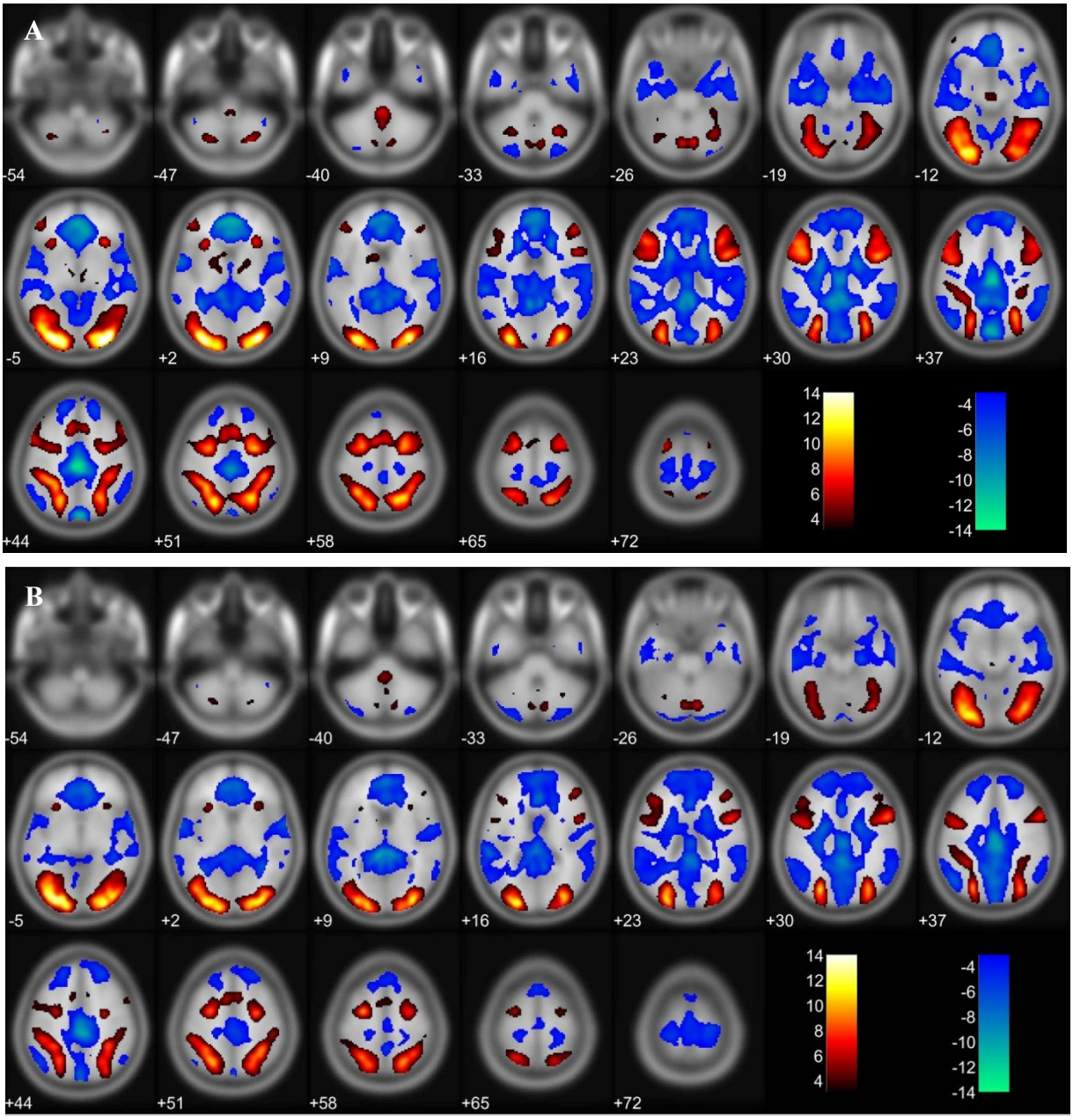

Figure 3. Relative changes in the RSPM task-related activity contrasted with inter-trial fixation-related activity displayed in axial section. Signal increases are shown in red-yellow and signal decreases are shown in blue-green. The regional variations in task-related activity are displayed using an uncorrected critical threshold of $p < .001$ for t-statistic maps overlaid on the SPM5 T1 template. Images are displayed using the neurological convention. Results are shown for (A) the non-autistic and (B) the autistic group.

TABLE V. Activity associated with the RSPM task. We show t-values for signal increases and decreases for the RSPM task vs. fixation baseline contrast in the non-autistic and autistic groups. Coordinates are in MNI space. Height threshold: $t = 4.88$, $p < .05$, FWE corrected. Extent threshold: k = 50 voxels.

(A) Local maxima of signal change in non-autistics.

		Left					***Right***				
Region label	**BA**	**x**	**y**	**z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
RSPM > fixation											
Occipital											
Inferior occipital gyrus	18	-30	-88	-8	14.65	2.49	30	-92	-4	17.36	2.96
							38	-86	-4	15.50	2.64
Middle occipital gyrus	18	-30	-92	4	13.79	2.35					
Superior occipital gyrus	19						32	-74	28	9.64	1.64
Cuneus	17	-18	-94	-4	13.58	2.31					
Parietal											
Superior parietal lobule	7	-18	-66	52	11.95	2.03	18	-64	58	11.02	1.88
							28	-62	40	9.65	1.64
							26	-62	52	11.19	1.90
Inferior parietal lobule	40	-34	-42	46	10.49	1.79					
Precuneus	19	-26	-74	32	10.24	1.74					
Frontal											
Middle frontal gyrus	6	-24	-2	54	9.42	1.60	28	-2	54	10.48	1.78
Inferior frontal gyrus	9						46	8	26	10.45	1.78
Middle frontal gyrus	9	-44	14	30	9.66	1.64	50	20	36	7.12	1.21
	46	-48	24	28	9.24	1.57	42	26	24	8.74	1.49
							48	38	16	6.43	1.09
Superior frontal gyrus	6	-6	8	56	7.03	1.20					
	8						6	16	52	6.79	1.16
Medial frontal gyrus	8	-8	18	48	7.02	1.19					
Middle frontal gyrus	10	-42	44	-2	5.72	0.97					
Insula	13	-30	24	-2	6.80	1.16	32	24	-2	8.11	1.38
Subcortical											
Cerebellar pyramis		-4	-74	-24	6.45	1.10	8	-74	-24	6.79	1.16
Cerebellar tonsil							0	-52	-40	5.35	0.91
Medulla							2	-38	-42	6.85	1.17

RSPM < fixation

Temporal											
Superior temp. gyrus	42	-58	-30	20	7.89	1.34					
Superior temp. gyrus	22	-58	2	4	7.66	1.30					
	38	-42	6	-12	5.59	0.95					
Parietal											
Precuneus	19						2	-82	40	11.78	2.00
Postcentral gyrus	43	-50	-12	14	5.41	0.92					
Posterior cingulate gyrus	31	-6	-44	32	9.77	1.66	4	-42	26	9.80	1.67
Frontal											
Anterior cingulate gyrus	32						4	48	0	11.01	1.87
Anterior cingulate gyrus	10						10	38	-4	10.61	1.81
Cingulate gyrus	31						0	-22	42	13.05	2.22
Subcortical											
Cerebellum Lobule VI		-6	-66	-8	5.24	0.89	6	-66	-6	5.58	0.95

(B) Local maxima of signal change in autistics.

		Left					***Right***				
Region label	**BA**	**x**	**y**	**z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
RSPM > fixation											
Occipital											
Inferior occipital gyrus	18	-28	-88	-4	13.62	2.32	28	-92	-4	13.45	2.29
		-38	-82	-6	13.21	2.25	38	-84	-4	11.40	1.94
	19										
Middle occipital gyrus	18	-24	-92	18	12.11	2.06	34	-88	2	11.65	1.98
	19	-32	-88	12	10.51	1.79	32	-88	10	11.51	1.96
							36	-76	-10	10.55	1.80
Cuneus	19	-26	-74	32	11.08	1.89					
Parietal											
Superior parietal lobule	7	-24	-64	52	10.03	1.71	34	-50	50	9.50	1.62
Frontal											
Inferior frontal gyrus	9						54	10	30	8.58	1.46
Middle frontal gyrus	6	-24	-4	56	9.64	1.64	28	-6	52	8.80	1.50
	9	-42	28	26	5.69	0.97					
	46						44	36	20	5.68	0.97

Precentral gyrus	6	-46	2	34	7.63	1.30					
RSPM < fixation											
Temporal											
Inferior temporal gyrus	20	-54	-22	-16	5.46	0.93	60	-14	-20	5.37	0.91
Middle temporal gyrus	39	-44	-64	28	5.77	0.98					
		-56	-60	12	5.20	0.89					
	21						62	-6	-12	5.85	1.00
Superior temporal gyrus	39	-52	-62	20	4.93	0.84					
	42	-56	-34	16	7.49	1.28					
	22	-64	-44	16	5.13	0.87	62	-46	20	5.38	0.92
		-60	0	0	6.31	1.07	62	4	-2	6.58	1.12
Fusiform gyrus	37						40	-36	-6	6.06	1.03
							36	-46	0	7.24	1.23
Parietal											
Precuneus	7						2	-66	36	8.18	1.39
	19						2	-84	36	7.17	1.22
Inferior parietal lobule	39	-48	-64	38	6.80	1.16					
Supramarginal gyrus	40	-60	-46	30	5.53	0.94	58	-48	32	5.40	0.92
Frontal											
Middle frontal gyrus	6	-22	-6	32	7.57	1.29	22	-2	26	7.46	1.27
Medial frontal gyrus	10						4	52	8	7.90	1.34
Superior frontal gyrus	8	-20	42	42	5.71	0.97					
Subcortical											
Cingulate gyrus	31						2	-28	42	10.73	1.83
							2	-42	28	9.10	1.55
Thalamus		-8	-36	10	10.37	1.76					
Anterior cingulate	32	-8	46	2	7.76	1.32	6	44	-4	8.13	1.38
							4	34	14	7.78	1.32
							12	34	-2	7.38	1.26
Parahippocampal gyrus	28						22	-18	-18	6.22	1.06

Between-group contrasts of RSPM task-related activity were conducted to verify if the balance of activity within that network was different in non-autistics and autistics. The autistic > non-autistic contrast revealed lower activity in autistics in the medial posterior parietal cortex and left middle frontal gyrus ($p < .001$ uncorrected; see Table VI and Figure 4 and 5) and higher activity in autistics in left cuneus and middle occipital gyrus (BA18).

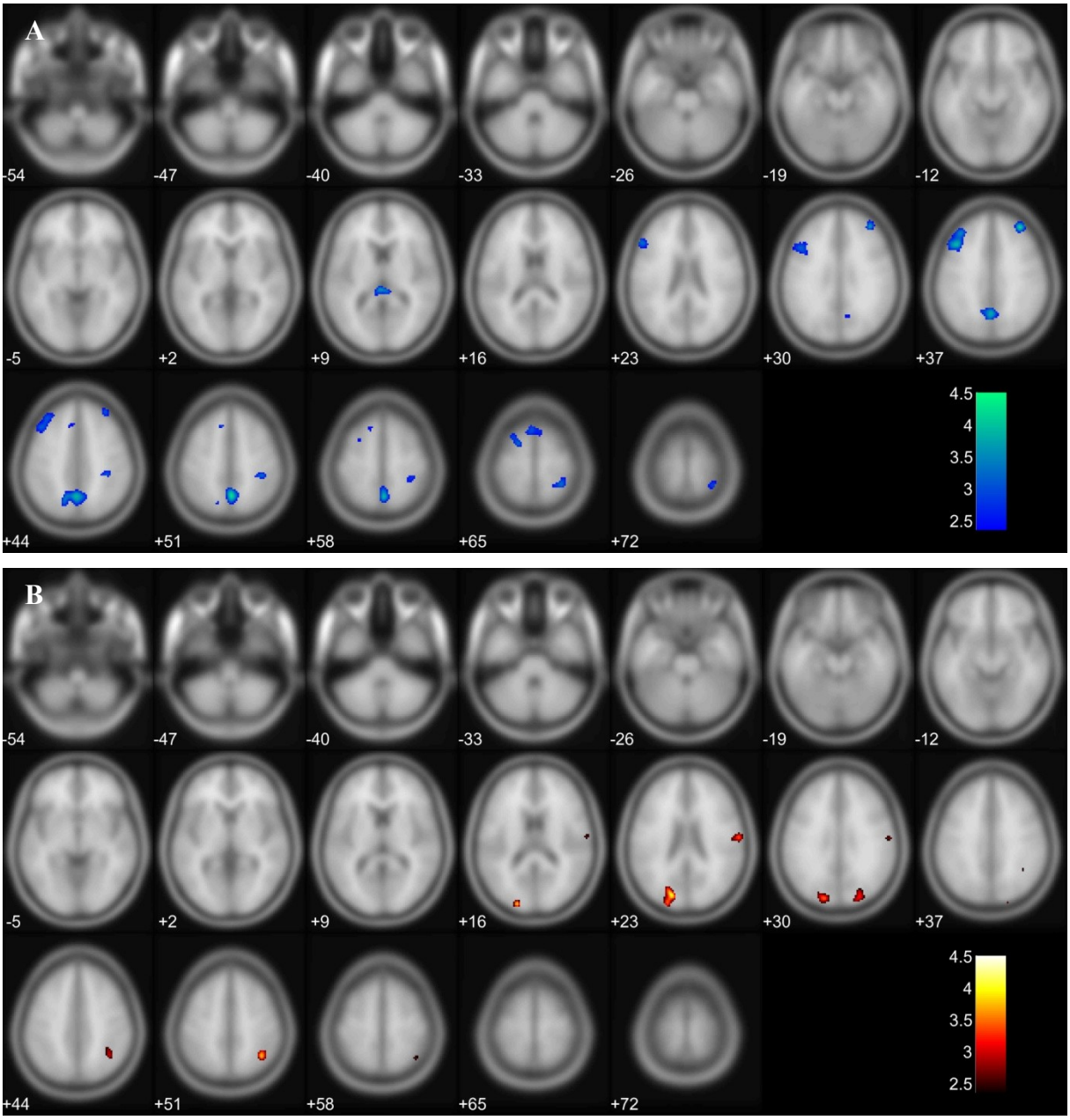

Figure 4. Group differences in RSPM task-related activity displayed in axial section. Areas in which the signal was greater in (A) the non-autistic compared to the autistic group are displayed in blue-green and areas in which the signal was greater in (B) the autistic compared to the non-autistic group are displayed in red-yellow. To show the spatial distribution of the task-related effects, an uncorrected critical threshold of p <.01 and an extent threshold of 140 voxels were used in overlaying the t-statistic maps on the anatomical template. Images are displayed using the neurological convention.

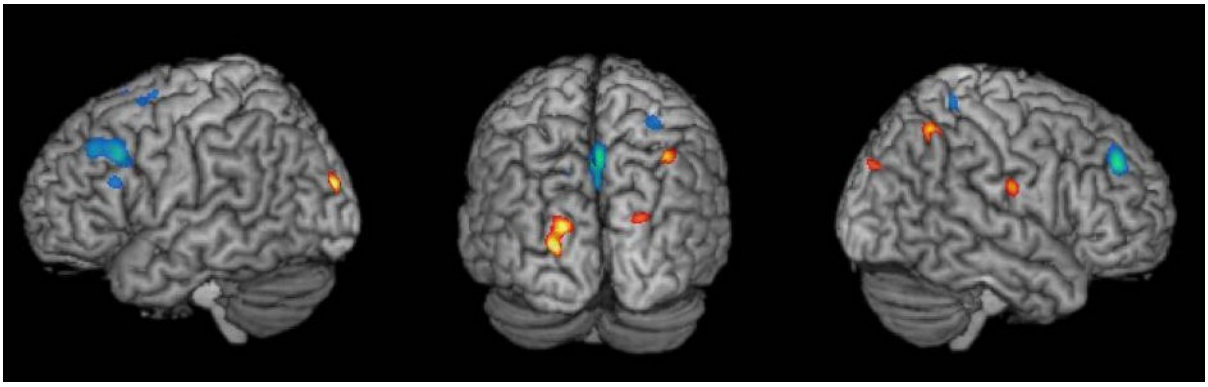

Figure 5. Volume renderings of group differences in RSPM task activity. Areas in which signal was greater in the autistic compared to the non-autistic group are displayed in red-yellow and areas in which the signal was greater in the non-autistic compared to the AUT group are displayed in blue-green. The spatial distribution of the task-related effects are displayed using an uncorrected critical threshold of $p < .01$ and an extent threshold of 140 voxels. Renderings of the t-statistic maps on LEFT, POSTERIOR and RIGHT views of the anatomical template are shown.

TABLE VI. Group differences and similarities in RSPM activity.

(A) Conjunction analysis of the RSPM task in non-autistic and autistic groups. Local maxima of signal increases and decreases are given for the conjunction null of the non-autistic and autistic groups on the RSPM task vs. fixation baseline contrast. Coordinates are in MNI space. Height threshold: $t = 4.88$, $p < .05$, FWE corrected. Extent threshold: k = 50 voxels.

		Left					***Right***				
Region label	**BA**	**x**	**y**	**z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
RSPM > fixation											
Occipital											
Inferior occipital gyrus	18	-28	-88	-4	13.55	2.31	28	-92	-4	13.45	2.29
							38	-84	-4	11.40	1.94
Middle occipital gyrus	18						34	-88	2	11.65	1.98
	19	-32	-88	12	10.51	1.79	32	-88	10	11.51	1.95
		-26	-92	16	11.38	1.94					

Parietal											
Precuneus	19	-26	-74	32	10.24	1.75	32	-74	30	9.50	1.62
	7	-22	-64	52	9.81	1.67					
Superior parietal lobule	7	-30	-50	50	8.72	1.48	22	-64	58	9.44	1.61
Frontal											
Inferior frontal gyrus	9						52	10	28	8.43	1.44
Middle frontal gyrus	6	-24	-2	56	9.26	1.54	28	-6	52	8.80	1.50
	9	-42	28	26	5.69	0.97					
	46						44	36	20	5.68	0.97
Precentral gyrus	6	-46	2	34	7.63	1.30					
RSPM < fixation											
Temporal											
Inferior temporal gyrus	20						60	-14	-20	5.37	0.92
	21						58	-8	-14	5.58	0.95
Middle temporal gyrus	39	-44	-64	28	5.77	0.98					
Sup. temporal gyrus	22	-60	0	0	6.31	1.07	62	2	2	6.38	1.09
	39	-52	-62	20	4.93	0.84					
	42	-58	-32	18	7.30	1.24					
Fusiform gyrus	37						36	-46	0	7.24	1.23
Fusiform gyrus	37						40	-38	-6	5.92	1.01
Parietal											
Inferior parietal lobule	40	-60	-42	24	5.05	0.86					
	39	-46	-68	38	6.49	1.10					
Frontal											
Middle frontal gyrus	6	-22	-6	32	7.57	1.29	22	-2	26	7.46	1.27
Superior frontal gyrus	8	-20	42	42	5.71	0.97					
Medial frontal gyrus	10						4	52	8	7.90	1.35
Subcortical											
Cingulate gyrus	31						2	-28	42	10.73	1.83
							2	-42	28	9.10	1.55
Posterior cingulate	29	-6	-44	12	7.55	1.28					
Anterior cingulate	32	-8	46	2	7.76	1.32	6	44	-4	8.13	1.38
							2	34	16	7.61	1.30
							12	34	-2	7.38	1.25
Parahippocampal gyrus	28						22	-18	-18	6.22	1.06
	30	-10	-36	6	9.10	1.46					
	36						40	-30	-12	5.37	0.92
Thalamus							14	-38	10	7.61	1.30

(B) Between-group differences in the RSPM task. Local maxima of differential activity for the RSPM task contrasted with the fixation baseline are shown for the autistic versus non-autistic groups. Coordinates are in MNI space. Height threshold: $t = 3.15$, $p < .001$, uncorrected. Extent threshold: k = 50 voxels.

		Left					*Right*				
Region label	**BA**	**x**	**y**	**z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
Non-autistic > Autistic											
Precuneus	7	-2	-60	40	3.99	0.68	2	-58	54	4.39	0.75
Precentral gyrus	9	-42	22	36	3.95	0.67					
Middle frontal gyrus	9	-36	34	38	3.51	0.60	36	42	34	4.30	0.73
Autistic > Non-autistic											
Middle occipital gyrus	18	-22	-92	18	4.17	0.71					
Cuneus	18	-18	-82	24	4.15	0.71					

Additional analyses were conducted on the RSPM task data to explore effects of item type and difficulty. First, the figural items were contrasted with the easiest analytic items, matched for difficulty. Increased activity associated with the analytical items was found in left extrastriate area (BA18), superior frontal gyrus (BA6) and medial precuneus (BA7; $p < .001$ uncorrected). We observed no significant between-group differences associated with processing complexity (analytical vs. figural items). Similarly, a parametric analysis examining 4 difficulty levels within the analytic items revealed increased activity in bilateral extrastriate areas (BA18), the middle frontal gyrus (left BA10 and right BA6) and bilateral superior frontal gyrus (BA6), as well as left supramarginal gyrus (BA40) associated with increasing difficulty ($p < .001$ uncorrected). There were no significant between-group differences in the effects of difficulty on task-related activity.

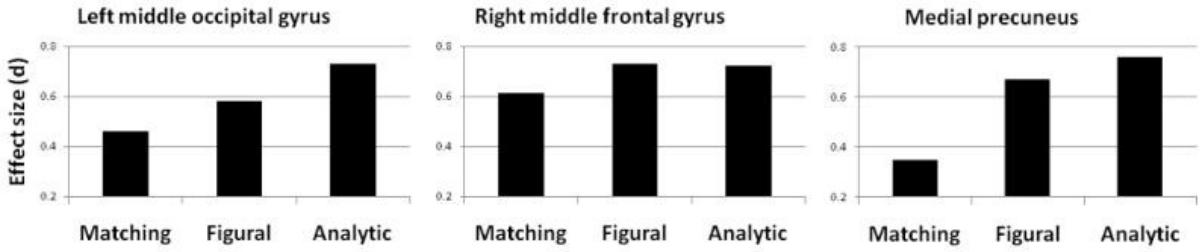

Figure 6. Effect size (*d*) for the between-group difference in the pattern matching, figural, and analytic problems at the coordinates of maximal between-group difference found in the RSPM tasks. Effect sizes are reported for the left middle occipital gyrus (-22, -92, 18) in the left panel, right middle frontal gyrus (36, 42, 34) in the middle panel, and for the medial precuneus (2, -58, 54) in the right panel.

Small volume correction analysis using a priori functional ROIs. Eight functional ROIs representing activity associated with the pattern matching task obtained from a previous study were used to test the EPF model prediction that autistic reasoning might more strongly engage higher-order visual processing centers (see Table VII). These regions were located in occipital and posterior parietal cortex, 4 in the left hemisphere and 4 in the right. In the pattern matching task data, the *a priori* ROI analyses did not reveal any significant differential between-group activity. However, in the analysis of RSPM task data, while none of the ROIs showed greater activity in non-autistics, two clusters of greater activity were observed in the autistics in the middle occipital gyrus and cuneus (BA18; $p < .05$; FWE-corrected), confirming the findings of the voxel-wise between-group contrasts.

TABLE VII. RSPM task: Small volume correction analysis of occipital and posterior parietal brain regions using *a priori* ROIs.

(A) ROIs used for small volume correction analyses. ROIs were defined by taking the four right local maxima and finding their corresponding left local maxima in the pattern matching task vs. fixation baseline contrast in a prior study (unpublished results). Height threshold: $t = 9.17$, $p < 10^{-9}$. The *t* and *d* values at those coordinates are reported for non-autistic and autistic groups during performance of the RSPM task.

		Left					***Right***				
Region label	**BA**	**x**	**y**	**Z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
Non-autistics											
Middle occip. gyrus/cuneus	19	-28	-84	20	9.95	1.69	30	-86	20	9.41	1.60
Middle occipital gyrus	19	-30	-90	10	12.67	2.16	32	-88	12	13.20	2.25
Fusiform gyrus	19	-26	-62	-12	5.73	0.98	30	-72	-12	6.86	1.17
Superior parietal lobule	7	-28	-58	56	9.52	1.62	26	-58	52	10.10	1.72
Autistics											
Middle occip. gyrus/cuneus	19	-28	-84	20	10.50	1.79	30	-86	20	8.43	1.44
Middle occipital gyrus	19	-30	-90	10	10.11	1.72	32	-88	12	11.37	1.94
Fusiform gyrus	19	-26	-62	-12	5.37	0.91	30	-72	-12	6.76	1.15
Superior parietal lobule	7	-28	-58	56	8.98	1.53	26	-58	52	8.82	1.50

(B) Local activity maxima for between-group differences determined using functional ROIs derived from a prior experiment. Local maxima of differential activity for the RSPM task are given for autistic versus non-autistic groups, using small volume corrections based on the ROIs reported in (A). Coordinates are in MNI space. Search radius: 10 mm sphere. Threshold: $p < .01$; FWE-corrected.

		Left					***Right***				
Region label	**BA**	**x**	**y**	**Z**	***t***	***d***	**x**	**y**	**z**	***t***	***d***
Non-autistic > Autistic											
No significant loci											
Autistic > Non-autistic											
Middle occipital gyrus	18	-22	-92	20	4.06	0.69					
Cuneus	18	-20	-80	22	3.78	0.64					

Differential group effects comparing matrix reasoning to pattern matching. A Group x Task interaction was computed to characterize the task specificity of any regional between-group differences. Of particular interest was whether areas in occipital or posterior parietal cortex would exhibit greater differential activity for matrix reasoning compared to the pattern matching conditions, and whether this difference would be larger for the autistics. The voxel-wise *t*-contrast shown in Figure 7 revealed an interaction in both left and right inferior occipital cortex (BA18; $p = .001$ uncorrected). As an additional exploration of these effects, we computed Cohen effect sizes at the coordinates of maximal between-group differences for pattern matching, figural and analytic problems. In the left middle occipital gyrus and the medial precuneus, the between-group effect size increased monotonically across the three task types (see Fig 6), suggesting progressively stronger between-group differences in the engagement of these areas as the reasoning demands of the task increased. In the right middle frontal gyrus, effect size differences were somewhat smaller compared to the corresponding location in the left hemisphere.

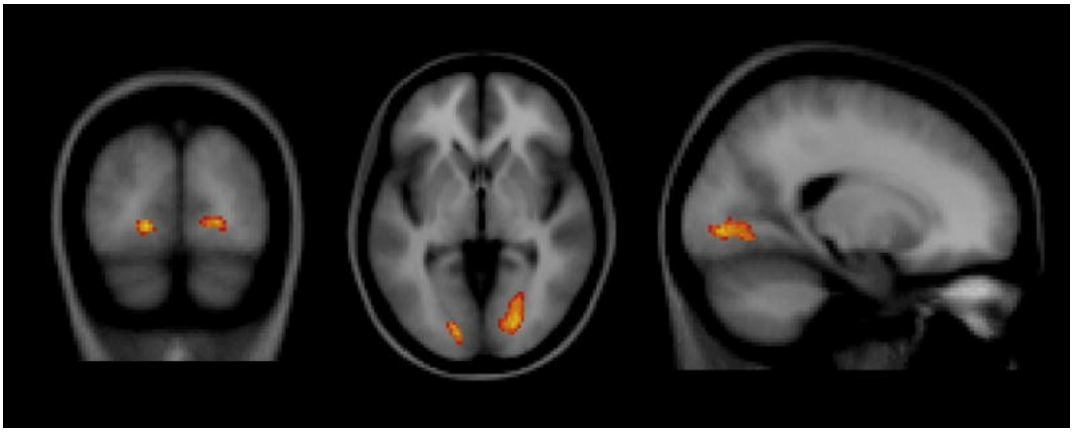

Figure 7. Group differences in matrix reasoning contrasted with the pattern matching control condition displayed in coronal, axial and sagittal sections. This Group × Task interaction represents additional inferior occipital activity in the autistic group in the matrix reasoning compared to the pattern matching condition. The regional variations in task-related activity are displayed using an uncorrected critical threshold of $p < .01$ for t-statistic maps overlaid on the SPM5 T1 template. Peaks of activity were detected bilaterally in BA 18/19 (MNI coordinates -14,-86,-06 and +24,-78,-04, $p < .001$). Axial and coronal images are displayed in neurological convention

Comparative analyses of the complete sample. Assuring the compatibility of groups contrasted in observational imaging studies is not an entirely straightforward matter, as the goal of matching task performance characteristics must be balanced against the need to avoid unduly introducing sample bias. To explore the latter possibility, we repeated the analyses of the behavioral data using the entire participant sample, in which the autistic group responded more rapidly than the non-autistic group (15 autistics and 18 non-autistics). A Group x Task ANOVA on accuracy again revealed a main effect of Task, F (2, 60) = 138.50, $p < .01$. The ANOVA on RT revealed a Group x Task interaction, F (2, 60) = 6.01, $p < .01$. While there was no difference in mean RT between the two groups on the pattern matching task ($p = .37$), autistics were on average 40% faster than non-autistics in the RSPM task (all items; 13.65 s vs. 19 s, $p = .01$), and by item type, 23% faster than non-autistics on the figural (6.55 s vs. 8.07 s, $p = .05$) and 42% faster on the analytic items (16.22 s vs. 22.97 s, $p = .01$). In the RSPM

task, the more difficult an item, as indexed by mean accuracy in the 26-adult sample, the greater the speed advantage enjoyed by the autistics, $r = .56$, $p < .01$ (see Table II).

The between-group imaging data analyses were also repeated in the entire sample. In both the pattern matching and RSPM tasks, we observed between-group differences qualitatively similar to those seen in the performance-matched group analyses, confirming that the group performance matching procedure did not appear to materially bias the functional neuroimaging results.

DISCUSSION

While solving the RSPM items, autistic and non-autistic participants activated similar spatially extended networks, encompassing occipital, posterior parietal, prefrontal, insular and cerebellar cortical areas. A difference in the balance of activity between the two groups was evidenced by higher left occipital activity and lower medial posterior parietal and left lateral prefrontal activity in autistics compared to non-autistics. Whereas both groups exhibited similar task accuracy, the autistics generated answers more rapidly than did the non-autistics. The potentially confounding effects of this group performance difference were dealt with by selecting a subsample of participants additionally matched on response time. Analysis of both the performance-matched and complete samples yielded similar results.

Pattern matching in non-autistics and autistics

The comparison pattern matching task was designed to be similar to the RSPM task with respect to the spatial arrangement of stimuli and requirements for response selection. Task accuracy and response times were not significantly different between groups. Both groups engaged the same regions, including occipital, posterior parietal, frontal and cerebellar cortex. In contrast to the results seen in the RSPM task, we observed no between-group differences in occipital activity. The task-related activity seen in both groups was similar to that observed during visual search tasks involving simple figures, where increases are seen in occipital cortex (BA18 and 19), the intraparietal sulcus (BA7 and 40) and the precuneus (BA7), with increasing recruitment of prefrontal cortex (mainly BA6, 9, 46 and 47) with increasing task

difficulty (Anderson, et al. 2007). The mainly occipito-parietal and premotor task-related activity observed in our study is consistent with the results of other studies using pattern matching tasks (Dickins 2005).

We did observe between-group differences bilaterally in the precentral and middle frontal gyri, with relatively greater activity in autistics. These areas are believed to be strongly involved in processes related to response selection and execution. As there were 8 distinct response choices from which participants had to select their answers, a differential between-group efficiency in mapping the selected answer to the corresponding response button is a plausible interpretation.

Non-autistics and the RSPM task

The frontoparietal distribution of activity associated with performance of the RSPM task in non-autistics is in agreement with previous neuroimaging studies of matrix reasoning (Duncan, et al. 2000; Kroger, et al. 2002; Lee, et al. 2006; Prabhakaran, et al. 1997), as well as studies of other types of reasoning (Goel and Dolan 2001; Monti, et al. 2007; Wendelken, et al. 2008b; Wright, et al. 2007) and working memory (Gray, et al. 2003). Our results also correspond well with the core functional and anatomical components of the P-FIT model (Jung and Haier, 2007), which include visual analysis and elaboration (occipital), abstraction (posterior parietal) and hypothesis testing (dorsolateral prefrontal). Additionally, the difficulty analysis and the analytic versus figural item analysis, which revealed increasing activity in bilateral middle frontal and inferior occipital gyri and left posterior parietal cortex, were consistent with previous findings (Kalbfleisch, et al. 2007; Kroger, et al. 2002; Lee, et al. 2006; Perfetti, et al. 2008; Prabhakaran, et al. 1997). Kalbfleisch et al. found prefrontal, posterior parietal and occipital activity to be modulated by difficulty and specifically identified the left middle frontal gyrus as the key region modulated by matrix reasoning difficulty. Overall, the RSPM results obtained in the non-autistic group agree with findings in previous reasoning studies sampling typical populations, confirming that it is possible to study fluid reasoning using an ecologically sound, completely self-paced design employing the same 60 RSPM items comprising the paper version of the test.

Autistics and the RSPM task: A. Faster performance

The tendency for the autistics to respond much more quickly during the RSPM task, without exhibiting a concomitant accuracy decrement, was an unexpected and striking finding. While no more rapid than the non-autistic group in the pattern matching task, the autistics were 23% faster in solving the figural RSPM items and 42% faster in solving the analytic RSPM items. While the participants were not asked to provide answers as rapidly as possible, instead being told to take the time necessary to be reasonably certain of finding the best answer, the large observed discrepancy in response times could have arisen from a processing advantage unique to the autistic group. However, we cannot exclude other plausible explanations based on motivational or other transient state differences in the 2 groups that might influence a participant's intent or ability to respond briskly. Of note in this context is the fact that this response time finding is concordant with other studies where autistics have responded more quickly in a range of speeded tasks, including visual search, disembedding figures and block design (Caron, et al. 2006; de Jonge, et al. 2006; Edgin and Pennington 2005; Falter, et al. 2008; Jolliffe and Baron-Cohen 1997; O'Riordan M 2004; O'Riordan and Plaisted 2001; O'Riordan, et al. 2001; Plaisted, et al. 1998; Shah and Frith 1993). Although the response time advantage for difficult RSPM problems we observed may reflect an underlying processing advantage in reasoning mechanisms enjoyed by autistics, additional studies directed at this specific question will be required to fully explore this possibility.

Autistics and the RSPM task: B. Regional differences in activity

The pattern of activity we observed in autistic participants was highly similar in its spatial distribution to that seen in non-autistic participants. However, in autistics the activity within this network was higher in extrastriate areas, and lower in the middle frontal gyrus and medial precuneus.

Occipital findings. Increased activity in autistics during the RSPM task was seen in left cuneus, with a similar trend found in right cuneus. The cuneus is thought to be involved in updating information in working memory (Roth and Courtney 2007) and making comparisons among visual images (Ferber, et al. 2007). Its role in visual attention includes shifts of

attention (Makino, et al. 2004) and selective attention, with higher activity in the cuneus when the control of attention is more "bottom-up" and stimulus-driven than "top-down" and guided by expectations (Hahn, et al. 2006; Yeh, et al. 2007). The visual search literature in autism might also be informative regarding the involvement of extrastriate areas in autistic cognition. While searching for a target embedded in a complex figure, autistics performed more rapidly but did not differ from non-autistics in saccade frequency (Keehn, et al. 2008b). Instead, autistics had significantly shorter fixations, suggesting they were faster at encoding and analyzing the visual information contained in the complex figures. In addition, in fMRI studies, autistics show increased activity in right occipital cortex when searching for a target placed among a field of distracters (Keehn, et al. 2008a) or embedded in a complex figure (Manjaly, et al. 2007; Ring, et al. 1999). The possibly stronger engagement of visual encoding, analysis and attention systems in autistics provides a number of plausible physiological mechanisms by which autistics might exhibit faster or more accurate performance in complex cognitive tasks.

There is ample prior evidence for involvement of extrastriate cortical areas during reasoning in typical individuals. For example, a correlation between scores on Wechsler Scales and the volume of gray matter or cortical thickness in BA18 and BA19 has been reported (Colom, et al. 2006; Shaw, et al. 2006). Moreover, half the PET studies and nearly half the fMRI studies in Jung and Haier's (2007) review reported activity in occipital areas BA18 and BA19 in relation to various types of reasoning. The observations that occipital areas are commonly engaged in typical individuals during reasoning make them plausible candidates to support these same roles in autistics. Furthermore, according to Jung and Haier's P-FIT model, if autistics are more facile in the recognition, elaboration or manipulation of visual input, processes presumably carried out in occipital and parietal cortex, the need for subsequent hypothesis testing, manipulation and evaluation, processes relying more heavily on prefrontal mechanisms, might be reduced.

Prefrontal findings. Activity in bilateral middle frontal gyrus and left precentral gyrus was decreased in autistics relative to non-autistics. In the typical population, the dorsolateral

prefrontal cortex is thought to be involved in manipulation and integration of information in working memory, decision processes and cognitive control (Cole and Schneider 2007; Koch, et al. 2005; Wendelken, et al. 2008a). The middle frontal gyrus has been more specifically implicated in updating and manipulating the spatial information stored in parietal cortex, managing task difficulty and evaluating response correctness (Kalbfleisch, et al. 2007; Kroger, et al. 2002; Owen 2004; Tanaka, et al. 2005).

There are now many reports of decreased activity in prefrontal cortex in autistics relative to non-autistics. These studies employ a broad range of tasks, including working memory (Koshino, et al. 2005; Luna, et al. 2002), embedded figure search (Lee, et al. 2007; Ring, et al. 1999), spatial attention (Haist, et al. 2005), categorization (Gaffrey, et al. 2007), sentence comprehension (Kana, et al. 2006) and the attribution of mental states to animated shapes (Castelli, et al. 2002). However, there are also reports of relatively increased prefrontal activity in autistics, in tasks involving motor sequence learning (Muller, et al. 2003), visually guided saccades (Takarae, et al. 2007) and visual search (Keehn, et al. 2008a). Therefore, the aggregate findings to date do not support the existence of a *general*, task-independent, and spatially invariant decrease in frontal cortical activity in autistics. In our results, both groups engaged the same prefrontal cortical regions during the RSPM task and the modulation of activity in the cortical regions as a function of difficulty and problem type did not differ. Although speculative, the differential between-group dorsolateral prefrontal activity may represent a reduced need to engage working memory in the autistic group, resulting from their stronger engagement of more posterior visual encoding processes.

Parietal findings. The lower medial precuneus activity seen in autistics might result from more efficient perceptual processing. The precuneus is involved in networks responsible for maintaining and updating visuospatial information in working memory, visual detection and attention, mental rotation and visual imagery (Brown, et al. 2006; Cavanna and Trimble 2006; Hufner, et al. 2008; Owen 2004; Suchan, et al. 2006; Yeh, et al. 2007). Most importantly, better visuospatial skills have been correlated with lower precuneus activity during reasoning (Ruff, et al. 2003), in exactly the same area where we observed lower activity in autistics.

Thus, enhanced perceptual functioning in autistics might be causally associated with lower medial precuneus activity. Although increased activity in the right precuneus has been found in autistics in a visual search paradigm (Keehn et al., 2008), the particular part of the precuneus involved in visual search was more lateral and anterior than the area of decreased activity in our study. Interestingly, while we observed a trend towards increased activity in autistics in the right inferior parietal cortex (see Figure 5) in the RSPM task, the test statistic did not exceed our critical threshold for significance.

Task-related decreases in activity. Extensive cortical areas of decreased activity were found during the RSPM task in both groups, with no significant between-group difference in the magnitude of decrease. These regions correspond to the "default network", whose core components encompass medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule, lateral temporal cortex and the hippocampal formation (Buckner, et al. 2008; Raichle, et al. 2001). Decreased activity is typically observed within this network when individuals are engaged in demanding cognitive tasks. Accordingly, the areas of decreased activity appeared more extended during the much more demanding RSPM task than during the pattern matching task. The absence of a group difference in the extent of decreased activity is consistent with Cherkassky et al. (2006), who reported a similarly extended default network in both autistics and non-autistics, although there was decreased synchronization within the regions of this network in autistics, compared to non-autistics.

Brain mechanisms for perception and reasoning in autistics

The EPF model predicts stronger engagement of visual perceptual mechanisms in autistic cognition, including in reasoning (Mottron, et al. 2006). Consistent with this prediction, we recently demonstrated that autistics would preferentially rely on perceptual and visuospatial strategies during deductive reasoning, whereas non-autistics would show an advantage for semantic strategies (Sahyoun, et al. 2009). Our current findings add physiological evidence that perception indeed plays an atypically prominent role in autistic reasoning and problem solving.

Existing fMRI studies have already demonstrated increased activity in autistics in brain regions believed primarily to be specialized for perceptual functions, in visuospatial tasks such as the Embedded Figures Test (Manjaly, et al. 2007; Ring, et al. 1999), visual search (Keehn, et al. 2008a) and a modified version of the Wechsler Block Design task (Hubl, et al. 2003). Moreover, accumulating evidence from experiments involving working memory and reasoning tasks also suggests a stronger engagement of brain regions specialized for visual processing. First, autistics performed an n-back task using a sequence of alphabet letters with equivalent speed and accuracy as non-autistics, while displaying increased activity in inferior temporal and extrastriate cortex (Koshino, et al. 2005). Second, a study of sentence comprehension comparing high to low imagery content also showed increased activity in parietal and occipital regions in autistics (Kana, et al. 2006). Finally, in an fMRI study of semantic reasoning (e.g. Does a hammer belong to the tools category?), Gaffrey et al. (2007) found extended bilateral activity in extrastriate areas in autistics, whereas these areas were not active in non-autistics. In agreement with our results, both Kana et al. (2006) and Gaffrey et al. (2007) specifically reported increased activity in the cuneus (BA18 and 19). Finally, the observation of increased activity in posterior cortical areas in autistics was concomitant with decreased activity in left inferior and middle frontal gyri in two of these three studies (Kana, et al. 2006; Koshino, et al. 2005).

In typical individuals, recent studies exploring the functional neuroanatomy of skill acquisition and expertise converge on the notion that, with increasing expertise in a task, increased activity is observed in brain regions fundamental to that task (Bor and Owen 2007; Debaere, et al. 2004; Guillot, et al. 2008; Hanakawa, et al. 2003; Kucian, et al. 2008; Meyler, et al. 2007; Olesen, et al. 2004) and activity in "supportive" brain regions often decreases (Debaere, et al. 2004; Guillot, et al. 2008; Kucian, et al. 2008; Poldrack, et al. 2005). For example, after the acquisition of a complex bimanual skill, decreased activity was seen in attention and action correction systems, and concomitant activity increases were seen in regions supporting memory-driven actions (Debaere, et al. 2004). Similar findings were recently obtained in matrix reasoning studies. When comparing participants with high and average fluid reasoning abilities, those with higher reasoning abilities exhibited stronger activity in posterior parietal

cortex during a matrix reasoning task (Lee, et al. 2006). In a similar manner, individuals who have higher activity in occipital BA18 tend to exhibit better performance on Raven's Matrices (Haier, et al. 2003), a finding interpreted by the authors as evidence supporting the role of this region in integrating and resolving competition among visual inputs during reasoning. It is therefore plausible that autistic individuals, who have well-documented advantages in some aspects of visual processing, could use these perceptual strengths to support reasoning.

Alternative accounts

Eye movements. Differences in ocular movements between autistics and non-autistics could confound neuroimaging studies where frequent saccades occur, as is seen during RSPM task performance. Analysis of orbital fluctuations in BOLD-contrast signal revealed no between-group difference in this measure of eye movement, for either the RSPM or pattern matching task. This finding is consistent with most of the visual saccade studies employing non-social stimuli in autism, in which no between-group differences in latency, peak velocity or amplitude of visually guided saccades have been reported (Kemner, et al. 2004; Luna, et al. 2007; Luna, et al. 2002; Mercadante, et al. 2006; Takarae, et al. 2004; Takarae, et al. 2007; Thakkar, et al. 2008). Moreover, in a recent review of oculomotor activity in childhood disorders it was noted that, "overall, [visually guided saccades] appear normal in autism and there is insufficient evidence to claim difficulties with attentional engagement within the oculomotor domain for children with autism" (Rommelse, et al. 2008 p.401). As for fMRI studies of visual saccades in autism, we found no overlap between the areas showing between-group differences during visual saccades (frontal eye fields, dorsolateral prefrontal cortex, anterior/posterior cingulate cortex, posterior parietal cortex, precuneus, area V5, thalamus and cerebellum) and the occipital and prefrontal activity differences seen in relation to the RSPM task (Takarae, et al. 2007; Thakkar, et al. 2008). Moreover, none of the peaks of saccadic activity reported in the most recent studies employing non-autistic samples (frontal eye fields, supplementary eye fields, supplementary motor area, superior and middle temporal gyrus, intraparietal sulcus, basal ganglia and cerebellum) overlapped with the regions of between-group differences identified in our RSPM task (Anderson, et al. 2008; Hufner, et al. 2008; Schraa-Tam, et al. 2009).

The only possible area of concern involves the medial precuneus finding, where there is an overlap with studies of saccades in autism, which also found decreased activity in autistics (Takarae, et al. 2007; Thakkar, et al. 2008). However, the relevance of these findings to our interpretation is tempered by the fact that a third study of visual saccades in autism, which used an ROI approach, did not find any between-group difference in the precuneus or any of the 13 other ROIs examined (Luna, et al. 2002).

In summary, while the difference observed in the precuneus in our study could be related to saccadic activity, the other between-group differences and specifically those involving occipital areas, which are the main findings of our study, are not likely to be explained by differences in ocular movements per se.

Increased sensitivity to visual stimulation. One possibility is that increased activity in occipital cortex simply reflects a general increase in autistic sensitivity to all things visual. Against that account is the fact that our between-group differences were more apparent in the RSPM than in the pattern matching task. Specifically, the higher activity in the left cuneus was only seen in the RSPM task and there was no between-group activity difference in occipital or parietal cortex in a pattern matching task that was specifically designed to be visually similar to the RSPM task, but with minimal reasoning components. Increased recruitment of occipital cortex in autistics was limited to the RSPM task, which could suggest a specific role for visual perceptual mechanisms in autistic reasoning.

Origin of neural differences in matrix reasoning between autistics and non-autistics

Regarding possible developmental mechanisms leading to the atypical autistic activity patterns seen in our study, clues may be found in recent studies of white matter microstructure (Barnea-Goraly, et al. 2004; Courchesne, et al. 2001; Herbert, et al. 2004; Ke, et al. 2008; Keller, et al. 2007) and functional connectivity differences in autism (Just, et al. 2004). In autistics, Just and colleagues have observed reduced functional connectivity between frontal and parietal cortex in a variety of tasks, including sentence comprehension (Just, et al. 2004;

Kana, et al. 2006), n-back working memory tasks (Koshino, et al. 2005; Koshino, et al. 2008) and response inhibition tasks (Kana, et al. 2007). Similarly, reduced functional connectivity between early visual areas (BA17) and inferior frontal cortex was found in autistics during a visuomotor coordination task (Villalobos, et al. 2005), but this decrease was concomitant with increased functional connectivity between the thalamus and its frontal targets (Mizuno, et al. 2006). Given existing reports of atypical connectivity in autism, there are several available explanations for our findings.

One possibility, based on proposals advanced by Just and colleagues (2004), is that increased use of occipital brain regions in autistics reflects compensatory activity arising from an atypical neurodevelopmental trajectory, based on significant communication restrictions between prefrontal and occipital regions. In this scheme, inefficiencies in engaging prefrontal mechanisms could result in the development of compensatory strategies and processing mechanisms more heavily reliant on occipital and posterior parietal cortical regions. These compensatory mechanisms would have to be as effective in supporting reasoning as the more typical mechanisms relying on prefrontal function.

An alternative possibility, based on the EPF model, is that stronger engagement of occipital regions represents a "default" processing mode for autistics, resulting in more locally efficient, and therefore more conveniently engaged, visual processing mechanisms. Decreased prefrontal activity in autistics could be a consequence of an alternate resource allocation strategy based on the availability of more efficient processing in occipital cortex, leading to the sort of reduced functional connectivity observed in other studies.

Another possibility, equally consistent with the EPF model, is that a stronger overall functional independence of perceptual processes from higher-order cognitive control permits autistics a greater engagement of perception in a wide range of tasks which are not typically considered perceptual in nature. In non-autistics, the role of perception would be relatively more restricted through the operation of mandatory or automatic higher-order processes which are optional in autism (Soulières, et al. 2007). Across development, enhanced functional

independence could result in the type of atypical activity patterns exemplified in our findings. While non-autistics could easily engage perceptual mechanisms in a pattern matching task, their engagement of visual perceptual mechanisms in the service of abstract reasoning might be, in comparison with autistics, significantly curtailed.

More specific investigations of the differences in structural, functional and effective connectivity will be required to further differentiate these intriguing possible explanations for the differential activity patterns seen in our study.

Summary and conclusion

We have shown that autistics, a group with relatively enhanced performance on the RSPM compared to their performance on Wechsler IQ tests (Dawson, et al. 2007; Hayashi, et al. 2008), rely more extensively on occipital, and less on prefrontal, cortex while solving RSPM problems. While these findings are difficult to interpret in the context of strongly localized prefrontal models of reasoning, they may be more easily interpreted in the context of distributed frontoparietal models of reasoning. These models allow for task-specific spatial redistribution of activity guided by resource allocation mechanisms taking advantage of individual processing strengths. In this regard the distributed frontoparietal model seems more promising as a general model of reasoning, as it provides explanatory mechanisms encompassing differences in reasoning complexity, individual abilities and the unique characteristics of human subgroups.

Higher level visual processes most likely play a more prominent role in reasoning in autistics, with the specific mechanism of this enhanced utilization of occipital regions an obvious object of future study. A next step could be to dissect the components of RSPM in order to better understand *how* atypical perceptual mechanisms, and their more prominent utilization by autistics, support reasoning. This knowledge could potentially inform educational practice by suggesting ways to optimize the form in which information is made available to autistics during their development.

ACKNOWLEDGEMENTS

We thank Morton Ann Gernsbacher for help in designing the study, and Dara Manoach for access to her imaging dataset. This work was supported by Canadian Institutes for Health Research [grant MOP-84243] and Autism Speaks [grant 2706] to L.M., as well as a postdoctoral award from Canadian Institutes for Health Research to I.S. Data collection was done at the Unité de Neuroimagerie Fonctionnelle, Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM, Canada). The paradigm development and data analysis were done at the Martinos Center for Biomedical Imaging, which is supported by the National Institutes of Health [grant P41 RR14075] and the Mental Illness and Neuroscience Discovery Institute (MIND).

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Annexe III. Enhanced connectivity between visual cortex and other regions of the brain in autism: A REM sleep EEG coherence study

Enhanced connectivity between visual cortex and other regions of the brain in autism: A REM sleep EEG coherence study

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ABSTRACT

Functional interregional neural coupling was measured as EEG coherence during REM sleep, a state of endogenous cortical activation, in 9 adult autistic individuals (21.174.0 years) and 13 typically developed controls (21.574.3 years) monitored for two consecutive nights in a sleep laboratory. Spectral analysis was performed on 60 s of artefact-free EEG samples distributed equally throughout the first four REM sleep periods of the second night. EEG coherence was calculated for six frequency bands (delta, theta, alpha, sigma, beta, and total spectrum) using a 22-electrode montage. The magnitude of coherence function was computed for intra- and interhemispheric pairs of recording sites. Results were compared by Multivariate Analysis of Variance (MANOVA). Each time the autistic group showed a greater EEG coherence than the controls; it involved intrahemispheric communication among the left visual cortex (O1) and other regions either close to or distant from the occipital cortex. In contrast, lower coherence values involved frontal electrodes in the right hemisphere. No significant differences between groups were found for interhemispheric EEG coherence. These results show that the analysis of EEG coherence during REM sleep can disclose patterns of cortical connectivity that can be reduced or increased in adults with autism compared to typically developed individuals, depending of the cortical areas studied. Superior coherence involving visual perceptual areas in autism is consistent with an enhanced role of perception in autistic brain organization.

Keywords: autism; occipital cortex; REM sleep EEG; EEG coherence; visual perception; neural coupling

Introduction

Autism is a neurodevelopmental behavioral phenotype characterized by atypical anatomical connectivity and decreased functional synchrony between brain regions. One of the most consensual findings in autism is volume reduction or microstructural atypicalities in the corpus callosum (Alexander et al., 2007). At the intrahemispheric level, Courchesne and Pierce (2005) systematized results from anatomical, functional and postmortem studies by proposing a ‘’distance rule’’, i.e., increased short-distance connections and diminished long-distance connections in autism. In a related direction, Just and colleagues (2007) elaborated a cortical underconnectivity model of autism based on inferior fronto-posterior activity synchrony, interpreted by magnetic resonance imaging (MRI) functional connectivity studies. At the cognitive level, the two previous models are considered consistent with a dissociation in autism between impairments in some (but not all) high-order tasks (e.g. verbal problem-solving) versus intact or enhanced visuo-spatial, perceptual tasks (e.g. block design).

These two models, however, do not account for all available information regarding anatomical and functional neural connectivity in autism. Indeed, Rafelson et al. (2008) reviewed 18 studies and reported that 12 of them supported the notion of long-distance underconnectivity in autism, but four showed the reverse and two were inconclusive. Concerning short-distance (local) networks, only one study out of four made a case for underconnectivity, two found the opposite and one gave negative results. Moreover, at the cognitive level, autistics display strengths in complex reasoning and novel problem-solving on Raven’s Progressive Matrices, the paradigmatic measure fluid intelligence (Dawson et al.,2007; Soulieres et al., 2009).

An alternative account for reduced physical connectivity as well as for atypical synchrony in functional MRI studies would be that communication between regions within the autistic brain is governed by the cognitive functions associated with these regions rather than by their sheer physical distance. As proposed by the enhanced perceptual functioning (EPF) model (Mottron et al., 2006), one of the main differences between autistic and non-autistic cognition is the overfunctioning of processes and brain regions typically involved in perceptual functions. Compared to typically-developed individuals, autistics display more activation of primary and associative visual areas together with less activity in the prefrontal area, but no underconnectivity at the level of occipital areas, while performing at typical levels

in working memory (Koshino et al., 2005) and reasoning tasks (Kana et al., 2006; Gaffey et al., 2007)..

The present study investigates the hypothesis that autistics should present *higher* EEG coherence between brain regions typically involved in perceptual functions, instead of overall diminished long-distance coherence. Intra- and interhemispheric EEG coherence were measured in autistics and typically-developed individuals during REM sleep. This vigilance state was selected because it features a spontaneous, endogenous activation of the CNS at a time during which access of external stimuli to the cortex is almost completely inhibited (Steriade et al., 1993). REM sleep thus is an ideal context to assess the organization of neural networks, such as the thalamo-cortical loop upon which EEG generation is based. Moreover, REM sleep is associated with activation of the visual system. REM sleep, therefore, constitutes an optimal state to test one aspect of the EPF model by monitoring the activity of the visual system without external inputs.

Methods and Materials

Participants

The participants included 9 autistic individuals (AUT: 21.1±4.0 years) and 13 typically-developed individuals (TYP: 21.5±4.3 years) similar in age, gender and Performance IQ (group averages: AUT=107.5, TYP=113.3; Global IQ: AUT=101.3, TYP=115.7). All participants gave their informed consent to participate in the study, and the experimental protocol was approved by the Ethics Committee of Hôpital Rivière-des-Prairies. Autistic participants were diagnosed by a trained clinician (LM) with standardized instruments (ADOS-G and ADI-R; Lord et al., 1994; Lord et al., 2000). Exclusion criteria for all participants were a past history of sleep disorders and a personal or familial (first-degree) history of psychiatric or neurological disorders. A regular sleep-wake schedule was kept for 14 days before coming to the laboratory. Napping and taking CNS-active medications, including alcohol and caffeine, were not allowed on recording days.

EEG recording and analysis

All participants were recorded for two consecutive nights with a 22-electrode montage according to standard methods (American Encephalographic Society, 1994) (Figure 1). Recordings were derived from a Grass Neurodata Model 15 polygraph equipped with 12A5

amplifiers. EEG electrodes were referenced to linked earlobes (A1+A2) with a serial 10-kΩ resistor for impedance equilibrium purposes. Fifteen 4-s artefact-free epochs were selected during the first four REM periods and pooled (total: 60 s). Using a dedicated software (Harmonie® v6.0a, Stellate, Montréal, Québec, Canada), EEG samples were Fast Fourier Transformed with a resolution of 0.25 Hz and cosine window smoothing. Power amplitude was extracted for delta (0.75-3.75 Hz), theta (4.00-7.75 Hz), alpha (8.00-12.75 Hz), sigma (12.00-14.00 Hz), beta (13.00-20.25 Hz) and total spectrum (0.75-20.25 Hz). EEG coherence measured the linear relationship between pairs of neocortical regions in multi-channel EEG recordings (Nunez et al., 1997; Shaw, 1981), with values ranging between 0 and 100% (0%: random relation, 100%: linear of power/phase relation). The magnitude of coherence was calculated for 51 intrahemispheric and 10 interhemispheric pairs of recording sites.

Statistical analysis

REM sleep characteristics in autistics and typically-developed individuals were compared with t-tests for independent samples with a significance criterion set at 0.05.

Statistical analyses were conducted to identify group differences (autistics versus typically-developed individuals) with a significance criterion set at 0.05, on log-transformed data (Pivik et al., 1993). The main analysis included twelve hypothesis-driven comparisons focusing on coherence values obtained from electrode pairs located in targetted brain regions: frontal areas (FP1-F3, FP1-F7, F3-F7, FP2-F4, FP2-F8, F4-F8), a frontal electrode coupled to a distant one (FP1-T7, FP1-P7, Fp1-O1, FP2-T8, FP2-P8, Fp2-O2), pairs of electrodes located in the visual areas (P3-O1, P7-O1, P3-P7, P4-O2, P8-O2, P4-P8), pairs of electrodes coupling occipital areas with more anterior locations (C3-O1, F3-O1, F7-O1, FP1-O1, C4-O2, F4-O2, F8-O2, FP2-O2) and interhemispheric homologous locations (FP1-FP2, F3-F4, F7-F8, C3-C4, T7-T8, CP5-CP6, TP7-TP8, P3-P4, P7-P8, O1-O2, FZ-PZ). For each of those sets of electrode pairs, an omnibus MANOVA is applied to test the null hypothesis. Whenever the result of the omnibus test is statistically significant, univariate F tests are applied on each electrode pairs to further identify the source of the difference.

General exploratory analyses were conducted on a set of electrode pairs not involving the most anterior and posterior regions (F3-C3, C3-P3, F3-P3, F7-T7, F7-P7, T7-C3, T7-CP5,

T7-CP5, T7-TP7, TP7-CP5, CP5-C3, TP7-C3, F4-C4, C4-P4, F4-P4, F8-T8, F8-P8, T8-C4, T8-CP6, T8-CP6, T8-TP8, TP8-CP6, CP6-C4, TP8-C4).

This statistical strategy permitted a limited number of statistical tests, thus avoiding multiple comparison procedures that result in less statistical power. Also, because of the small sample sizes, all univariate results have been compared to those of a Mann-Withney nonparametric test.

Results

As shown in Table I, no significant differences were obtained between groups on REM sleep parameters. Table II displays significant MANOVA tests on EEG coherence values for clusters of electrode pairs in AUT and in typically developing individuals (TYP). Analyses of intrahemispheric coherence values showed that the electrode pairs displaying higher EEG coherence always involved an electrode located in the left primary visual area (O1) of the autistic group, one pair being a short-distance combination and the other representing a long-distance one. Only one pair of electrodes revealed significantly lower EEG coherence value for the autistic group compared to the controls and was located in the right frontal area. Significant differences were obtained in theta and delta frequencies only. There were no significant effects for interhemispheric (homogenous left–right hemisphere locations) Figure 1 summarizes significant results and trends.

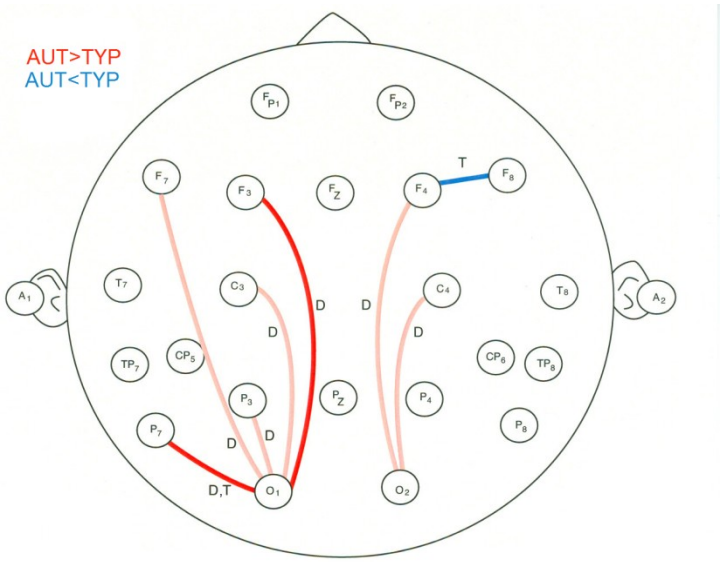

Figure 1. Group differences in EEG coherence during REM sleep. The solid lines connecting electrode sites indicate significant increases (red lines) and decreases (blue lines) in coherence for autistics (AUT) compared to typically developed participants (TYP). Solid lines represent significant results (Po0.05); pink lines represent P values between 0.05 and 0.1. All results shown are in the delta and theta ranges (see Table I). The full montage includes Fz, Pz, Fp1, F3, F7, C3, T7, CP5, TP7, P3, P7, O1, Fp2, F4, F8, C4, T8, CP6, TP8, P4, P8, and O2 (see Methods). AUT, autistics; TYP, typically developed individuals.

Table I. REM Sleep Characteristics in the Autism and Control Groups (mean ± SD)

	Autistics	Controls	*P**
REM sleep latency (min)	72.1 ± 17.1	70.5 ± 18.4	n.s.
REM sleep periods (*n*)	4.6 ± 0.9	4.9 ± 0.6	n.s.
REM sleep duration (min)	111.8 ± 35.3	98.7 ± 18.1	n.s.

*t-tests for independent samples.

Table II. Significant MANOVA Tests on EEG Coherence Values for Clusters of Electrode Pairs in AUT and TYP

Frequency	*F* Omnibus test	df_H	df_E	*P*	Pairs of electrode	*P*	Mean coherence AUT	Mean coherence TYP
Delta	5.38	3	14	**0.011****	P3-01	**0.073***	1.85	1.74
OL					P7-01	**0.024****	1.88	1.82
					P3-P7	0.196	1.84	1.76
Theta	3.66	3	14	**0.039***	P3-01	0.144	1.84	1.69
OL					P7-01	**0.031****	1.89	1.83
					P3-P7	0.261	1.83	1.70
Delta	4.53	4	13	**0.016****	C3-01	**0.065***	1.53	1.17
ODL					F3-01	**0.005****	1.10	0.71
					F7-01	**0.081***	0.83	0.42
					FP1-01	0.468	0.83	0.67
Theta	3.63	3	17	**0.034****	FP2-F4	0.262	1.85	1.87
FR					FP2-F8	0.906	1.86	1.86
					F4-F8	**0.003****	1.83	1.88
Delta	2.40	4	15	**0.096***	C4-02	0.069	1.42	1.22
ODR					F4-02	0.038	0.99	0.69
					F8-02	0.345	0.75	0.57
					FP2-02	0.590	0.75	0.62

$P<0.05$; (*) $0.05<P<0.1$; (**).

OL, occipital left; ODL, occipital to distant left; FR: frontal right; ODR, occipital to distant right; AUT, autistics; TYP, typically developing individuals.

Discussion

This is the first study to analyze intra- and interhemispheric EEG coherence outside of the wake state, i.e., during REM sleep, in a group of autistic adults. Despite a relatively small number of partcipants, significant under- and overconnectivity differences between autistic and control participants were selectively observed between intrahemispheric regions. Although significant results were selectively found in slow EEG frequencies (delta and theta), it may be premature to separately interpret the specificity of each of these frequency band findings at this point. The main study result that will be discussed is rather based on functional interregional neural coupling as such, i.e., the higher level of intrahemispheric coherence involving the occipital area we found in the short- and long-distance range, as well as lower coherence between nonvisual, more anterior recording sites.

Increased intrahemispheric EEG coherence in a resting state such as REM sleep, a condition during which access of external stimuli to the cortex is almost completely inhibited while the CNS is spontaneously, endogenously activated (Steriade et al., 1993), could reflect a high potential for information processing and sharing (Petsche et al., 1988) between visual (O1, O2) and long-range areas. As such, superior intrahemispheric EEG coherence is not a completely new observation in autism. Indeed, Cantor et al. (1986) investigated EEG coherence using a 19-electrode montage in autistic children during the wake state, with eyes open, and found that they generally displayed higher interhemispheric coherence values in the parieto-occipital and central-parietal regions compared to an age-matched group of typically-developed children and a group of intellectually disabled participants. More recently, Coben and colleagues (2008) studied EEG coherence in a group of autistic children and found conflicting results. One of their results was a decreased delta and theta intrahemispheric coherence in AUT for both short to medium and longer inter-electrode distance. Because analyses were pooled on the basis of inter-electrode distances instead of being specifically grouped on the basis of scalp localization, only limited comparisons can be done with our results. Moreover, the authors did not specify the time of day EEG recordings were performed, a methodological control that has been shown to be significant (Daoust et al., 2004). Finally, autistic participants in Coben et al. (2008) were diagnosed on the basis of DSM-IV criteria,

which possibly result in a broader phenotype than that resulting from the application of stringent ADI and ADOS criteria.

The only significant lower connectivity measure for the autistic group in the present study was located in a pair of right hemisphere frontal electrodes (F4-F8). Murias et al. (2007 also found the frontal area to be a sensitive region for wake EEG coherence differences in 18 autistic male adults and 18 controls during the wake state with eyes closed, but lower and higher frontal coherence values were both found, depending on the EEG frequency range analyzed (theta and alpha, respectively).

The present findings are the first to show systematic differences in EEG coherence involving brain functions related to the visual system. Together with higher activation of the occipital cortex described in multiple fMRI investigations, our results provide physiological support for an enhanced role of perceptual areas in autistic cognition, as proposed by the EPF model (Mottron et al., 2006). A greater role of perceptual processes in autism for tasks that are not necessarily of strictly perceptual nature is supported by several studies that have observed a reduced frontal activity associated with greater occipital activity (Soulières et al., 2009, Gaffrey et al., 2007; Kana et al., 2006; Koshino et al., 2005).

Both series of differences in coherence documented in the present study are lateralized (increased coherence in the left, decreased coherence in the right hemisphere in autistics compared to controls). The interpretation for differences in lateralization in autism is twofold. First, autistics could have overall less lateralized functions than non-autistics (McPartland et al. 2004, Bailey et al. 2005, Koshino et al. 2005). Second, the major lateralized function in humans, language, is typically delayed in its development and modified in its functions in autistics. For example, diminished leftward asymmetry of language areas was observed in autism (Herbert et al. 2005, Gage et al. 2009). An increased EEG coherence in AUT compared to neurotypicals might therefore reflect the laterality specificities of those two populations, leading to selective hemispheric differences. In other words, coherence differences would be more pronounced in the left hemisphere due an overall less lateralized allocation of function in the autism group. Consistent with this interpretation, Dawson et al (1995), using spectral activity to study brain activation of autistic children during an alert baseline condition, found reduced EEG power in the frontal and temporal region predominantly in the left hemisphere.

The data of the present study challenges the "distance rule" proposed by Courchesne and Pierce (2005) as well as the proposition of Just et al. (2007) according to which fronto-posterior connectivity suffers from an overall reduction in autism. Indeed, we found that primary and nonprimary visual areas maintain increased EEG coherence with extrastriate areas through short-range as well as long-range connections including with frontal areas, thus reflecting an overconnectivity based on functions rather than physical distance. The only case of decreased EEG coherence was within the right frontal region. It is noteworthy that our protocol differed from that of Just et al. (2007) in that we measured endogenous, not task related, spontaneous activity using REM sleep EEG activity.

In conclusion, we found that atypical cerebral functional connectivity in autism does not follow a homogenous distribution pattern, but rather a function-specific pattern, with the occipital areas being overconnected to other regions. These results underscore the importance to investigate enhanced functioning that exist in a subset of neurocognitive functions in autism, in addition to the mainstream, deficit-oriented approach.

Acknowledgments

This work was supported by an operating grant from the Canadian Institutes of Health Research (CIHR, No. 81898, Studies of Sleep, EEG, and Cognitive Performance in Autism) to R. Godbout and L. Mottron, a studentship from the Fonds de la recherche en sante du Québec (FRSQ) to C. Léveillé, studentships from the CIHR to E.B. Barbeau, C. Bolduc and É . Limoges, and a research scholarship from the FRSQ to L. Mottron. The authors want to thank the participants for their invaluable contribution to this project.

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Annexe IV. Increased Topographical Variability of Task-related Activation in Perceptive and Motor Associative Regions in Adult Autistics

Increased Topographical Variability of Task-related Activation in Perceptive and Motor Associative Regions in Adult Autistics

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Abstract

Background: An enhanced plasticity is suspected to play a role in various microstructural alterations, as well as in regional cortical reallocations observed in autism. Combined with multiple indications of enhanced perceptual functioning in autism, and indications of atypical motor functioning, enhanced plasticity predicts a superior variability in functional cortical allocation, predominant in perceptual and motor regions.

Method: To test this prediction, we scanned 23 high-functioning autistic and 22 typical participants matched on age, FSIQ, Raven scores and handedness during a visuo-motor imitation task. For each participant, the coordinates of the strongest activation peak were extracted in the primary (Brodmann Area 4) and supplementary (BA6) motor cortex, the visuomotor superior parietal cortex (BA7), and the primary (BA17) and associative (BA18+19) visual areas. Mean signal changes for each ROI in both hemispheres, and the number of voxels composing the strongest activation peak were individually extracted to compare intensity and size of the signal between groups. For each ROI, in each hemisphere, and for every participant, the distance from their respective group average was used as a variable of interest to determine group differences in localization variability using repeated measure ANOVAs. Between-group comparison of whole-brain activation was also performed.

Results: Both groups displayed a higher mean variability in the localization of activations in the associative compared to the primary visual or motor areas. However, despite this shared increased variability in associative cortices, a direct between-group comparison of the individual variability in localization of the activation revealed a significantly greater variability in the autistic than in the typical group in the left visuo-motor superior parietal cortex (BA7) and in the left associative visual areas (BA18+19).

Conclusion: Different and possibly unique strategies are used by each autistic individual. That enhanced variability in localization of activations in the autistic group is found in regions typically more variable in non-autistics raises the possibility that autism involves an enhancement and/or an alteration of typical plasticity mechanisms.

Keywords: autism; fMRI; plasticity; primary areas; associative areas

INTRODUCTION

Autism is characterized by social and communication alterations, as well as by repetitive behaviors and restrictive interests, combined with a large diversity among symptomatic profiles and individual developmental trajectories (American Psychiatric Association, 2013; Newschaffer et al., 2007). The variability of autistic phenotype may result from the heterogeneity of environmental constraints and upbringing. However mechanisms for heterogeneity may also be intrinsic to what autism is. The most obvious factor for phenotypic heterogeneity is the wide range of chromosomal regions and the several hundreds of polymorphisms that have been associated with autism (Scherer & Dawson, 2011). Whereas autism is understood as a final common pathway of these various mutations (Ben-David & Shifman, 2012), each genetic alteration may produce its own footprint on the phenotype. For instance, in the case of "syndromic autism", autism accompanied by Tuberous Sclerosis will differ from that accompanied by Fragile X. Another putative source of heterogeneity may be that the common effect of these mutations (either involved in syndromic or non syndromic autism) is an increase in synaptic plasticity, a mechanism which may increase the experience-dependant variability in brain functional allocation (Chung, Bey, & Jiang, 2012; Markram & Markram, 2010; Mottron et al., 2013; Zoghbi & Bear, 2012). However, empirical arguments in favor of enhanced plasticity in autism are mostly indirect –based on examining in animal models the effect of genetic (Baudouin et al., 2012; Kelleher & Bear, 2008) or environmental (Markram & Markram, 2010) alterations– and mostly related to *microstructural* alterations (Markram & Markram, 2010).

Enhanced *functional* plasticity should also be present at the macroscopic level, and predict a greater variability in the autism group in regional allocation of brain functions (Barnes & Finnerty, 2010). Spatial variability in functional allocation is not identically distributed on the surface of the cortex. In an fMRI resting state study in typical individuals, Mueller and collaborators (Mueller et al., 2013) demonstrated that functional connectivity in hetero-modal association cortices (lateral prefrontal regions, temporo-parietal junction) is substantially more variable than in unimodal perceptual and motor cortices. Regions of this increased inter-subject variability overlap with regions displaying more variable cortical folding, as well as with regions implicated in individual cognitive differences and regions

displaying the largest evolutionary expansion between monkeys and humans. Autistics should therefore present more within-group variability in terms of functional allocation in associative regions, because these regions are intrinsically more variable and less genetically constrained in humans (Brun et al., 2009). There are indications that an autistic-specific plasticity process favors these regions, as manifested by their enhanced gyrification (Wallace et al., 2013), as well as by these regions being the primary locus of structural alterations, as revealed by the latest structural meta-analysis (Nickl-Jockschat et al., 2011). At the functional level, a recent ALE meta-analysis of 26 neuroimaging experiments using visual stimuli in autistic individuals revealed a material-specific functional reallocation of visual occipitoparietal associative areas, in the form of atypical spatial distribution of neural activity, and decreased activity in some frontal areas, in autistic relative to non-autistic individuals (Samson, Mottron, Soulières, & Zeffiro, 2012).

Pierce and collaborators (Pierce, Muller, Ambrose, Allen, & Courchesne, 2001) were the first to report a greater individual variability in localization of cerebral activations in autistics. Whereas hypo-activation of the fusiform gyrus was observed in autistics at the group level during a face perception task, each autistic participant had a unique functional hot spot in response to faces (ranging from frontal lobe to occipital lobe and fusiform gyrus), while locations in non-autistics all fell within the fusiform face area. Similar increased inter-individual spatial variability in functional activations was also found in autistic groups during a visuomotor sequence learning task (Muller, Cauich, Rubio, Mizuno, & Courchesne, 2004; Muller, Kleinhans, Kemmotsu, Pierce, & Courchesne, 2003). In these studies, the 3D distance between the group's strongest activation peak in a specific region and each individual's closest peak was used as a direct measure of individual spatial variability. The premotor (BA6) and the superior parietal (BA7) cortices were used as target regions. Compared to typical individuals, autistics showed greater inter-individual spatial variability and decreased activation in the right superior parietal region (BA7) during the early learning stage, and greater variability and greater activation in the right premotor region (BA6) during the late learning stage. Scherf and collaborators (Scherf, Luna, Minshew, & Behrmann, 2010) used a similar computation of the individual variability in a study involving face, object and place processing. Greater variability in localization of activations was observed within the autistic

group, but only in the fusiform gyrus during face processing. Whereas these findings are consistent with our hypothesis of enhanced variability, they are post-hoc findings, and do not compare primary and associative perceptual and motor regions. This distinction is of interest because the main difference in variability reported in typical individuals involves contrasting primary and associative regions (Mueller, et al., 2013; Tahmasebi et al., 2012).

The aim of the study was to use functional magnetic resonance imaging (fMRI) to determine whether there is increased inter-individual variability in the localization, intensity and size of cerebral activations within the primary and associative areas of both visual and motor modalities in autistic individuals, as compared to non-autistic individuals. Between-group comparisons of whole brain activations were also performed to determine if individual variability is associated with between-group differences in task-related activity. We distinguished primary and associative areas of visual and motor modalities recruited during a visuo-motor imitation task, using anatomical ROIs. An easy, visuo-motor task was chosen in order to produce a combined activation of visual and motor cortices. BA4 (primary motor cortex), BA6 (premotor cortex and supplementary motor area, SMA), and BA7 (visuomotor superior parietal cortex) were selected as ROI to investigate motor functions. BA18 (V2: secondary visual cortex) and BA19 (associative visual cortex) were grouped together to represent the global associative areas of the visual cortex, and BA17 (V1: primary visual cortex) composed the visual ROI.

METHODS

Participants

The initial experimental sample comprised 26 high-functioning autistic participants and 23 typically developing participants recruited from the research database of the Université de Montréal Autism Center of Excellence at the Rivière-des-Prairies Hospital (Montreal, Canada). The autistic and non-autistic groups were matched on age, gender, Wechsler Full-scale and Performance IQ (WISC-III or WAIS III, Canadian norms), Raven's Progressive Matrices (North American norms) (Raven, 1976) and manual preference estimated using the Edinburgh Handedness Inventory (Oldfield, 1971). Two left handed autistics were not included in the analysis, in order to satisfy group matching in handedness. Most autistic participants were diagnosed using a multidisciplinary assessment that included a clinical

evaluation based on DSM-IV criteria, the Autism Diagnostic Interview Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) and the Autistic Diagnostic Observation Schedule (ADOS-G module 3-4) (Lord et al., 1989). However, some participants were characterized using expert interdisciplinary judgment only (one participant) or combined with either ADOS-G (two participants) or ADI-R (two participants). Typical participants were screened for personal or familial neurological or medical conditions known to affect brain function. Exclusion criteria were uncorrectable visual impairment, current use of psychoactive or vasoactive medications and use of drugs or alcohol exceeding 2 drinks per day. All structural scans were reviewed by a neurologist to ensure that no participant had any anatomical abnormalities. Written informed consent was obtained from all participants in accordance with the Regroupement Neuroimagerie/Québec IRB approved protocol #08-09-003. All participants received monetary compensation for their participation.

Stimuli and procedure

The visuomotor imitation task included 15 different hand gestures drawn in black and white, each illustrated twice to represent both left and right hands. These visual stimuli were presented so that the participants saw the hands with the palm facing them and could distinguish clearly the configuration of the fingers (Figure 1). A practice session outside the scanner ensured that the participants familiarized themselves with the different gestures, understood the task and could imitate the gestures with their hand while minimizing movement of the rest of the body. During the fMRI scanning session, participants were lying on their back in the scanner with their hands on the sides of the body, palms facing up. No visual feedback could be used during the task, as participants had to look continuously at the stimuli presented. Visual stimuli were presented using the Matlab Psychtoolbox (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007; Pelli, 1997), on a screen at the back of the scanner bore. The participants saw the stimuli through an individually adjusted mirror attached in front of their eyes on the head coil. Vision correction with fMRI compatible lenses for participants with myopia or hyperopia was applied in concordance with their optometrist's prescription. A total of 96 hand gestures were presented during the session, in 16 blocks of 6 trials. The session started with a 10 seconds fixation cross. Then, each of the 16 blocks included a 2.5 second instruction slide indicating the hand to be used to imitate the hand gesture presented

(left hand or right hand condition) for the following 6 trials. The stimuli were presented pseudo-randomly (3sec/stimulus) in the same visual field as the hand to be used to imitate. A fixation cross (9.5 second duration) ended each block and served as the baseline. The total duration of the session was 490 seconds.

Figure 1. Two different sample stimuli from the visuo-motor imitation task.

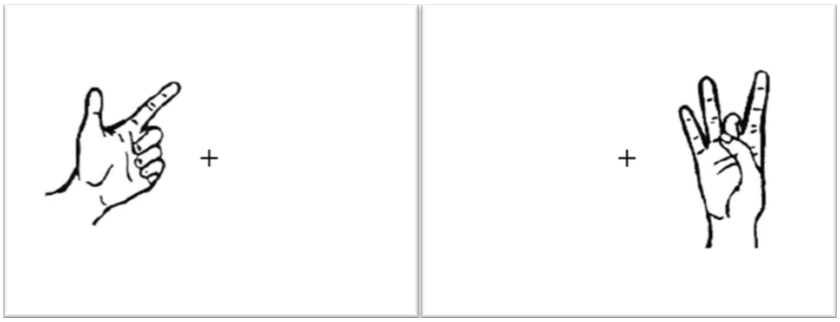

Image Acquisition

Images were acquired on a Siemens Tim Trio 3T scanner with a 32 channels phased-array head coil at the "Unité de Neuroimagerie Fonctionnelle" (University of Montreal). The scanning session included anatomical T1-weighted structural brain images using an ME-MPRAGE 4-Echo sequence (176 slices, $1mm^3$ voxels, TR = 2530 ms, TE = 1.64/ 3.5/5.36/7.22ms, flip angle = 7°). Acquisition of functional data used an echo planar imaging (EPI) pulse sequence (150 acquisitions, TR = 3330ms, 60 slices, matrix size 80x80, voxel size 2.5x2.5x2 mm^3, slice thickness: 2mm with a 0.5mm gap, TE = 30ms, flip angle = 90°). Gradient echo phase and magnitude field maps were then acquired (60 slices, matrix size = 80x80, voxel size 2.5x2.5x2.0mm^3, slice thickness = 2mm with a 0.5mm gap, TR = 488ms, TE short = 4.92ms, TE long = 7.38ms, flip angle = 60°) to correct image distortions and improve co-registration accuracy using the field map toolbox in SPM.

Image analysis

SPM8, MRICRON and SPSS were respectively used for image preprocessing, visualization and statistical analysis.

Preprocessing

Image preprocessing steps started with a two-pass realignment involving initial registration of all images to the first image of the time series within the run, followed by

registration of the images to the mean of the images computed after a first realignment, and then followed by resampling using 4th degree b-spline interpolation. Slice time correction was applied using interpolation between time points at each voxel taking the last slice of the EPI volume as reference. Images were then spatially transformed and spatially normalized into the ICBM152 MNI space. Normalized images were finally smoothed using 3D Gaussian filtering kernel of 8mm FWHM.

Statistical modeling

After inspection of functional activations (at uncorrected $p < .001$), participants were excluded if they presented an aberrant pattern of activation with no activation in the visual and motor-related areas (1 per group). The final sample included 23 autistic and 22 typical participants (Table 1). Head motion parameters during the functional scanning session were inspected and did not exceed 1.5 mm of translation and 0.05 degree of rotation for any of the participants. Independent-sample *t*-tests were performed on the translation and rotation parameters. The groups did not differ in the magnitude of maximal translation ($t(43) = .624$, $p = .536$) or rotation ($t(43) = -.724$, $p = .473$).

To allow longitudinal magnetization equilibration, the first two volumes of the session were discarded. Model specification of the first level analysis included a design matrix for each of the two active conditions (left/right hand) and the baseline condition (fixation cross) corresponding to the timing described above in the procedure section 2.2. Six head motion estimates were included in the model as covariates of no interest. A high-pass temporal filter with a cutoff of 128 seconds was also used to remove low-frequency noise. A GLM model was used for statistical analysis. The hemodynamic response was modeled using the canonical hemodynamic function implemented as boxcar basis functions in SPM8. In the first-level analysis, the following contrasts were computed**:** left and right hand respectively vs. the fixation cross baseline. To allow inference at the population level, the mixed effect model included a second-level analysis where the first-level contrasts were entered in a random-effect model with three factors: Subject (55 levels), Group (2 levels), which was assumed to have unequal variance, and Condition (2 levels). The mixed effect model covers the first-level analysis (accounting for within-subject variability) followed by second level analysis

(accounting for between-subject variability). The critical threshold was $t = 5.38$, $p < .05$, FWE with an extent threshold of k = 20 voxels.

Table 1
Participant characteristics

	TYPICAL	AUTISM	*p* value
Sample size (gender)	22 (3F, 19M)	23 (3F, 20M)	
Age (years)			
Mean (SD)	22.6 (5.56)	19.8 (4.72)	0.125
Range	15-35	14-30	
Full-scale IQ			
Mean (SD)	107.3 (12.51)	100.3 (10.48)	0.056
Range	87-127	86-118	
Performance IQ			
Mean (SD)	104.7 (13.14)	105.1 (11.74)	0.709
Range	82-122	92-127	
Verbal IQ			
Mean (SD)	108.7 (11.81)	99.8 (14.87)	0.017
Range	91-127	67-119	
Raven			
Mean (SD)	68.1 (25.41)	75.5 (15.99)	0.268
Range	25-96.5	50-100	
Handedness			
Mean (SD)	+74.05 (38.57)	+62.35 (59.06)	0.460
Range	-87.5 to +100	-80 to +100	
ADOS score			
Mean (cut-off)			
Communicative	-	4.95 (3)	
Social	-	9.57 (6)	
Social+communicative	-	14.52 (10)	
ADI score			
Mean (cut-off)			
Social	-	21,48 (10)	
Communicative	-	16,86 (8)	
Behavior	-	6,14 (3)	

Note. Groups were matched on gender, age, full scale IQ, performance IQ, Raven Progressive Matrices percentile scores and manual preference, which is reported as the Edinburgh score (from -100 completely left handed to +100 completely right handed). ADI: Autism Diagnostic Interview, ADOS: Autism Diagnostic Observation Schedule. Group differences were assessed using independent t-tests.

Computing parameters of individual variability

Individual variability corresponds to the magnitude of the within-group variability, and is measured through three different parameters based on the strongest activation peak of task-related activity: its *localization*, its *mean signal change* between task and baseline and its *size*. In order to compute individual variability for these three parameters, regions of interest (ROIs), which were defined from a Brodmann area (BA) atlas using the WFU Pickatlas SPM Toolbox (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003), were used to measure the individual activations in the visual and motor regions involved in the task. Using these ROIs defined from a template rather than from each individual is justified for this study because the size of individually defined ROIs depends on the statistical significance of the functional responses, which were a function of the variability and the response amplitude (Dinstein et al., 2010). As the goal of this study is to investigate individual variability in autistic compared to typical individuals, the use of anatomically defined ROI masks gave us a legitimate comparison point. Computations of the three parameters determining individual variability were all based on the strongest activation peak for each ROI, within each hemisphere. Separate repeated measure ANOVAs were performed for the visual and motor modalities with Region (Primary, Associative), Side (Left, Right) and Group as factors. Significant main effects and interactions were then further investigated using two-tailed independent-samples *t*-tests. Since this measure of variability is associated with standard deviation of the parameters computed, Levene's tests (homogeneity of variance) were applied.

Localization. Coordinates of the strongest activation peak were extracted from the functional images with an uncorrected threshold ($p < .001$) for each participant, ROI and hemisphere. Using a lower uncorrected threshold is justified given our goal, as it does not affect the localization of the activation, only its intensity and its size. Based on the method used by Müller et al. (Muller, et al., 2003), distances in three-dimensional stereotactic space were computed between the group mean maxima and the individual maxima. For example, if the strongest activation in the right BA17 for one participant was located at [20, -84, 10] and occurred at [18, -93, -4] for the group mean, the distance was $\sqrt{2^2+9^2+14^2} = 16.76$ mm. The variable obtained was thus the geometric distance from the group mean activation, and was

therefore used to measure intra-group variability in localization of activations, or spatial variability.

Mean signal change. To compare the intensity of the signal between groups, mean signal changes of activated voxels of each individual for each ROI and hemisphere were extracted from the strongest activation peak (Chung et al., 2007). Only those which reached the more conservative threshold of $p < .05$ FWE corrected were included in the analyses. An average of 2 measures was excluded in each group and ROI**,** except for the BA7 ROI**;** about 7 measures had to be excluded in each group.

Size of activation. The size of activation was determined by computing the number of voxels that reached the conservative threshold of $p < .05$ FWE corrected within the ROI.

Group analysis: whole brain task-related activity

In order to disentangle region-specific individual variability from group differences in whole brain activation, the latter was computed through repeated measures ANOVA with Subject, Group (typical or autistic) and Condition (left hand or right hand) as factors.

Voxel-Based Morphometry

Image Preprocessing. A Voxel-based morphometry (VBM) analysis was conducted using the SPM8 VBM-DARTEL procedure (Ashburner, 2010) to see whether the group differences observed in terms of functional variability could be explained by an anatomical difference in the same grey matter regions. First the T1 images were visually inspected for artifacts and 3 subjects were rejected at this level. The images were segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the *New Segment* tool. The resulting grey mater images for each subject were then used in the DARTEL (create Templates) procedure. The resulting template files of each subject were smoothed, spatially normalized and Jacobian scaled to MNI space. A 10 mm FWHM Gaussian kernel was used.

Statistical Analysis. A t-test was performed to investigate whole-brain group differences in grey matter correcting for total intra-cranial volume (GM+WM+CSF) using global normalization.

RESULTS

Individual variability differences

Spatial Localization (figure 2). Mean distances and their standard deviation for each group, ROI and hemisphere are presented in Table 2.

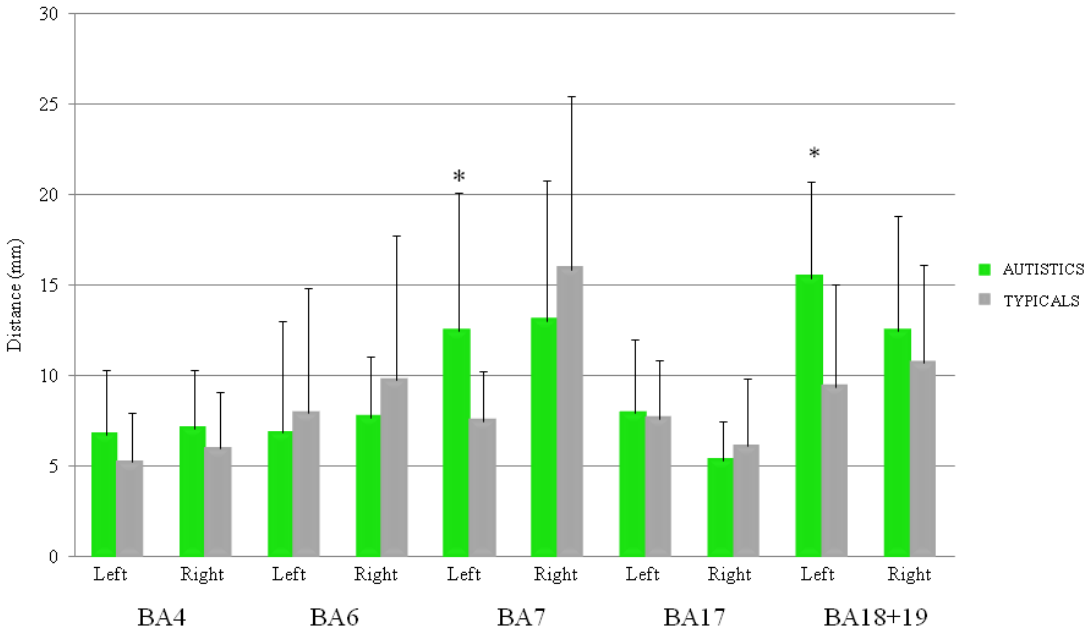

Figure 2. Mean distances in millimeters from the group mean activation peak in the motor and visual ROIs in autistic and typical groups during the visuo-motor imitation task. Differences between groups reaching significance (p<.05) are indicated by an asterisk (*).

Table 2
Mean distances from the individual activation peak to the group mean activation peak, and standard deviation for each group, ROI and hemisphere.

	TYPICALS	AUTISTICS
Region and hemisphere	Mean (SD)	Mean (SD)
Visual		
BA17 Left	7.63 (3.22)	7.92 (4.08)
BA17 Right	6.08 (3.72)	5.32 (2.12)
BA18+19 Left *	9.37 (5.68)	15.41 (5.35)
BA18+19 Right	10.72 (5.39)	12.45 (6.40)
Motor		
BA4 Left	5.21 (3.69)	6.74 (3.56)
BA4 Right	5.96 (3.09)	7.09 (3.22)
BA6 Left	7.94 (6.89)	6.85 (6.13)
BA6 Right	9.75 (7.98)	7.69 (3.37)
BA7 Left *	7.49 (2.76)	12.44 (7.64)
BA7 Right	15.87 (9.61)	13.02 (7.74)

Note. Distances are in millimeters. Significant group differences ($p<.05$) are indicated by an asterisk (*).

Visual areas. The repeated measure ANOVA revealed significant Region ($F(1,39) = 50.79$, $p < .001$) and Side ($F(1,39) = 5.15$, $p = .029$) main effects, as well as a Region X Group interaction ($F(1,39) = 6.38$, $p = .016$). In both groups the variability was more important in the left hemisphere. Independent *t*-tests showed that the variability of individual distances from the group mean activation peaks were greater in the autistic group than in the typical group in Left BA18+19 (associative visual regions: $t(43) = 3.67$, $p = .001$) but not in Left BA17 ($t(41) = .257$, $p = .799$). This group difference was not present for the right hemisphere (Right BA 18+19: $t(42) = .979$, $p = .333$, Right BA 17: $t(40) = -.821$, $p = .417$). See figure 3. The Levene's tests did not reach significance.

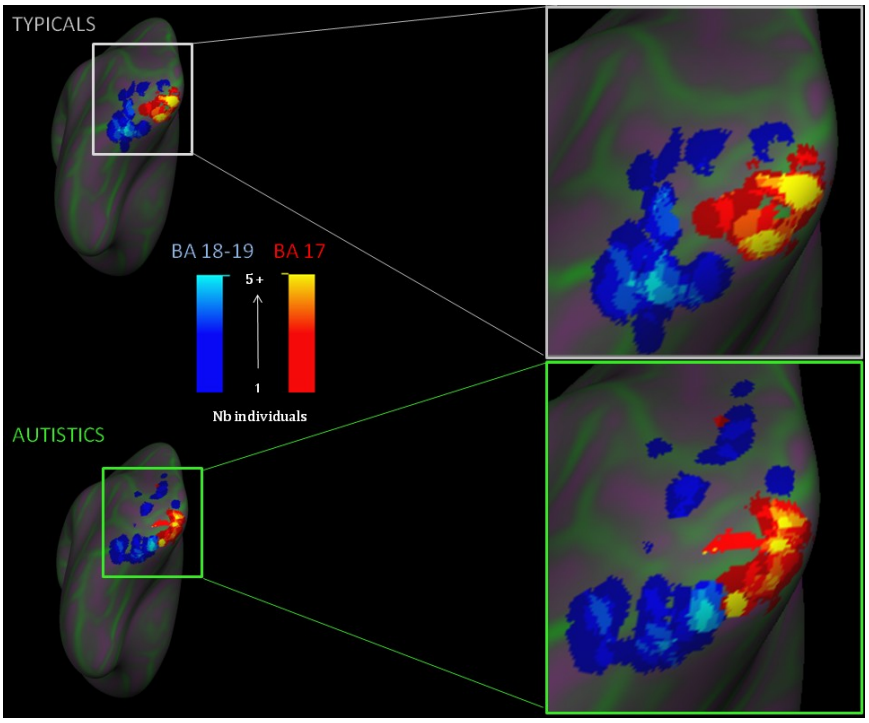

Figure 3. Localization of all individual peaks of activation in the left visual ROIs. Each peak is represented as a 1cm diameter sphere projected on the cortical surface using Freesurfer. The color scale represents the overlap of individual peaks, darker being 1 individual and brighter 5 and more. The primary area (BA 17) is in red and the associative area (BA 18-19) is in blue. The autism and typical groups are displayed separately.

Motor-related areas. The repeated measure ANOVA revealed significant Region ($F(1,35) = 26.29$, $p < .001$) and Side ($F(1,35) = 11.72$, $p = .002$) main effects, a Side X Group interaction ($F(1,35) = 6.06$, $p = .019$) as well as a three-way Region X Side X Group interaction ($F(1,35) = 6.00$, $p = .019$). The independent t-tests revealed that autistics exhibited greater variability than typicals in BA7 only and on the left side only ($t(37) = 2.67$, $p = .014$) the latter being associated with a significant Levene's test ($p = .032$) as well. The independent t-tests and Levene's tests did not reach significance ($p > .05$) for the between-group differences in the primary motor ROIs (BA4, BA6) (see figure 4).

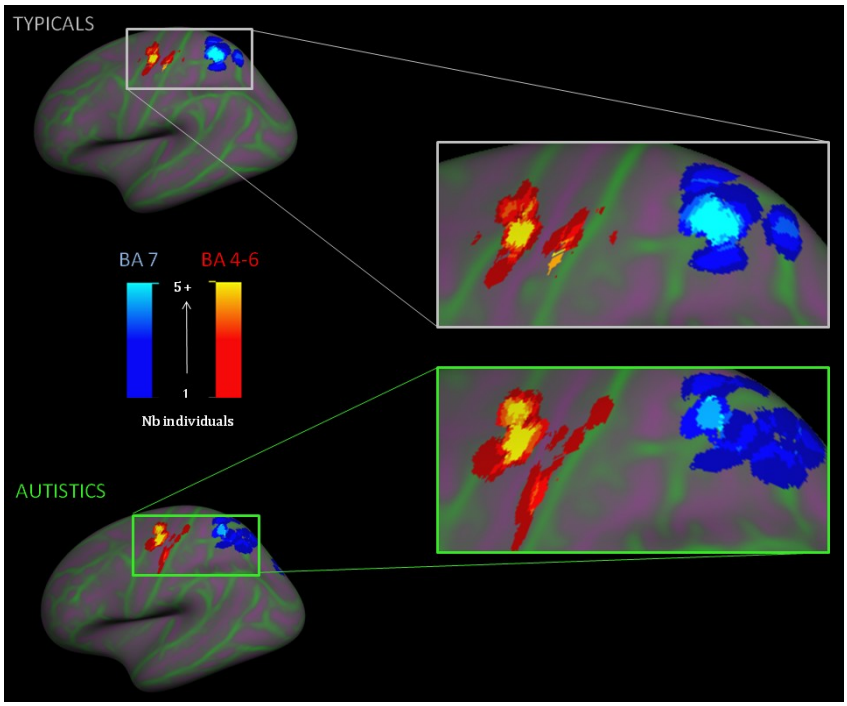

Figure 4. Localization of all individual peaks of activation in the left motor ROIs. Each peak is represented as a 1cm diameter sphere projected on the cortical surface using Freesurfer. The color scale represents the overlap of individual peaks, darker being 1 individual and brighter 5 and more. The primary area (BA 4-6) is in red and the associative area (BA 7) is in blue. The autism and typical groups are displayed separately.

Mean signal change (figure 5). No significant between-group difference was observed in mean signal change ($p > .05$). Levene's tests were not significant, except for the left BA4 ($p = .039$).

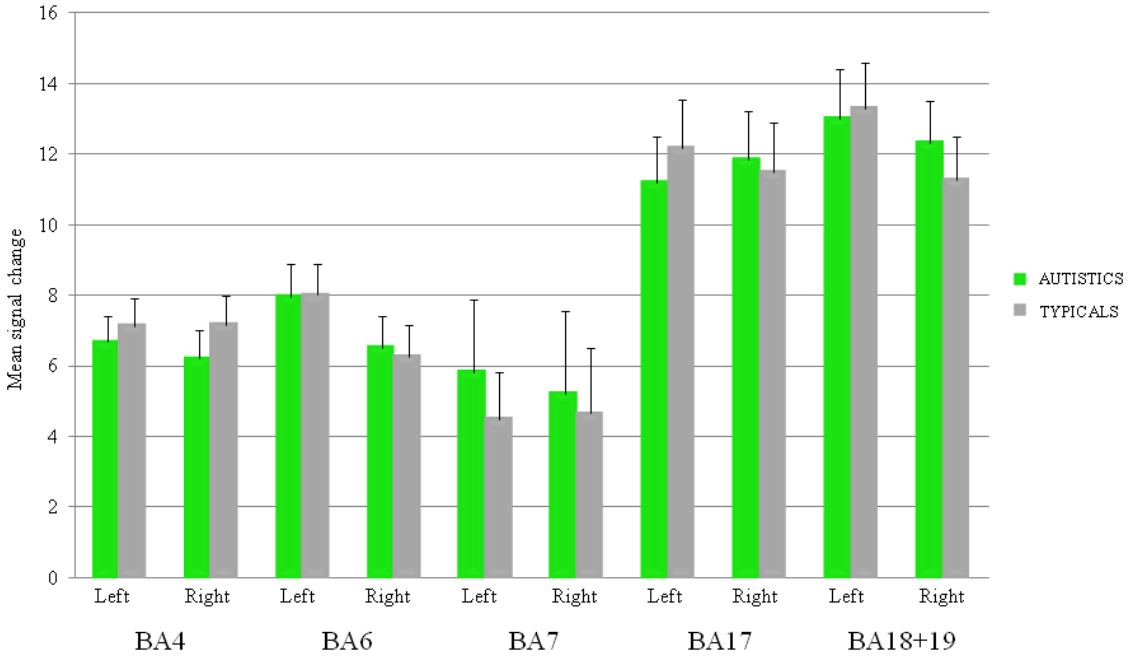

Figure 5. Mean signal change in motor and visual ROIs in autistic and typical individuals during the visuo-motor imitation task. No difference between groups was observed.

Size of activation (figure 6). No significant between-group difference was observed in size of activation ($p > .05$). Levene's tests were not significant.

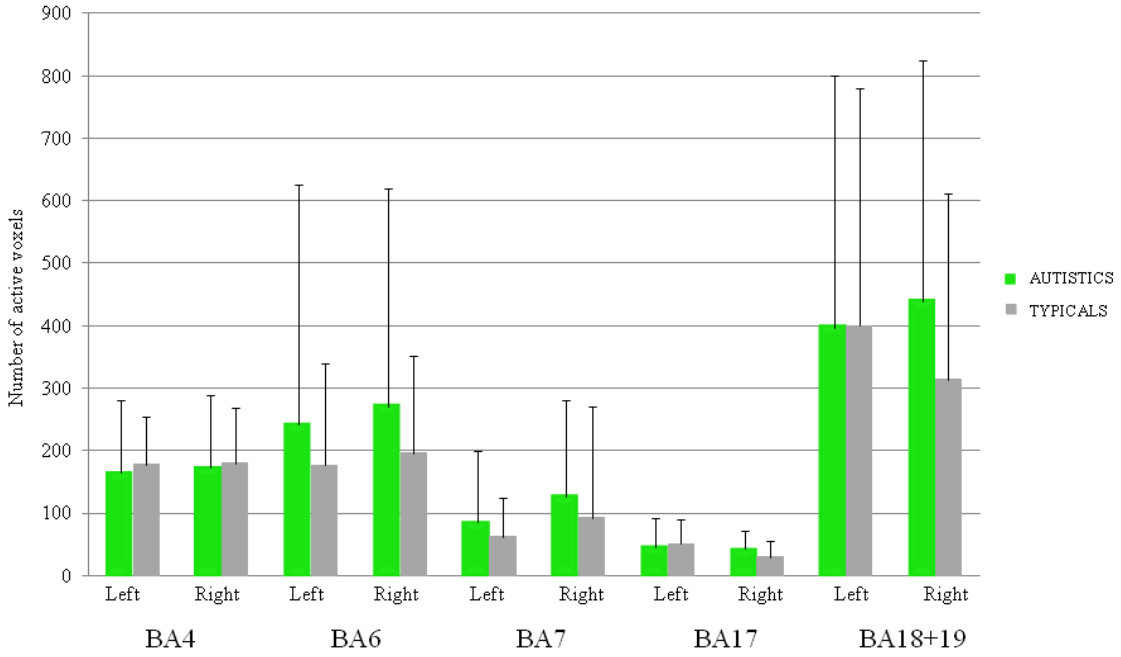

Figure 6. Mean size of activation in motor and visual ROIs in autistic and typical groups during the visuo-motor imitation task. No difference between groups was observed.

Group analysis: whole brain task-related activity

Within-group contrasts

In each group, every ROI showed functional engagement during the task. Both groups showed the same pattern of activation in the middle occipital gyrus, inferior semi-lunar lobule and middle frontal gyrus. However, unlike the autistic group, the typical group recruited frontal regions, including superior, inferior and superior frontal gyrus. The autistic group showed activations in the middle occipital gyrus, inferior semi-lunar lobule, nodule and caudate, regions that the typical group did not significantly recruit. Results are presented in Table 3.

Table 3

Activity associated with the visuo-motor imitation task in each group.

		Left					Right				
Region label	BA	*x*	*y*	*z*	*t*	*d*	*x*	*y*	*z*	*t*	*d*
TYPICALS											
Both conditions											
Occiptal											
Middle occipital gyrus	18	-36	-86	-8	52.09	15.92	28	-86	-8	46.93	14.35
		-28	-86	4	47.20	14.42					
Posterior											
Inferior semi-lunar lobule		-26	-62	-52	13.30	4.07	30	-60	-52	10.33	3.16
		-20	-70	-50	11.41	3.49	20	-72	-48	10.11	3.09
Frontal											
Superior frontal gyrus	9	-42	42	32	12.39	3.78					
		-34	54	32	6.72	2.05					
Inferior frontal gyrus	46						52	40	12	9.48	2.89
Middle frontal gyrus	10						42	40	8	6.49	1.98
Superior frontal gyrus	9						38	48	34	9.44	2.88
AUTISTICS											
Both conditions											
Occipital											
Inferior occipital gyrus	18	-34	-84	-10	47.67	14.57					
Middle occipital gyrus	18	-30	-88	-2	40.21	12.29	28	-86	-8	45.91	14.03
Posterior											
Inferior semi-lunar lobule		-18	-62	-52	11.17	3.41	22	-64	-52	9.52	2.91
		-28	-58	-52	9.96	3.04	14	-76	-46	8.67	2.65
		-14	-72	-48	9.13	2.79					
Frontal											
Middle frontal gyrus	9						42	46	32	10.17	3.11
							36	38	28	6.95	2.14
Anterior Lobe											
Nodule							2	-56	-34	6.66	2.04
Sub-Lobar											
Caudate		-18	28	-4	6.89	2.11					

Note: Specific activations for each group in both conditions (left+right hand). The coordinates are in MNI space. BA refers to Brodmann Area and *d* represents Cohen's effect size. The critical threshold was $t = 5.38$, $p<.05$, FWE. Extent threshold: k = 20 voxels.

Between-group contrasts

For the *left hand* condition, between-group contrasts revealed greater activation for the autistic compared to the typical group in the left lingual gyrus (BA19), while the typical group showed greater activation in the middle occipital gyrus (BA19) and the middle temporal gyrus (BA39) compared to autistics ($p < .05$, FWE). For the *right hand* conditions, typical individuals showed the same pattern of increased activity in the middle occipital gyrus (BA19) and the middle temporal gyrus (BA39) ($p < .05$, FWE). No region was significantly more active in the autistic group than in the typical group for the *right hand* condition. When *left and right hand* conditions were combined, typical individuals still showed greater activation in the middle occipital (BA19) and middle temporal gyrus (BA39) bilaterally, as well as in the left inferior occipital gyrus (BA18) ($p < .05$, FWE). These results are consistent with those obtained by Tanaka and Inui (Tanaka & Inui, 2002) and Mühlau and collaborators (Mühlau et al., 2005) in similar imitation tasks. The autistic group showed greater activity than the typical group in a number of regions involved in visual and motor processing: bilateral middle occipital gyrus (BA19 and BA18) in a more superior portion than the typical group's active region, left cuneus (BA18), lingual gyrus (BA18+BA19) and precuneus (BA31) bilaterally, right medial frontal gyrus (BA6) and superior frontal gyrus (BA6) and bilateral superior parietal lobule (BA7). Results are shown in Table 4.

Table 4
Between-group differences in the visuo-motor imitation task.

		Left					Right				
Region label	BA	*x*	*y*	*z*	*t*	*d*	*x*	*y*	*z*	*t*	*d*
TYPICALS > AUTISTICS											
Both conditions											
Occipital											
Inferior occipital gyrus	18	-40	-86	-4	8.29	2.53					
Middle occipital gyrus	19	-30	-84	4	8.40	2.56	44	-74	0	8.48	2.59
Temporal											
Middle temporal gyrus	39	-44	-76	14	6.27	2.46	54	-72	10	7.41	2.26
							58	-62	4	6.66	2.03
Left hand condition											
Occipital											
Middle occipital gyrus	19						44	-74	0	6.68	2.59
Temporal											
Middle temporal gyrus	39						54	-72	10	6.20	2.26
Right hand condition											
Occipital											
Middle occipital gyrus	19	-30	-84	4	6.32	2.56					
		-38	-86	6	6.07	2.34					
Temporal											
Middle temporal gyrus	39	-46	-76	14	6.70	2.39					
AUTISTICS > TYPICALS											
Both conditions											
Occipital											
Middle occipital gyrus	19	-32	-84	18	8.55	2.61					
	18						38	-92	10	6.33	1.93
							14	-94	14	6.76	2.06
Precuneus	31	-20	-76	20	6.60	2.01	26	-78	22	7.67	2.34
Cuneus	18	-2	-86	18	6.58	2.01					
Lingual gyrus	19						30	-88	24	6.17	1.88
	18	-20	-70	-6	6.72	2.05	18	-72	-8	6.61	2.02
							20	-78	-16	6.25	1.91

Parietal											
Superior parietal lobule	7	-22	-74	50	7.66	2.38	28	-70	52	6.96	2.12
Postcentral gyrus	2	-32	-28	38	6.21	1.89					
Sublobar											
Caudate		-18	28	-4	6.61	2.02					
Frontal											
Superior frontal gyrus	8						26	34	52	6.37	1.94
Medial frontal gyrus	6						6	-20	70	6.16	1.88
Left hand condition											
Occipital											
Lingual gyrus	19	-24	-68	-8	6.00	1.89					
Right hand condition											
No significant loci											

Note. Activity associated with group differences in both conditions (left + right hand), left hand condition and right hand condition. The coordinates are in MNI space. BA refers to Brodmann Area and *d* represents the Cohen's effect size. The critical threshold was $t = 5.38$, $p<.05$, FWE. Extent threshold: k = 20 voxels.

Voxel-Based Morphometry

No significant difference was observed between groups in terms of regional grey matter increases or decreases (with a threshold of FWE $p< .05$).

DISCUSSION

The aim of this study was to test the prediction that, given enhanced plasticity in autism, this group should display increased spatial variability of activations in motor and visual associative areas. We also investigated between-group differences in the magnitude of activation in these regions, which may interact with this variability. Consistent with our prediction, inter-individual variability in localization of activation was greater in the autistic, as compared to the typical group, in the left associative visual areas (BA18+19) and in the superior parietal cortex (BA7). These results are not likely to be explained by anatomical grey matter variability, since the VBM analysis did not reveal any group differences. No group differences in terms of variability of intensity and size of the activations were observed.

Validity and sensitivity of individual variability measurements

Individual variability in *localization* was measured using the Euclidean distance between the stereotactic coordinates of an individual's strongest activation peaks and that of the group mean. Compared to a surface-based analysis, drawing the most direct line between two activation peaks underestimates their actual distance, as it neglects the grey matter curvilinear morphology. However, despite its limits in precision, the use of Euclidean distance for this purpose has been well documented and validated. In addition, the effective slice thickness limits the resolution of spatial distances to 2 mm but this bias is shared by the two populations under study, and therefore should not mask group differences. The mean distances (between 4 and 23 mm) computed per regions and hemispheres were largely above the spatial resolution used in this study. Our technique can therefore be considered as a satisfying measure of localization variability.

The absence of behavioral measures prevents us from disentangling group differences in topographical brain activity from those associated with performance. However, whether or not the groups differed in terms of accuracy in the imitation task should not affect our results as we were interested in within-group individual variability. Since all participants trained successfully at the task before scanning**,** and since this elementary task is performed at ceiling level in adults of average measured intelligence (Salowitz et al., 2013; Williams, Whiten, & Singh, 2004), the possible role of within-group difference in performance variability in our findings should be minimal.

Another limitation of this study is that individual variability was assessed using a single measure per subject. Mueller et al (Mueller, et al., 2013) used several measures taken 6 months apart and subtracted intra-subject variability from overall variability to obtain residual inter-subject variability. Our single-measure procedure may therefore overestimate inter-subject variability. However, it could not overestimate group differences in this regard, as the two groups shared this bias.

Individual variability in localization of visual and motor activations

Primary and associative visual areas. No difference related to localization of activation was observed in either left of right primary visual cortices (BA17). A similar

magnitude of activation in primary visual areas (BA17) in both groups is concordant with Hadjikani's (Hadjikhani et al., 2004) findings that the early sensory visual areas are typically organized in autistic adults. Although a greater variability could be influenced by a greater task-specific cognitive demand in autistic participants, greater variability parameters in the associative than in the primary areas was shared by both groups. The fact that mean variability in the localization of activations was higher in the associative than in the primary visual areas for both groups is consistent with associative areas being more variable than primary perceptual ones (Mueller, et al., 2013). It is also in line with the increase in variability of localization paralleling the hierarchy of levels of processing (Tahmasebi, et al., 2012).

The main difference between groups in terms of variability resided in an even greater variability in localization of activation in autistic than in typical individuals in the left associative visual areas (BA18+19). The autistic group displayed greater bilateral activation in the middle occipital gyrus (BA18+BA19), lingual gyrus (BA18+BA19) and precuneus (BA31)**,** as well as in the left cuneus (BA18). A greater variability in associative visual regions in the autistic group is consistent with the greater implication of the associative visual areas during tasks involving visual stimuli in autism (Samson, et al., 2012), and particularly BA18 (Soulieres et al., 2009).

Primary and associative motor-related areas. Following a pattern similar to that for visual regions, mean distances between the individual activation peak and the group mean activation peak of each group drastically increased between BA4 and BA7. This trend is more pronounced in autistics, who showed greater spatial variability of activations in the left hemisphere in BA7, an associative visuomotor region, while no difference was observed in the primary motor area, BA4, and premotor cortex/SMA, BA6. BA7 is localized in the superior parietal cortex, and is involved in the integration of visual and motor information. This region receives afferences from the visual areas and sends information to the premotor areas (BA6). The second level analysis revealed that the autistic group showed greater activation than the typical group in the right medial and superior frontal gyrus (BA6) and in the bilateral superior parietal lobule (BA7). Increased activation in the superior parietal cortex was also reported in autism during a visuo-spatial task (Damarla et al., 2010) and was associated with a greater functional importance of the visuo-spatial processing in autistics compared to typicals. Our

results are consistent with the behavioral literature of motor skills in autism, showing an atypical role of sensory-perceptual input/feedback in autistics when executing a motor task (Gowen & Hamilton, 2013; Izawa et al., 2012; Linkenauger, Lerner, Ramenzoni, & Proffitt, 2012).

Effect of Lateralization. The three series of group differences reported here are all limited to the left hemisphere. This may at least partially result from autistics displaying an atypical reduction of lateralization in functions which are usually lateralized in typical individuals. In the autism literature, most differences in lateralized functions independent of handedness are in the form of an absence of asymmetry in language-related regions (De Fosse et al., 2004; Herbert et al., 2002; Rojas, Bawn, Benkers, Reite, & Rogers, 2002; Rojas, Camou, Reite, & Rogers, 2005) and face processing areas (Conturo et al., 2008; Kleinhans et al., 2010; Kleinhans et al., 2008). However, since the visual and motor functions under study here are not known to be lateralized, and the variability under study in this paper is not directly associated with superior activation, we do not know if this explanation can be applied to the current set of findings.

Mechanisms of topographical variability

In the context of atypical microstructural plasticity and multiple de-novo mutations of genes involved in the construction of local neural networks in autism (Kelleher & Bear, 2008), an increased variability of cortical functional allocation may be attributed to the alteration of the neurobiological and experience-dependant plasticity mechanism responsible for this variability in typical individuals (Mottron, et al., 2013; Mueller, et al., 2013) . Regions of enhanced variability in autistics are, at least partially (for visual tasks), overlapping with regions also displaying an enhanced activity, and are functionally associated with peaks of ability (Soulieres, et al., 2009)**.** This suggests that this alteration of dominant functional allocation is related to one of the most specific aspect of autistic cognition. Moreover, considering that perceptual peaks of performance are not found to the same extent in autistics people with and without speech onset delay (Barbeau, Soulières, Dawson, Zeffiro, & Mottron, 2013; Bonnel et al., 2010), this variability may also contribute to the difference between the autism and the Asperger subgroups, based on contrasted speech acquisition and perceptual performance (Mottron, et al., 2013).

Methodological consequences of variability

Finally, the fact that individual variability of the functional allocation of brain resources interferes with between-group differences in activations has important heuristic consequences for future fMRI studies of autistic people. Our results are consistent with those of Müller et al. (Muller, Pierce, Ambrose, Allen, & Courchesne, 2001) and Pierce et al. (Pierce, et al., 2001) in that the autism group is characterized by spatial inconsistencies in the activations across subjects, as can be observed in figure 3 and 4 of the present study; sites of activations specific to one individual are more numerous and distant in the autism group than in the typical group. Autistic-Control fMRI group differences are usually interpreted as evidence of functional deficits at the group level (Gernsbacher, 2007). The current study suggests, rather, that hypo activation at the group level may result from each individual successfully completing a task using a unique brain allocation, even by comparison to his own group. This is confirmed by an ALE meta-analysis (Samson, et al., 2012) demonstrating that heterotopic activation can coexist with typical group performance. This highlights the necessity to assume that, for fMRI second level analysis, autistic samples have unequal variance, particularly when the task involves motor and perceptive associative regions. We therefore encourage an investigation of individual variability, including its measurement using distance computation between individual activations and their group mean activations, or using surface-based analysis.

CONCLUSION

Preliminary investigations of autistic topographic variability in task-related brain activation (Pierce, et al., 2001; Scherf, et al., 2010) reveal greater and more heterogeneous implication of the associative visual areas. Our study adds a new element to the interpretation of this variability: in the visual and motor-related domain, autistics display an increased functional variability in the regions where typical individuals also show enhanced topographical variability relative to other regions, raising the possibility that autism involves an enhancement and / or an alteration of typical plasticity mechanisms.

Acknowledgments

This work was supported by an operating grant from the Canadian Institutes of Health Research (CIHR, No. MOP-84243) to L. Mottron and a studentship from the CIHR to E.B. Barbeau. The authors want to thank the participants for their invaluable contribution to this project, Arnaud Boré for the images and Agnès Jacob for proof reading the article.

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Annexe V. Are autistic traits autistic?

Commentary

Are autistic traits autistic?

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Abstract

According to the extreme male brain theory of autism (Baron-Cohen, 2002), autistic traits would be extreme manifestations of typical male behaviours. The Auyeung *et al*. (2008) paper establishes a link between autistic traits and higher foetal testosterone (fT) levels in typically developing children. We argue that the construct behind this relationship needs further investigation. First, the link between fT levels and sexually dimorphic traits, that are for example, associated to empathizing and systemizing, is controversial. Likewise, describing autistic behaviours as being extreme male-like is debatable. The laterality pattern of autistics also seems to differ from the pattern typically observed in males. Moreover, the parallel that should exist, according to the fT theory, between autistics and individuals with Congenital Adrenal Hyperplasia (CAH), because of their high fT levels, is unclear. The theory implying fT levels in autism fails to account for a big part of autism, and the link between fT and normal "autistic traits" hardly demonstrate the causal link between fT and autism.

Auyeung and colleague's (2008) paper is in line with the theory of Baron-Cohen's group suggesting that autism represents an extreme form of the typical male brain (EMB theory: Baron-Cohen, 2002). According to this theory, autistic traits, described as extreme male traits, are related to prenatal exposure to high testosterone levels. To date, this relationship has been deduced mainly from the findings that autistics have a lower 2nd to 4th finger length ratio (2D:4D) (Manning, Baron-Cohen, Wheelwright, & Sanders, 2001). The 2D:4D ratio has been shown to be sexually dimorphic with males having a lower 2D:4D ratio than women (Lutchmaya, Baron-Cohen, Raggatt, Knickmeyer, & Manning, 2004). It has been argued that low 2D:4D ratios are associated with high levels of prenatal testosterone and low levels of estrogen, whereas high 2D:4D ratios are associated with low levels of testosterone and high levels of estrogen *in utero* (Manning, Scutt, Wilson, & Lewis-Jones, 1998; Manning, 2001).

In order to test the link between foetal testosterone (fT) levels and autistic traits with a more direct measure than the digit ratio, Auyeung and colleagues have studied 235 typical children for which they had a sample of amniotic fluid (amniocentesis performed for clinical reasons like older maternal age or other risk factors). When the children reached 6-10 years of age, a questionnaire was then sent to the parents to evaluate their number and severity of autistic traits, which then in turn were correlated with the levels of fT to which they were exposed *in utero*.

Testosterone and normal sexually dimorphic behaviours

Gonadal sex steroid hormones, such as testosterone have a potent influence on human behaviour and are responsible for certain sexually dimorphic traits. According to Baron-Cohen's Empathizing-Systemizing (E-S) theory (Baron-Cohen, 2002; Baron-Cohen, Richler, Bisarya, Gurunathan, & Wheelwright, 2003), males and females in the general population are differentially distributed on the Systemizing Quotient (SQ) and Empathizing Quotient (EQ), with men being more skewed toward high SQ and low EQ scores and women having a higher EQ and a lower SQ. Developmental precursors of empathy in children include language development and social interests, indexed by eye contact and attention to faces. The precursors of systemizing involve attention to details and narrow interests (Auyeung *et al*., 2008). Specifically, men are better at mental rotation, disembedding and targeting (e.g. Falter,

Arroyo, & Davis, 2006). However, the link between testosterone and the performance on those tasks remains unclear. For example, two recent studies (Falter *et al*., 2006; Hooven, Chabris, Ellison, & Kosslyn, 2004) argue that superior performance of men compared to women on the mental rotation tasks is unrelated to prenatal testosterone. Hines (2006) has found that prenatal levels of testosterone did not have an effect on mathematical or visuospatial abilities, but influenced play behavior. Hines and colleagues (2003) suggest that what could have an influence on mental rotation abilities are the levels of postnatal testosterone. The role of other steroid hormones, as well as psychosocial factors, such as socialization into appropriate gender roles, and type of education, cannot be excluded. For example, the Baron-Cohen group showed that the SQ and EQ depend not only on gender but also on the type of college degree (Wheelwright *et al*., 2006). The EQ and SQ actually differed to the same extent according to university degree (sciences or humanities) as according to gender (male or female). Therefore, being a good systemizer is not only an effect of gender/testosterone but also an effect of degree/interests/expertise. Another study (Wang *et al*., 2003) compared expression and awareness of ethnocultural empathic feelings in a white and a non-white population and found that the difference between whites and non-whites was of the same order than the difference between men and women (in fact, it was bigger on two of the empathy measures). It is also important to note that, even though there appear to exist a negative correlation between the EQ and the SQ, it is rather weak, implying only partly overlapping, but mostly independent underlying mechanisms, which are not mutually exclusive (Wheelwright *et al*., 2006).

The EMB theory of autism

The E-S theory extends into Baron-Cohen's EMB autism theory according to which, autistics should be better at tasks on which men excel and would have more difficulties on tasks on which women are better because, among other factors, of their exposure to higher fT levels.

There are, however, contradictory results regarding some aspects of the theory. For example, Falter, Plaisted, & Davis (2008) studied in autistics, the relationship between fT levels and performance on tasks associated with systemizing (at which men are usually better than women), including mental rotation, targeting and figure disembedding. As expected,

autistics performed better than typically developing males on the mental rotation task. However, their superior performance was due to an advantage on the *non-rotational* aspects (speed of mental comparison of objects, decision making) of the task, while men were better than women at the *rotational* aspect of the task (the speed of rotation itself). Therefore, at least in this case, it would be faulty to infer that the autistics' performance was an extreme version of the typical male performance. Falter *et al*. (2008) concluded that the performance of autistics at mental rotation wasn't correlated with 2D:4D ratios.

Although Baron-Cohen's research group is focused on trying to relate autism to exaggerated male behaviours, there is growing evidence that autistics would also perform well on more feminine tasks. For example, a recent review from Gernsbacher, Stevenson, Khandakar, & Goldsmith (2008) concluded that "every empirical study to date has shown that autistic individuals across a wide range of age are capable of understanding the intentions of other people's actions". Autistics actually outperform typically developing individuals at the Meltzoff intentionality tasks (see also Aldridge, Stone, Sweeney, & Bower, 2000). A different review (Jemel, Mottron, & Dawson, 2006) of facial emotion recognition in autism, which has been thought to be deficient and which is typically superior in women, failed to support that deficit. The only face processing atypicality in autism would be a bias towards local features but not to the detriment of facial or emotional recognition. A study by Walenski, Mostofsky, Gidley-Larson, & Ullman (2007) showed that lexical knowledge was also spared in autism: the performances of autistics were more similar to girls' performances than boys'. All these studies suggest that autism can be characterized by good performances on some tasks at which women are typically better than men, and which are not associated with higher testosterone levels.

At the neurobiological level, it is thought that higher levels of fT would enhance the growth of the right hemisphere and inhibit the growth of certain regions of the left hemisphere, explaining the laterality dimorphism that exists between normally developing males and females (Manning, 2001). This could account for better spatial abilities in men and better language skills in women. Traditionally, the right hemisphere has been associated with the processing of more global, holistic aspects of a stimulus, whereas the left hemisphere has been implicated in the more local, finer detail processing (Cahill & van Stegeren, 2003). If

more testosterone tends to favour the development of the right hemisphere, according to the EMB theory, autistics should be better at processing the features more globally. However, autistics show a bias towards local features rather than global aspects (Mottron *et al*., 2006).

Another point that remains to be clarified is why would the testosterone levels affect cognitive function but not have any effect on physical traits that we know depend to a great extent on hormonal levels? Also, why are autistics not better at manual tasks and sports like men in the general population are? Finally, in the Auyeung *et al*., paper, no correlation was found between fT levels and IQ or the Block Design sub-test scores; how to explain that there is no effect on one of the most solid candidates for the autistic endophenotype indexed by the Block Design peak (Caron *et al*., 2006)?

The AQ to test autistic traits and its link to testosterone

The questionnaires used by Auyeung and colleagues to assess the construct of "autistic traits'' were the Child Autism Spectrum Quotient (AQ-Child) and the Childhood Autism Spectrum Test (CAST), reported to measure the number and severity of autistic traits in a non-autistic population. The data presented by the authors indicate a statistically significant link between fT and the AQ-Child and CAST in males, which is only minimal in females (i.e., for girls only, there was no relationship found between fT and CAST scores, and only a weak relationship between the fT and the AQ-Child; this could have been due to a much more restricted range of fT values for females, nevertheless it is possible that some other mechanisms/hormones play a role here. This could also indicate that this is actually an effect of sex rather than testosterone, or that the underlying mechanism is not the same for autistic girls and boys). Lastly, according to the EMB theory, autistics score on the AQ more like males than females because their overall behaviour and characteristics are more male-like. If traits that are to be correlated to testosterone levels are already male traits, it is to be expected that a correlation between these traits and testosterone will be found. That would also explain why the correlation is very weak in girls.

The argument implicating fT in autism could be strengthened by investigating a few additional elements. First, it would be justified to measure if fT correlates with behavioural traits beyond those that are pre-determined in the AQ. Accordingly, there might be traits

correlated with testosterone because they are male traits (or not) but have nothing to do with autism. Second, it would be informative to investigate correlations with other sex steroid hormones than testosterone, as autism could be characterized by wider hormonal atypicalities. It would even be interesting to see if the scores at the AQ correlate with other physiological aspects that are already known to be part of autism, like brain size or regional grey and white matter properties.

Individuals with Congenital Adrenal Hyperplasia (CAH) represent a good target population to test the high testosterone hypothesis of autism because CAH is a genetic condition characterized by high levels of intrauterine testosterone. It is argued that the high testosterone levels in those individuals make them score higher on the AQ test. However, they score higher only on the subscales measuring social skills and imagination, whereas autistics score high on all the subtests. Also, even if CAH women score higher than normal men in those subtests, their scores are still much lower than the average scores of autistics. If it was indeed primarily testosterone that induced these high scores, then one would expect individuals with CAH to score much higher than individuals with autism as the levels of fT are much higher in CAH than those reported in autism. Also, women with CAH score lower than unaffected women on the attention to detail subscale, which is usually higher in autistics than in non-autistics (and not higher in men than in women) (Knickmeyer *et al*., 2006). Therefore, CAH women seem to tend more towards a male pattern (which is consistent with the fact that they have more testosterone) than an autistic pattern at the AQ (which is not consistent with the hypothesis that higher testosterone levels cause an autistic behaviour). It is also known that both boys and girls with CAH have smaller amygdalae volumes but the brain morphometry of girls with CAH did not otherwise significantly differ from controls (Giedd *et al*., 2006). Autistics however, are known to differ significantly from non-autistics in terms of brain morphometry and functions, one of those differences, as Auyeung *et al*. mention, being an enlarged amygdala in autistics (Hazlett *et al*., 2005; Amaral *et al*., 2008).

Conclusion: Are autistic traits autistic?

We would argue the main limitation of the Auyeung *et al.* study is that what is actually measured, are male traits in a normal population rather than a correlation between testosterone and autism. The measured traits cannot be labelled *autistic* since the children are not autistics, they are typical traits found in typical individuals at different levels, together with all the normal behavioural traits. Finding a correlation between those traits and testosterone in the normal population does not imply that their presence in autism results from the same causal pathways. Provocatively, we would conclude that the main result of this study is to demonstrate that the AQ is unable to differentiate cognitive and behavioural gender differences, from the signs that actually describe autism, two unrelated and dissimilar series of features. The autistic brain functions differently, sometimes more like men, sometimes more like women, but we should consider that it might actually function in its own unique way.

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