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Bases cérébrales de la perception auditive simple et complexe dans l'autisme

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Bases cérébrales de la perception auditive simple et complexe dans l'autisme

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Résumé

La perception est décrite comme l'ensemble des processus permettant au cerveau de recueillir et de traiter l'information sensorielle. Un traitement perceptif atypique se retrouve souvent associé au phénotype autistique habituellement décrit en termes de déficits des habilités sociales et de communication ainsi que par des comportements stéréotypés et intérêts restreints. Les particularités perceptives des autistes se manifestent à différents niveaux de traitement de l'information; les autistes obtiennent des performances supérieures à celles des non autistes pour discriminer des stimuli simples, comme des sons purs, ou encore pour des tâches de plus haut niveau comme la détection de formes enchevêtrées dans une figure complexe.

Spécifiquement pour le traitement perceptif de *bas niveau*, on rapporte une dissociation de performance en vision. En effet, les autistes obtiennent des performances supérieures pour discriminer les stimuli définis par la luminance et inférieures pour les stimuli définis par la texture en comparaison à des non autistes. Ce pattern dichotomique a mené à l'élaboration d'une hypothèse suggérant que l'étendue (ou complexité) du réseau de régions corticales impliquées dans le traitement des stimuli pourrait sous-tendre ces différences comportementales. En effet, les autistes obtiennent des performances supérieures pour traiter les stimuli visuels entièrement décodés au niveau d'une seule région corticale (simples) et inférieures pour les stimuli dont l'analyse requiert l'implication de plusieurs régions corticales (complexes).

Un traitement perceptif atypique représente une caractéristique générale associée au phénotype autistique, avec de particularités rapportées tant dans la modalité visuelle qu'auditive. Étant donné les parallèles entre ces deux modalités sensorielles, cette thèse vise à vérifier si l'hypothèse proposée pour expliquer certaines particularités du traitement de l'information visuelle peut possiblement aussi caractériser le traitement de l'information auditive dans l'autisme.

Le premier article (Chapitre 2) expose le niveau de performance des autistes, parfois supérieur, parfois inférieur à celui des non autistes lors du traitement de l'information auditive et suggère que la complexité du matériel auditif à traiter pourrait être en lien avec certaines des différences observées.

Le deuxième article (Chapitre 3) présente une méta-analyse quantitative investiguant la représentation au niveau cortical de la complexité acoustique chez les non autistes. Ce travail confirme l'organisation fonctionnelle hiérarchique du cortex auditif et permet d'identifier, comme en vision, des stimuli auditifs pouvant être définis comme simples et complexes selon l'étendue du réseau de régions corticales requises pour les traiter.

Le troisième article (Chapitre 4) vérifie l'extension des prédictions de l'hypothèse proposée en vision au traitement de l'information auditive. Spécifiquement, ce projet compare les activations cérébrales sous-tendant le traitement des sons simples et complexes chez des autistes et des non autistes. Tel qu'attendu, les autistes montrent un patron d'activité atypique en réponse aux stimuli complexes, c'est-à-dire ceux dont le traitement nécessitent l'implication de plusieurs régions corticales.

En bref, l'ensemble des résultats suggèrent que les prédictions de l'hypothèse formulée en vision peuvent aussi s'appliquer en audition et possiblement expliquer certaines particularités du traitement de l'information auditive dans l'autisme. Ce travail met en lumière des différences fondamentales du traitement perceptif contribuant à une meilleure compréhension des mécanismes d'acquisition de l'information dans cette population.

Mots-clés : Audition, Complexité, Autisme, Imagerie par Résonance Magnétique fonctionnelle (IRMf)

Abstract

Perception involves the processes allowing the brain to extract and understand sensory information. Atypical perceptual processing has been associated with the autistic phenotype usually described in terms of impairments in social and communication abilities, as well as restricted interests and repetitive behaviours. Perceptual atypicalities are reported across a range of tasks. For instance, superior performance in autistics compared to non autistics is observed for pure tone discrimination as well as for complex figure disembodying tasks.

One particular study reported atypical low-level visual processing in autism. In this experiment, autistics displayed enhanced performance for identifying the orientation of luminance-defined gratings and inferior performance for texture-defined gratings in comparison to non autistics. This dichotomous pattern led to the formulation of a hypothesis suggesting an inverse relation between the level of performance and the extent (or complexity) of the cortical network required for processing the stimuli. Specifically, autistics would perform better than non autistics during processing visual stimuli involving one cortical region (luminance-defined or simple stimuli), while they would show decreased performance for processing stimuli involving a network of cortical region (texture-defined or complex stimuli).

Atypical perceptual processing is described as a general feature associated with the autistic phenotype and is reported for both the visual and the auditory modalities. Considering the existing parallels between the two sensory modalities, the principal purpose of the presented doctoral dissertation it to verify whether the hypothesis proposed to explain atypical visual processing in autism could also apply to audition.

The first article (Chapter 2) is an exhaustive literature review of studies on autistics' auditory processing abilities. Taken together, the results suggest that the level of performance of autistics on auditory tasks could be related to the acoustic complexity of the stimuli.

The second article (Chapter 3) uses quantitative meta-analysis to investigate how auditory complexity is represented at the cortical level in non autistics. This study confirms the hierarchical functional organization of the auditory cortex and allows defining simple and complex auditory stimuli based on the extent of the cortical network involved in their processing, as it was done in vision.

The third article (Chapter 4) verifies if the predictions of the hypothesis proposed in vision could also apply in audition. Specifically, this study examines the cortical auditory response to simple and complex sounds in autistics and non autistics. As expected, autistics display atypical cortical activity in response to complex auditory material that is stimuli involving a network of multiple cortical regions to be processed.

In sum, the studies in this dissertation indicate that the predictions of the hypothesis proposed in vision could extend to audition and possibly explain some of the atypical behaviours related to auditory processing in autism. This thesis demonstrates fundamentally different auditory cortical processing in autistics that could help define a general model of perceptual differences in autism which could represent a key factor in the understanding of information acquisition.

Keywords : Auditory, Complexity, Autism, functional Magnetic Resonance Imaging (fMRI)

Table des matières

Liste des tableaux

Chapitre 3

Chapitre 4

Liste des figures

Chapitre 1

Chapitre 3

Chapitre 4

Chapitre 5

Liste des sigles et abréviations

ADI-R: Autism Diagnostic Interview – Revised

ADOS: Autistic Diagnostic Observation Schedule

ALE: Activation Likelihood Estimation

ASP: Asperger

AUT: Autiste

BOLD: Blood Oxygen Level Dependant

EPF: Enhanced Perceptual Functioning

FDR: False Discovery Rate

FM: Frequency modulated

FWE: Family Wise Error

HG: Heschl’s gyrus

IFG: Inferior frontal gyrus

IRMf: Imagerie par Résonance Magnétique fonctionnelle

PAC: Primary Auditory Cortex

PP: Planum Polare

PT: Planum Temporale

STG: Superior Temporal Gyrus

STS : Superior Temporal Sulcus

TYP : Individu à développement typique (Non autiste)

À mes parents.

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Introduction

La perception, c'est-à-dire l'ensemble des processus par lesquels le cerveau recueille et analyse l'information sensorielle, est un élément systématiquement identifié comme étant atypique chez les autistes[1]. En situation écologique, ces différences sont rapportées sous la forme d'hypo ou d'hyper sensibilité à certains stimuli, par exemple, un intérêt accru pour les parties d'objets ou encore des réactions aversives au bruit de l'aspirateur ou d'une sirène d'alarme. Ces comportements pourraient possiblement être compris comme des conséquences d'un traitement cortical atypique de l'information dans l'autisme (Belmonte, Cook, et al., 2004). Spécifiquement, une récente hypothèse suggère que certaines particularités du traitement de l'information visuelle dans cette population pourraient être expliquées en regard de l'étendue du réseau cortical impliqué (Bertone, Mottron, Jelenic, & Faubert, 2005); les autistes traitant plus difficilement que les non autistes les stimuli visuels dont l'analyse requiert plus d'une région corticale fonctionnelle. Considérant que les particularités perceptives des autistes sont rapportées tant pour la modalité visuelle qu'auditive, il est possible qu'une hypothèse originalement proposée pour expliquer certaines particularités du traitement visuel puisse aussi s'appliquer au traitement de l'information auditive dans cette population.

Le présent travail explore d'abord les données de la littérature rapportant des particularités du traitement de l'information auditive dans l'autisme (Chapitre 2). Ensuite, un résumé quantitatif de la littérature investigue l'organisation fonctionnelle du cortex auditif chez les non autistes afin de vérifier si un parallèle peut être tracé entre les modalités visuelle et auditive (Chapitre 3). Enfin, ceci permet de directement vérifier la généralisation de l'hypothèse proposée en vision à la modalité auditive dans l'autisme (Chapitre 4). Les résultats seront discutés en lien avec les données de la littérature portant sur les particularités du traitement de l'information auditive dans l'autisme ainsi que les modèles pertinents.

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[1] L'utilisation du terme « autistes » (en anglais, « autistics ») plutôt que « personnes avec autisme » tout au long de cette thèse est faite dans un esprit respectueux (Sinclair, 1999).

Chapitre 1. Contexte théorique

1.1 La perception

1.1.1 Perception et niveaux de traitement

La cognition inclut l'ensemble de processus mentaux servant à acquérir, transformer, emmagasiner et utiliser l'information. Cet ensemble contient divers processus comme la perception, le raisonnement, la mémoire et la prise de décision. La cognition représente donc l'éventail de processus s'intercalant entre un stimulus et la réponse y étant associée; la perception comprend un sous-ensemble de ces processus, soit les étapes entre la détection et la représentation mentale d'un stimulus.

La perception définit l'ensemble des processus par lesquels le cerveau recueille, analyse et interprète les informations sensorielles. La perception est donc à la base des processus cognitifs plus complexes. Percevoir ne se limite par contre pas à la simple réception de l'information sensorielle. Les mécanismes perceptifs décrivent plutôt les interactions entre la réception et l'organisation des informations, en lien avec les connaissances, attentes et expériences préalables. Ainsi, percevoir est un acte complexe impliquant divers niveaux de traitement, soit les processus de *bas niveau* (« low-level »), de *niveau intermédiaire* (« mid-level ») et de *haut niveau* (« high-level »). Cette nomenclature sera utilisée au long de cette thèse. Le traitement de *bas niveau* regroupe les processus liés à l'analyse de caractéristiques psychophysiques de base comme l'orientation, le contraste ou la fréquence. Les processus de *niveau intermédiaire* concernent l'assemblage et l'organisation des caractéristiques de base, la perception de l'objet ainsi que sa ségrégation par rapport à l'arrière-plan. Enfin, le traitement de *haut niveau* comprend les processus d'identification, de catégorisation et de reconnaissance de l'input sensoriel. Il est important de noter que cette division des niveaux de traitement perceptif devrait être considérée comme une classification globale des différentes étapes de traitement de l'information plutôt qu'une catégorisation stricte des processus perceptifs. En effet, de plus en plus d'études démontrent une distribution non linéaire du traitement de l'information à travers les systèmes sensoriels ainsi que de la présence de nombreuses connexions complexes entre les différents niveaux de traitement.

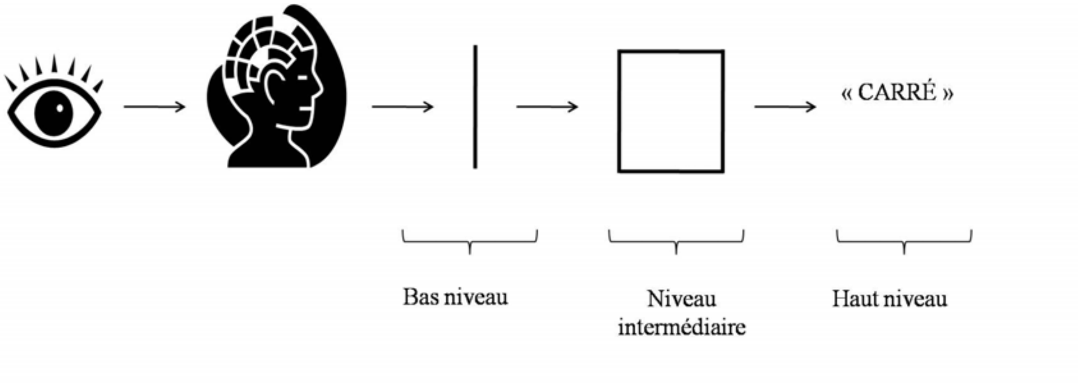


Figure 1. Schématisation des niveaux de traitement au sein de la perception

1.1.2 Niveaux de traitement et organisation corticale

Les niveaux de traitement perceptif se reflètent dans les niveaux de traitement cortical de l'information. Chaque système débute à partir des régions corticales recevant l'input sensoriel et progresse le long de voies directes et indirectes jusqu'aux régions dites associatives et spécialisées. Donc, un système de traitement cortical représente un ensemble de plusieurs étapes successives au sein desquelles l'input sensoriel est décodé, analysé et interprété (Bartels & Zeki, 1998). Précisons encore une fois que cette organisation linéaire représente une simplification de la réalité et qu'il existe de multiples connections et voies efférentes servant à moduler le traitement de l'information en amont. Par exemple, plusieurs études démontrent une modulation de l'activité des régions corticales sensorielles (Ahveninen et al., 2006; Crist, Li, & Gilbert, 2001; Fritz, Elhilali, & Shamma, 2005; Fritz, Shamma, Elhilali, & Klein, 2003) ou des régions sous corticales (O'Connor, Fukui, Pinsk, & Kastner, 2002) selon les demandes de la tâche à effectuer et les modulations attentionnelles. De manière similaire, d'autres travaux rapportent une modulation de l'organisation fonctionnelle des régions corticales primaires via des processus de haut niveau liés à l'apprentissage (Karni & Sagi, 1991; Polley, Steinberg, & Merzenich, 2006). Il est donc important de mentionner que, bien que reflétant une conception générale adéquate, l'organisation linéaire hiérarchique présentée ici représente une vue simplifiée de la réalité.

D'abord, au niveau périphérique, les stimuli parvenant aux différents organes sensoriels sont transformés en signaux électriques ensuite véhiculés par les nerfs sensoriels. Les influx nerveux sont acheminés au cortex sensoriel primaire via des relais sous-corticaux, principalement le thalamus (excepté pour l'information olfactive qui ne transige pas par cette région et rejoint plutôt directement le cortex olfactif primaire (Haberly & Price, 1977; Scott, McBride, & Schneider, 1980)). Le cortex primaire est une région fonctionnelle constituée de neurones sensibles aux propriétés psychophysiques élémentaires des stimuli sensoriels qui ont des champs récepteurs restreints et spécifiques. Par exemple, les neurones au sein de l'aire visuelle primaire répondent de manière préférentielle à une orientation ou encore à une position particulière dans le champ visuel (Bauer, Dow, & Vautin, 1980; Hubel & Wiesel, 1963) tandis que les cellules de l'aire auditive primaire répondent, entre autres, à des fréquences sonores spécifiques (Merzenich & Brugge, 1973; Morel, Garraghty, & Kaas, 1993). De plus, les régions primaires visuelle et auditive présentent toutes deux une organisation topographique, signifiant qu'on y retrouve une cartographie similaire à celle des organes périphériques, respectivement la rétine de l'œil (rétinotopie) (Wandell, Dumoulin, & Brewer, 2007) et la membrane basilaire de la cochlée (tonotopie) (Talavage, Ledden, Benson, Rosen, & Melcher, 2000; Woods et al., 2009). Il est cependant important de noter qu'une partie du traitement de l'information est aussi faite au niveau sous-cortical; en audition par exemple, l'information en provenance des deux oreilles est intégrée au niveau des noyaux de l'olive supérieure dans le tronc cérébral (Heffner & Heffner, 1989). Au-delà des aires primaires, l'information progresse vers les régions sensorielles dites secondaires ou non primaires. À ce niveau, l'assemblage des propriétés élémentaires des stimuli permet l'extraction de propriétés plus globales. En effet, les neurones de ces régions ont des champs récepteurs plus grands que ceux des neurones des régions primaires, ce qui leur confère une fonction d'intégration des attributs préalablement décodés. Par exemple, les neurones des régions auditives non primaires latérales répondent fortement aux sons incluant un éventail de fréquences comme les vocalisations (Tian, Reser, Durham, Kustov, & Rauschecker, 2001), tandis qu'au niveau du cortex visuel, les neurones des régions non primaires intègrent les composantes élémentaires liés à la position, à l'orientation et au contraste afin de définir le contour, les patterns, le mouvement et les formes (Van Essen, 2003). Aussi, bien que toujours présente, la représentation topographique de l'information au niveau des régions non primaires est moins bien définie et incomplète (Hall, Hart, & Johnsrude, 2003; Van Essen, 2003). Ensuite, au sein des étapes de traitement perceptif, on trouve aussi diverses régions dites « spécialisées » répondant de manière préférentielle à un type d'information de plus haut niveau comme, par exemple, l'activité du gyrus fusiforme associée au traitement des visages (Kanwisher, McDermott, & Chun, 1997) ou encore la réponse du sulcus temporal supérieur à l'écoute de stimuli vocaux (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000). Enfin, au-delà des régions plus strictement définies comme étant perceptives, le traitement cortical de l'information progresse vers des régions associatives qui permettent la conjugaison des informations sensorielles et des représentations mémorisées, ainsi que des connaissances. On retrouve donc des connections entre les régions dites perceptives et les régions corticales sous-tendant des fonctions de plus haut niveau, par exemple le cortex frontal, pariétal ou encore certaines régions du système limbique impliquées dans le traitement des émotions (amygdale) et les fonctions mnésiques (hippocampe). D'ailleurs, certaines de ces régions sont maintenant définies comme faisant partie des systèmes de traitement de l'information visuelle (Felleman & Van Essen, 1991) et auditive (Peelle, Johnsrude, & Davis, 2010). Au niveau cortical, la progression du traitement de l'information des régions primaires jusqu'aux régions associatives semble donc grossièrement correspondre aux étapes de traitement perceptif à partir du bas niveau jusqu'au haut niveau, en passant par le niveau intermédiaire.

À mesure que le traitement de l'information progresse, les réponses neuronales deviennent plus spécialisées, par opposition aux premières étapes de traitement pouvant être considérées comme majoritairement associées à l'analyse des aspects plus fondamentaux des stimuli sensoriels (Bartels & Zeki, 1998). L'organisation fonctionnelle du traitement cortical de l'information peut donc être définie comme étant *hiérarchique*. Au niveau cortical, ce traitement hiérarchique est représenté par l'augmentation de la sensibilité de la réponse associée aux propriétés complexes des stimuli des aires sensorielles primaires vers les régions non primaires et associatives; le traitement des stimuli les plus simples n'impliquant que les régions sensorielles primaires (Moutoussis & Zeki, 1997; Rauschecker & Scott, 2009; Wessinger et al., 2001). Bien que la hiérarchie représente une caractéristique fondamentale du traitement cortical de l'information, l'organisation des différents niveaux de traitement ne doit pas être considérée comme étant strictement séquentielle. L'analyse de l'information sensorielle implique plutôt à la fois des connections directes (« feedforward ») ainsi que des connections de rétroaction (« feedback ») entre les différentes régions fonctionnelles (Felleman & Van Essen, 1991;

Gueguin, Le Bouquin-Jeannes, Faucon, Chauvel, & Liegeois-Chauvel, 2007). Via ces interactions, les niveaux « inférieurs » influencent les niveaux de traitement « supérieurs » et vice-versa. Les connections de rétroaction servent principalement à mettre en évidence, à contrôler et à préciser les informations analysées en amont alimentant ensuite les processus perceptifs en aval, de plus haut niveau.

En plus des interactions entre les différents niveaux de traitement, on trouve aussi des interactions directes et de rétroaction au sein de chacun de ces niveaux. Entre les neurones, des connections excitatrices et inhibitrices permettent de préciser et d'amplifier le signal qui sera acheminé aux étapes de traitement subséquentes. Par exemple, il existe des connections latérales entre les cellules permettant d'augmenter le contraste et la définition des composantes élémentaires des stimuli. Spécifiquement, les connections d'un neurone excité vers ses plus proches voisins et vers lui-même sont principalement excitatrices tandis que les connections latérales vers les voisins plus éloignés sont plutôt inhibitrices, processus que l'on appelle inhibition latérale. Ce type de connections a été décrit tant au niveau de la modalité visuelle (Ratliff, Miller, & Hartline, 1959) qu'auditive (Houtgast, 1972). De par ces connexions, il est possible d'amplifier le signal des neurones répondant préférentiellement aux caractéristiques du stimulus présenté en inhibant l'activité des neurones adjacents. Par exemple, la réponse sélective des colonnes de neurones du cortex visuel primaire à l'orientation des stimuli est largement dépendante des connections inhibitrices latérales entre les colonnes (Andrews, 1965). Une organisation en colonnes est aussi retrouvée au sein du cortex auditif primaire (Abeles & Goldstein, 1970) et l'inhibition latérale semble être un mécanisme précisant la réponse neuronale dans cette région (Oswald, Schiff, & Reyes, 2006). Il est donc possible de considérer que l'inhibition latérale pourrait permette de préciser la réponse associée à une caractéristique spécifique à ce niveau, par exemple une fréquence sonore donnée, tout en éliminant la réponse des cellules voisines ayant une réponse préférentielle à des caractéristiques similaires, soit des fréquences un peu plus aigües et un peu plus graves.

1.1.3 Hiérarchie et complexité

L'organisation fonctionnelle hiérarchique au niveau cortical représente une caractéristique importante à la base de la compréhension du traitement perceptif. Dans une hiérarchie, l'information est analysée via une succession d'étapes de plus en plus complexes permettant ultimement d'obtenir un percept unique. Autrement dit, les composantes élémentaires, ou simples, d'un stimulus sont d'abord décodées et ensuite conjuguées afin d'en obtenir une représentation complète. La notion de hiérarchie implique la notion de *complexité*, qu'il devient nécessaire de définir.

D'abord, la complexité peut être définie selon les propriétés physiques des stimuli sensoriels à traiter. Une onde sonore est principalement décrite selon sa fréquence, son amplitude et sa durée (Moore, 2003). Au niveau le plus simple, on retrouve les sons constitués d'une seule onde sonore de fréquence et d'amplitude fixe, appelés sons purs. À partir d'un son pur, il est possible d'augmenter la complexité acoustique du son, soit en y ajoutant des composantes fréquentielles ou soit en faisant varier ses composantes dans le temps. D'une part, en ajoutant des composantes au son, c'est-à-dire en combinant des ondes de différentes fréquences, on augmente la complexité au niveau *spectral* (ex. son harmonique). D'autre part, lorsque les composantes du son varient dans le temps, on augmente la complexité au niveau *temporel* (ex. son modulé par la fréquence). En effet, il n'est pas possible de proposer une classification des stimuli auditifs selon un axe unique de complexité, du plus simple au plus complexe. De par leur composition, deux types de stimuli auditifs peuvent être considérés comme étant complexes, mais il devient difficile de les comparer, d'établir un ordre unidimensionnel au sein de différents stimuli complexes. Globalement, les sons dont les composantes physiques sont multiples et variables dans le temps sont donc considérés comme complexes par rapport à des sons purs. De manière similaire, les variables physiques à la base d'un stimulus visuel comme la luminance, l'orientation et la fréquence spatiale peuvent être considérées comme des composantes simples, tandis que l'agglomération de ces variables lors de la perception d'objets, de formes et de patterns représente un niveau de complexité physique plus élevé.

D'un autre point de vue, la complexité peut être définie selon l'étendue du réseau cortical requis pour analyser un type d'information donné, le cortex étant divisé en régions fonctionnelles distinctes. La division du cortex en une quarantaine de régions a d'abord été établie par Brodmann (1909) selon l'étude de la distribution anatomique des neurones dans les différentes couches corticales (organisation cytoarchitecturale). Cette classification anatomique, en combinaison avec les techniques actuelles de neuroimagerie, a permis d'associer des tâches fonctionnelles aux différentes régions du cortex de manière assez précise.

L'organisation du cortex en régions fonctionnelles permet de conceptualiser la complexité des stimuli à traiter selon l'étendue du réseau de régions corticales requises. Ainsi, un stimulus ne requérant qu'une étape de traitement, au sein d'une région fonctionnelle restreinte, est considéré simple. Alternativement, un stimulus requérant l'implication d'un réseau cortical étendu, impliquant plusieurs étapes de traitement avant d'être entièrement décodé, est considéré comme complexe. À titre d'exemple, en vision, une telle dichotomie existe entre le traitement de stimuli définis par la luminance (attribut de premier ordre) et ceux définis par la texture (attribut de deuxième ordre). En effet, les mécanismes opérant au niveau de l'aire visuelle primaire (V1 ou aire de Brodmann 17) suffisent pour filtrer et analyser les attributs de premier ordre tandis que l'analyse des attributs de deuxième ordre requiert des opérations supplémentaires effectuées au niveau de régions visuelles non primaires (V2 et V3 ou aires de Brodmann 18 et 19) (Bertone & Faubert, 2003; Chubb & Sperling, 1988). En décrivant la complexité des stimuli selon la complexité du réseau cortical impliqué dans leur traitement, les stimuli définis par la luminance sont donc considérés comme simples et les stimuli définis par la texture, complexes.

Il est important de noter que les deux approches utilisées pour définir la notion de complexité ne sont pas mutuellement exclusives, par exemple, les sons purs, considérés comme simples de par leur composition acoustique, sont aussi définis comme simples en regard de la complexité de leur traitement cortical qui est entièrement complété au sein de l'aire auditive primaire (A1 ou aire de Brodmann 41) (Hall, et al., 2003). Cependant, on peut parfois définir des stimuli comme étant simples et complexes l'un par rapport à l'autre au niveau physique, sans que cette dissociation soit également retrouvée au niveau cortical. Par exemple, les phonèmes, éléments à la base des stimuli vocaux, sont considérés comme simples comparativement à des mots complets et des phrases. Toutefois, le traitement des phonèmes au niveau cortical ne se limite pas au niveau des aires auditives primaires et doit donc être considéré comme complexe, bien qu'impliquant un réseau cortical plus restreint que le traitement des mots et des phrases (Uppenkamp, Johnsrude, Norris, Marslen-Wilson, & Patterson, 2006). De plus, la dissociation simple/complexe au niveau cortical doit aussi être différenciée de la difficulté à traiter les stimuli. En effet, il est assez difficile de discriminer des stimuli visuels définis par la luminance, malgré la simplicité de leur traitement cortical (Bertone, et al., 2005).

1.2 Organisation anatomique et fonctionnelle du système auditif

Le système auditif inclut un ensemble de structures s'étendant de la périphérie (oreille externe, cochlée) au centre du système nerveux (tronc cérébral, thalamus et cortex). Au niveau périphérique, l'oreille capte les ondes sonores qui font vibrer la membrane tympanique. Cette vibration est ensuite véhiculée via les osselets (marteau, enclume et étrier) jusqu'à la fenêtre ovale de la cochlée rejoignant ainsi la membrane basilaire. À ce niveau, la vibration entraîne un déplacement de la membrane qui se traduit en une déformation mécanique des cellules ciliées lesquelles génèrent ensuite des potentiels d'action transmis au système nerveux central via le nerf auditif. On trouve au niveau de la membrane basilaire une organisation tonotopique qui est maintenue à travers les différents relais auditif et ce jusqu'au cortex auditif primaire; par contre, la spécificité de la réponse fréquentielle diminue à mesure que l'information progresse vers le cortex. Tout au long du système auditif ascendant, le nombre de fibres nerveuses augmente considérablement ce qui indique un certain décodage du signal acoustique à mesure qu'il voyage de la périphérie au cortex (Di Salle et al., 2003; Rauschecker, Tian, & Hauser, 1995; Winer & Lee, 2007).

Au niveau central, les connections du nerf auditif arrivent au noyau cochléaire qui reçoit les informations de l'oreille ipsilatérale. À partir du noyau cochléaire, les informations auditives sont transmises au complexe de l'olive supérieure ipsilatéral et controlatéral, ce qui confère à ce relais sous-cortical un rôle dans l'intégration inter-aurale et la localisation sonore (Heffner & Heffner, 1989). L'information auditive progresse ensuite le long du lemnisque latéral pour atteindre le collicule inférieur. Cette région sous-corticale est largement connectée, intègre l'information des autres noyaux sous-corticaux ainsi que de diverses régions corticales. Le collicule inférieur est impliqué dans de multiples fonctions comme la localisation sonore (Chase & Young, 2008), l'analyse des informations temporelles (Sinex & Chen, 2000), et même l'intégration multi-sensorielle (Champoux et al., 2006). Les projections du collicule inférieur atteignent le corps genouillé médian du thalamus bilatéralement qui est, entre autres, associé à l'attention auditive

(Christensen, Antonucci, Lockwood, Kittleson, & Plante, 2008; Hocherman & Yirmiya, 1990). Donc, les structures sous-corticales sont impliquées dans le traitement auditif simple et complexe et représentent des zones d'intégration de l'information auditive.

Ensuite, l'information auditive progresse vers les régions corticales et rejoint tout d'abord le cortex auditif primaire. Des études électrophysiologiques (Hackett, Preuss, & Kaas, 2001), cytoarchitectoniques (Morosan et al., 2001; Sweet, Dorph-Petersen, & Lewis, 2005) et d'imagerie fonctionnelle (Lockwood et al., 1999; Wessinger, et al., 2001) ont permis de localiser cette région au niveau de la partie médiane du gyrus de Heschl, correspondant à l'aire de Brodmann 41 (Brodmann, 1909). Les descriptions de l'organisation fonctionnelle du cortex auditif chez l'animal propose que les régions primaires (ou « core region ») seraient entourées par une ceinture (ou « belt ») incluant plusieurs champs non-primaires (Kaas & Hackett, 2000; Kaas, Hackett, & Tramo, 1999). Chez l'humain, la région correspondant à la ceinture inclut les régions supéro-temporale antérieure (planum polare) et postérieure (planum temporale) aux régions primaires (Hackett, et al., 2001; Sweet, et al., 2005). Une troisième région auditive est décrite au niveau de la portion latérale du gyrus temporal supérieur. Celle-ci semble coïncider à la région appelée « parabelt » chez l'animal (Kaas & Hackett, 2000) et correspondre à l'aire de Brodmann 22. Les régions auditives non primaires correspondant à la « belt » et la « parabelt » chez l'humain sont connectées entre elles, reçoivent des connections du cortex auditif primaire et projettent principalement vers les régions associatives temporales (sulcus temporal supérieur, lobe temporal inférieur), pariétales postérieures et frontales (gyrus frontal inférieur, cortex préfrontal) (Hackett, 2011; Rauschecker & Scott, 2009; Romanski, Bates, & Goldman-Rakic, 1999).

Au niveau fonctionnel, les régions auditives primaires sont impliquées dans le décodage des composantes acoustiques élémentaires, entre autres, la fréquence (Formisano et al., 2003; Humphries, Liebenthal, & Binder, 2010; Schonwiesner, von Cramon, & Rubsamen, 2002), l'intensité (Bilecen, Seifritz, Scheffler, Henning, & Schulte, 2002; Jancke, Shah, Posse, Grosse-Ryuken, & Muller-Gartner, 1998) et la localisation spatiale (Woods et al., 2010). Les études de neuroimagerie rapportent une activation des régions auditives non primaire à l'écoute de sons complexes comme le bruit (« broadband noise », Wessinger, et al., 2001), les sons spectralement complexes (Hall et al., 2002;

Schonwiesner, Rubsamen, & von Cramon, 2005), les séquences de sons (Hyde, Peretz, & Zatorre, 2008; Jamison, Watkins, Bishop, & Matthews, 2006; Zatorre & Belin, 2001) ou encore les modulations temporelles de fréquence (Hall, et al., 2002; Hart, Palmer, & Hall, 2003; Schonwiesner, et al., 2005; Thivard, Belin, Zilbovicius, Poline, & Samson, 2000) ou d'amplitude (Giraud et al., 2000; Hart, et al., 2003). Au-delà des régions strictement définies comme faisant partie du cortex auditif, on observe une activité sensible à des catégories auditives plus complexes. Par exemple, le traitement des indices phonétiques (Binder et al., 2000), de la parole (Davis & Johnsrude, 2003) et de la voix (Belin, et al., 2000) est associé à l'activation du sulcus temporal supérieur. Aussi, le gyrus inférieur frontal joue un rôle dans le traitement des stimuli langagiers (Joanisse & Gati, 2003; Zaehle, Geiser, Alter, Jancke, & Meyer, 2008) ainsi que pour le décodage de la syntaxe musicale (Koelsch et al., 2002; Maess, Koelsch, Gunter, & Friederici, 2001; Zatorre, Evans, & Meyer, 1994). La sensibilité accrue de la réponse auditive corticale des régions non-primaires et associatives aux aspects plus complexes et abstraits des stimuli est consistante avec la présence d'un traitement hiérarchique de l'information auditive au niveau cortical (Okada et al., 2010). L'organisation fonctionnelle du cortex auditif inclut aussi une spécialisation hémisphérique (Zatorre, Belin, & Penhune, 2002). En effet, le traitement des stimuli langagiers semble recruter de manière plus importante les régions auditives de l'hémisphère gauche (Alho et al., 1998; Belin & Zatorre, 2000; Szymanski et al., 2001) tandis que le traitement des stimuli musicaux est plutôt latéralisé au niveau de l'hémisphère droit (Griffiths, Johnsrude, Dean, & Green, 1999; Warrier & Zatorre, 2004). Considérant que le traitement adéquat de la parole repose principalement sur l'intégration des composantes temporelles (Shannon, Zeng, Kamath, Wygonski, & Ekelid, 1995) et celui de la musique sur la composition spectrale (Warrier & Zatorre, 2002), une asymétrie correspondante peut aussi être mise en lumière pour le traitement de ces caractéristiques acoustiques (temporel à gauche et spectral à droite; Jamison, et al., 2006; Okamoto, Stracke, Draganova, & Pantev, 2009; Okamoto, Stracke, Ross, Kakigi, & Pantev, 2007; Schonwiesner, et al., 2005; Zatorre & Belin, 2001).

Les descriptions récentes de l'organisation du système auditif mettent l'emphase sur la présence de multiples connections directes et de rétroactions à travers les différents relais de traitement de l'information auditive (Hackett, 2011). En effet, on décrit une organisation fonctionnelle interactive où l'activité des régions en amont est influencée par celle régions associées au traitement de plus haut niveau. Au niveau anatomique, l'existence de telles interactions est supportée par la présence de connections de rétroactions à travers le système auditif cortical et aussi entre les régions corticales et sous-corticales (De la Mothe, Blumell, Kajikawa, & Hackett, 2006; Hackett, Stepniewska, & Kaas, 1999; Kaas & Hackett, 2000; Rauschecker & Scott, 2009; Schofield, 2010; Winer & Lee, 2007). Au niveau fonctionnel, plusieurs études rapportent une modulation de l'activité des régions en amont via des connections efférentes provenant des régions en aval. Par exemple, on démontre une modulation de l'activité du relais auditif thalamique selon que l'attention soit dirigée vers les aspects acoustiques ou sémantiques de stimuli langagiers (von Kriegstein, Patterson, & Griffiths, 2008), une spécialisation de la réponse fonctionnelle des régions auditives non primaires suivant l'apprentissage d'une tâche requérant le traitement de caractéristiques acoustiques particulières (Polley, et al., 2006) ainsi qu'un effet associé aux demandes de la tâche ou aux modulations attentionnelles sur le niveau d'activité des régions corticales auditives primaires et non primaires (Fritz, et al., 2003; Fritz et al., 2005; Petkov et al., 2004; Rinne, Koistinen, Salonen, & Alho, 2009; Woods, et al., 2009).

En bref, le système auditif inclut un ensemble de structures sous-corticales et corticales à travers lesquelles l'information auditive est décodée et intégrée. Au niveau cortical, le traitement de l'information peut être caractérisé par une organisation hiérarchique ainsi qu'une spécialisation hémisphérique, et les projections du cortex auditif atteignent de multiples régions, principalement temporales, pariétales et frontales. Enfin, le système auditif est largement interconnecté et peut être adéquatement décrit comme un système interactif au sein duquel l'activité des différentes régions peut être modulée via des connections afférentes et efférentes selon le type de stimuli ou de tâche à réaliser.

1.3 La perception dans l'autisme

1.3.1 Définition de l'autisme

L'autisme est un trouble envahissant du développement caractérisé par des déficits au niveau des habiletés sociales et de communication verbale et non-verbale, ainsi que par des intérêts restreints et comportements stéréotypés (American Psychiatric Association, 2000). L'autisme est une des conditions décrites au sein des troubles du spectre autistique (« Autism Spectrum Disorders »), les autres étant le syndrome d'Asperger, caractérisé par une absence de retard au niveau cognitif et au niveau du développement de la parole, et le trouble envahissant du développement non spécifié, diagnostiqué lorsque la personne démontre des comportements atypiques, mais n'atteignant pas le seuil de critères diagnostiques pour l'autisme ou le syndrome d'Asperger. Les troubles envahissants du développement incluent donc les troubles du spectre autistique auxquels s'ajoutent le syndrome de Rett et le trouble désintégratif de l'enfance.

Par définition, les troubles envahissants du développement influencent le développement d'un individu, spécifiquement au niveau neurobiologique. Cependant, on ne connaît pas de marqueur biologique de l'autisme, le diagnostic reposant donc sur une évaluation des comportements (American Psychiatric Association, 2000). Au niveau social, les personnes autistes démontrent des difficultés à entrer en inter-relation, à faire un usage approprié des comportements non-verbaux comme le contact visuel ou l'expression faciale, à démontrer une réciprocité sociale et à partager leurs intérêts et émotions. Au niveau de la communication, les autistes montrent un retard ou, rarement, une absence de développement du langage oral et, chez la majorité qui développe la parole, on remarque un usage stéréotypé et répétitif du langage, ainsi qu'une difficulté à entamer et maintenir une communication. Enfin, certaines particularités comportementales comme des mouvements répétitifs, le besoin de respecter des routines et habitudes spécifiques, ainsi que le développement d'intérêts particuliers, intenses et restreints sont aussi caractéristiques des personnes portant un diagnostic d'autisme. On retrouve aussi dans l'autisme des pics d'habilités, c'est-à-dire des aptitudes de beaucoup supérieures au niveau de fonctionnement global d'un individu. Au niveau le plus extrême, certaines personnes autistes, appelées « savants », démontrent des forces exceptionnelles en musique, en calcul ou en dessin, en dépit d'un niveau intellectuel assez bas (Mottron, Dawson, & Soulieres, 2009).

À ce jour, on reconnaît l'origine génétique de ce trouble, les études rapportant un taux d'héritabilité allant jusqu'à 90%, signifiant que les facteurs génétiques jouent un rôle majeur dans l'apparition du phénotype (Folstein & Rosen-Sheidley, 2001; Monaco & Bailey, 2001). On estime à 60-70/10 000 la prévalence des troubles envahissants du développement et à 20/10 000 la prévalence de l'autisme, avec un ratio de 4.2 hommes pour 1 femme (Fombonne, 2009). Les études épidémiologiques rapportent des prévalences d'autisme de plus en plus élevées, ce qui a ouvert la porte à l'idée d'une épidémie. Bien qu'il soit possible que certains facteurs environnementaux contribuent à cette augmentation, les épidémiologistes attribuent plutôt cette hausse à la modification et à l'élargissement des critères diagnostiques, au développement et à la disponibilité de services, ainsi qu'à une plus grande connaissance des comportements autistiques tant chez les professionnels de la santé qu'au sein de la population générale (Fombonne, 2009).

On sait aussi maintenant que la majorité des personnes avec un trouble envahissant du développement présente un niveau d'intelligence normal. Les études épidémiologiques rapportent des taux variables de déficience intellectuelle, aux environs de 30% (Chakrabarti & Fombonne, 2005). Ces taux pourraient être revus à la baisse au cours des prochaines années, étant donné la mise en évidence de capacités intellectuelles plus élevées lorsque des outils d'évaluation intellectuelle plus adaptés au fonctionnement cognitif des personnes autistes sont utilisés. En effet, il a récemment été démontré que, lorsque mesurée en utilisant le test des Matrices de Raven (Raven, Raven, & Court, 1998), la capacité intellectuelle des autistes est de beaucoup supérieure à la mesure obtenue à l'aide des échelles de Wechsler (Wechsler, 1991, 1997), tandis que les non autistes obtiennent des performances comparables pour les deux tests (Dawson, Soulieres, Gernsbacher, & Mottron, 2007). Le test des Matrices de Raven est essentiellement non-verbal et consiste à trouver, à travers six ou huit alternatives, la forme complétant une matrice de formes géométriques dont une case est manquante. Ce test mesure la capacité de raisonnement et de résolution de problèmes et permet d'obtenir une mesure fiable de la capacité intellectuelle d'un individu (Mackintosh, 1998). Il a donc été suggéré que ce test, pour lequel toute l'information nécessaire à la résolution du problème est présentée simultanément et de façon non-verbale, puisse être mieux adapté pour révéler le véritable niveau intellectuel des autistes que les tests de Wechsler qui font appel à des habiletés verbales et de compréhension sociale. Ce fonctionnement cognitif atypique dans l'autisme semble aussi influencer les méthodes d'apprentissage dans cette population. Par exemple, l'apprentissage du langage se fait de manière atypique chez les autistes; que ce soit par l'utilisation de l'écholalie pour arriver à manier le langage oral ou encore par l'exposition libre à du matériel écrit complexe permettant de développer la capacité de lire (Dawson, Mottron, & Gernsbacher, 2008). En bref, l'autisme est une condition neurodéveloppementale se distinguant par un fonctionnement cognitif et social atypique, ainsi que par des domaines d'intérêts particuliers.

1.3.2 Traitement perceptif atypique

Parallèlement aux difficultés observées au niveau des habilités sociales et de communication, on associe maintenant fréquemment la présence d'un traitement perceptif atypique au phénotype autistique (Dakin & Frith, 2005). Les particularités perceptives des autistes ont été rapportées dès la première description de cette condition par Kanner (1943). En situation naturelle, les autistes réagissent de manière différente face à des stimulations sensorielles tant visuelles qu'auditives; par exemple, en regardant des objets du coin de l'œil (Mottron et al., 2007) ou à travers leurs doigts ou encore en démontrant des réactions négatives (ex., couverture des oreilles avec les mains) à l'écoute de certains sons, dont le bruit de l'aspirateur (Grandin & Scariano, 1986). De manière similaire, on rapporte la présence d'hyperacousie, ou hypersensibilité auditive, de manière plus fréquente dans cette population (Gomes, Rotta, Pedroso, Sleifer, & Danesi, 2004). Aussi, les enfants autistes sont souvent soupçonnés de surdité en bas âge vu leur manque de réaction à la voix, cette caractéristique faisant partie des signes utilisés pour établir le diagnostic (Lord, Rutter, & Le Couteur, 1994).

L'observation répétée de ces comportements au niveau clinique a motivé la réalisation de recherches empiriques visant à décrire et à comprendre les particularités perceptives des autistes. En 2004, Belmonte et ses collaborateurs ont suggéré que les particularités du traitement perceptif dans l'autisme pourraient représenter une caractéristique fondamentale du phénotype. En effet, il semble que ces particularités soient présentes chez des individus autistes montrant des niveaux variables de développement social et communicatif (Behrmann, Thomas, & Humphreys, 2006). Il a même été proposé que certaines des difficultés observées au niveau de l'expression sociale et émotionnelle puissent être associées à des processus perceptifs atypiques (Ben Shalom et al., 2006). De telles propositions justifient l'importance d'étudier le traitement perceptif et les mécanismes sous-jacents dans l'autisme.

Les particularités perceptives dans l'autisme sont observées à travers les différents niveaux de traitement et à travers les modalités visuelles et auditives. Pour le traitement de *bas niveau*, les autistes démontrent des performances supérieures à celles des non autistes; par exemple, pour discriminer et catégoriser des sons purs (Bonnel et al., 2010; Bonnel et al., 2003; Jones et al., 2009) ou encore pour discriminer l'orientation de stimuli visuels de premier ordre (Bertone et al., 2005). De plus, de multiples études mettent en lumière les corrélats neuro-fonctionnels d'un traitement de bas niveau atypique, que ce soit via des réponses électrophysiologiques de latence et d'amplitude différentes de celles des non autistes lors du traitement de sons simples (Gomot, Giard, Adrien, Barthelemy, & Bruneau, 2002; Lepisto et al., 2005) ou de fréquences spatiales visuelles (Boeschoten, Kenemans, van Engeland, & Kemner, 2007; Jemel, Mimeault, Saint-Amour, Hosein, & Mottron, 2010). Au niveau du traitement *intermédiaire*, on rapporte principalement des supériorités pour le traitement de l'information visuelle : pour trouver une cible visuelle parmi des distracteurs (Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009; M. A. O'Riordan, 2004), pour trouver une figure simple enchevêtrée dans une figure complexe (Jolliffe & Baron-Cohen, 1997; Shah & Frith, 1983) ou encore pour reproduire une figure complexe avec des petits blocs (Block Design Test, Caron, Mottron, Berthiaume, & Dawson, 2006; Shah & Frith, 1993). En audition, on peut considérer comme marque de traitement perceptif intermédiaire atypique les observations de la présence d'un biais local lors du traitement de stimuli musicaux; par exemple une supériorité par rapport à des non autistes pour détecter un changement dans un intervalle musical (Heaton, 2005) ou dans les notes composant un accord (Heaton, 2003) ainsi que pour détecter un changement local au sein d'une mélodie (Mottron, Peretz, & Menard, 2000). Enfin, pour le traitement de *haut niveau*, certaines études rapportent un traitement atypique des visages (Boucher, Lewis, & Collis, 1998; Joseph & Tanaka, 2003) ou encore des difficultés pour des tâches où il est demandé d'inférer l'état d'esprit d'une autre personne en observant son regard (Baron-Cohen, Leslie, & Frith, 1985). Cependant des performances similaires à celles des individus non autistes ont aussi été observées pour des tâches de reconnaissance de visages (Kleinhans et al., 2008; Uddin et al., 2008). Aussi, les autistes obtiennent un niveau de performance supérieur aux non autistes pour compléter le test visuo-perceptif des matrices de Raven (Soulières et al., 2009). Au niveau du traitement auditif, des réponses corticales atypiques sont observées principalement lors du traitement de stimuli langagiers (Gervais et al., 2004; Lepisto, et al., 2005; Lepisto et al., 2006; Whitehouse & Bishop, 2008).

Un autre aspect du traitement atypique de l'information dans l'autisme concerne la place que les processus perceptifs semblent occuper au sein de la cognition. En effet, certaines études suggèrent une augmentation du rôle de ces processus pour la réalisation de tâches impliquant, chez le sujet typique, des processus cognitifs plus complexes. Par exemple, au niveau auditif, de récentes études suggèrent que les personnes autistes utiliseraient plutôt les informations perceptives que les informations sémantiques lors du traitement de langage oral (Jarvinen-Pasley & Heaton, 2007; Jarvinen-Pasley, Wallace, Ramus, Happe, & Heaton, 2008). Aussi, lors de certaines tâches visuelles comme la recherche visuelle (Keehn, Brenner, Palmer, Lincoln, & Muller, 2008; Luna et al., 2002) ou encore le test de raisonnement des matrices de Raven (Soulières et al., 2009), des études de neuroimagerie rapportent une plus grande activité des régions associées au traitement de l'information visuo-perceptive chez les individus autistes comparativement aux individus non autistes.

Afin d'examiner la généralisation de ces résultats, une méthode de méta-analyse a été utilisée afin de résumer quantitativement les résultats de neuroimagerie où de l'information visuelle était présentée à des individus autistes et non autistes. Grâce à cette méthode, une plus grande implication des mécanismes visuo-perceptifs chez les autistes, et des régions frontales associées au traitement cognitif de plus haut niveau chez les non autistes, a été démontrée (Figure 2).

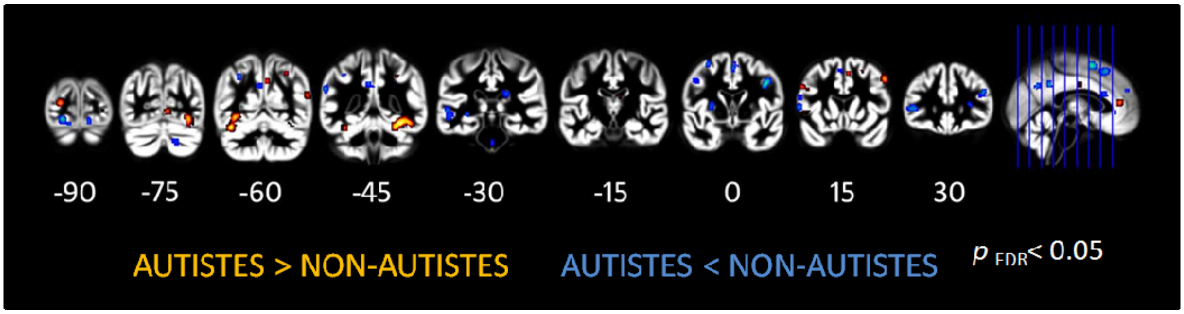


Figure 2. Résultats de la méta-analyse quantitative montrant une plus grande activité des régions visuo-perceptives chez les autistes (rouge/orange) et des régions frontales chez les non autistes (bleu) lors du traitement d'informations visuelles (adapté de Samson et al., sous presse).

Spécifiquement, les résultats de 26 études indépendantes ont été synthétisés pour permettre de révéler les régions les plus systématiquement activées lors du traitement d'informations visuelles chez un total de 357 individus autistes et 370 individus non autistes. Les différentes études incluses dans la méta-analyse ont utilisé une grande variété de stimuli visuels et des tâches diverses. En dépit de l'obtention de niveaux de performance comparables entre les deux groupes pour la majorité des études (18/26), les autistes ont montré une plus grande implication des régions occipito-temporales dédiées au traitement et à la manipulation de l'information visuelle ainsi qu'à la reconnaissance et à l'identification d'objets (Wandell, et al., 2007) et des régions pariétales servant à la recherche et la détection visuelle (Brown, Goltz, Vilis, Ford, & Everling, 2006; Hufner et al., 2008), ainsi qu'au maintien de l'information visuelle en mémoire de travail (Suchan, Botko, Gizewski, Forsting, & Daum, 2006; Yeh, Kuo, & Liu, 2007). Inversement chez les non autistes, une plus grande activité des régions frontales impliquées dans des processus de préparation et d'exécution motrices (Petrides, 2000), de contrôle cognitif (Brass, Derrfuss, Forstmann, & von Cramon, 2005) et dans la prise de décision (Badre & Wagner, 2007; Petrides, 2002) a été observée. Ces différences d'activité fonctionnelle ont donc permis de suggérer que les mécanismes perceptifs joueraient, de manière générale, un plus grand rôle lors de la réalisation de tâches cognitives chez les personnes autistes (voir Annexe 1; Samson, Mottron, Soulières, & Zeffiro, sous presse).

1.3.3 Modèle d'un surfonctionnement perceptif

Différents modèles neurocognitifs ont été élaborés pour tenter d'expliquer la présence d'un traitement perceptif atypique dans l'autisme.

Frith (1989) a d'abord proposé le modèle d'une faiblesse de la cohérence centrale (« Weak Central Coherence »). La cohérence centrale est définie comme étant la tendance démontrée par les individus non autistes de traiter l'information au niveau global, c'est-à-dire dans son ensemble, souvent au détriment du traitement des détails et des informations plus locales. Chez les autistes, une tendance inverse est souvent retrouvée, ceux-ci montrant plutôt un biais vers le niveau local de l'information, comme le démontre, par exemple, leur capacité supérieure à détecter une figure simple cachée dans une forme plus complexe (Shah & Frith, 1983). La théorie suggère que la supériorité démontrée par les autistes pour traiter les détails résulterait d'une incapacité à analyser le niveau global ou la cohérence d'éléments locaux. Cependant, on reconnaît maintenant la capacité des personnes autistes à traiter l'information au niveau global lorsqu'une telle stratégie s'avère essentielle à la réussite d'une tâche (e.g. Caron, Mottron, Berthiaume, & Dawson, 2006). Une plus récente version du modèle de Frith suggère plutôt la présence d'un biais vers le niveau local dans l'autisme plutôt qu'une supériorité au niveau local résultant d'un déficit du traitement global (Happe & Frith, 2006).

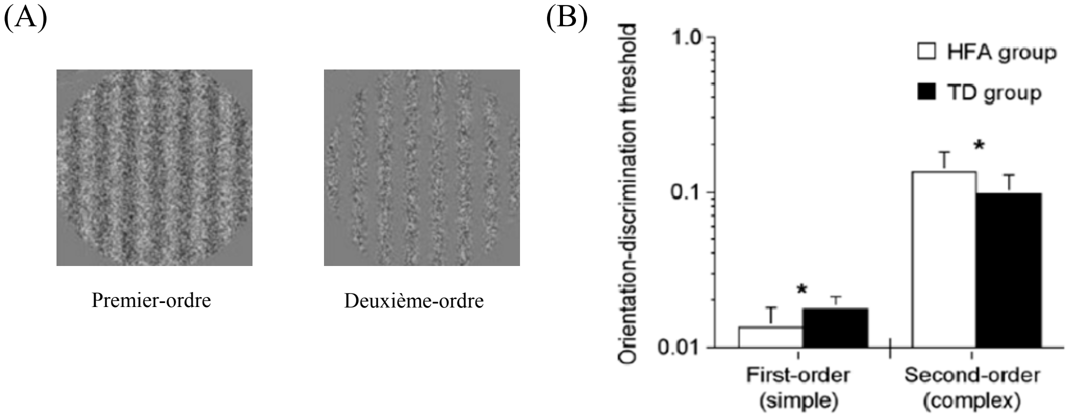
Le modèle d'une faiblesse de la cohérence centrale a longtemps été le modèle neurocognitif principal en autisme et celui-ci a été abondamment étudié. Par contre, à ce jour, c'est plutôt le modèle d'un surfonctionnement perceptif qui prédomine (« Enhanced Perceptual Functioning Model » EPF; Mottron, Dawson, Soulieres, Hubert, & Burack, 2006). Celui-ci décrit les particularités du traitement perceptif dans l'autisme. Principalement, ce modèle multimodal met l'emphase sur la présence d'une capacité supérieure de traitement de l'information perceptive dans l'autisme. Selon cette théorie, une telle supériorité entraînerait un biais vers les processus perceptifs se reflétant par une implication supérieure des mécanismes cérébraux associés à la perception lors de la réalisation de différentes tâches cognitives. Le modèle EPF propose que, chez les autistes, l'information est traitée « par défaut » au niveau perceptif, entraînant une plus grande efficacité et un plus grand rôle de ces processus au sein de la cognition. Dans la perception, ce modèle prédit aussi un biais vers les processus plus en amont, qui serait principalement reflété par une augmentation de l'activité des régions sensorielles primaires pour les tâches strictement perceptives.

La prédiction d'un plus grand rôle des processus perceptifs au sein de la cognition dans l'autisme a récemment été validée dans la modalité visuelle grâce à la méthode de méta-analyse quantitative (Samson, et al., sous presse). Comme les prédictions de l'EPF sont multimodales, c'est-à-dire qu'on y suggère la présence d'un biais vers le traitement perceptif visuel et auditif dans l'autisme, une étude similaire aurait idéalement aussi été réalisée pour les études de neuroimagerie présentant de l'information dans la modalité auditive. Bien que le nombre d'études portant sur le traitement de l'information auditive dans l'autisme soit trop restreint pour permettre une telle méta-analyse, certains résultats comportementaux semblent suggérer la présence d'un biais perceptif en audition également (Jarvinen-Pasley, Pasley, & Heaton, 2008; Jarvinen-Pasley, Wallace, et al., 2008).

1.4 Hypothèse spécifique à la complexité

Suivant les multiples observations confirmant la présence d'un traitement perceptif atypique dans l'autisme, des hypothèses plus spécifiques ont été élaborées. En effet, le modèle EPF décrit les particularités perceptives, sans toutefois proposer d'explications neurofonctionnelles sous-jacentes. Des études plus spécifiques servent donc à proposer des liens entre certains comportements atypiques et les mécanismes cérébraux les sous-tendant. Bien que les particularités de la perception semblent se retrouver à travers les différents niveaux de traitement dans l'autisme, c'est l'observation d'une dissociation de performance au sein de la perception visuelle de *bas niveau* qui a motivé la formulation de l'hypothèse spécifique à la complexité (« Complexity-specific hypothesis »; Bertone et al., 2005).

Spécifiquement, Bertone et ses collaborateurs (2005) ont observé que les personnes autistes obtiennent des performances supérieures pour discriminer l'orientation (horizontale ou verticale) de stimuli statiques de premier ordre (réseaux définis par la luminance, Figure 3A) et inférieures pour les stimuli statiques de deuxième ordre (réseaux définis par la texture, Figure 3A) par rapport à un groupe d'individus non autistes (Figure 3B).



Premier-ordre

Deuxième-ordre

Figure 3. (A) Exemple de réseaux de premier (gauche) et deuxième ordre (droite); (B) Seuil de discrimination de l'orientation des stimuli de premier (gauche) et deuxième ordre (droite) dans le groupe autiste (bandes blanches) et dans le groupe non autiste (bandes noires).

Tel que précédemment expliqué, ces deux types de stimuli peuvent être définis comme étant, respectivement, simples et complexes en regard de l'étendue du réseau cortical requis pour les traiter. En effet, les mécanismes opérant au niveau de l'aire visuelle primaire (V1) suffisent à décoder les attributs de premier ordre, tandis que des opérations supplémentaires au niveau des régions non primaires V2 et V3 sont nécessaires pour analyser les attributs de deuxième ordre (Chubb & Sperling, 1988; Berton et al., 2003). Ainsi, les auteurs ont proposé l'hypothèse selon laquelle la capacité de traitement de l'information visuelle de bas niveau dans l'autisme puisse être dissociée selon l'étendue du réseau cortical impliqué. Cette hypothèse propose que les personnes autistes obtiennent des performances inférieures à celles des non autistes pour traiter les stimuli nécessitant l'implication d'un réseau d'aires corticales pour être entièrement décodés (i.e. V1, V2 et V3). Inversement, leur performance serait supérieure à celle des non autistes pour traiter des stimuli pouvant être entièrement décodés via des mécanismes limités au sein d'une région corticale fonctionnelle restreinte (i.e. V1).

Selon le modèle de Bertone et al. (2005), la complexité est définie en fonction d'un traitement hiérarchique de l'information visuelle, soit une limitation du traitement de stimuli simples au niveau des aires visuelles primaires et une extension de la réponse aux régions non primaires en réponse à des stimuli complexes. Un traitement fonctionnel hiérarchique de l'information sensorielle représente donc un postulat à la base de la formulation de l'hypothèse de la complexité.

Investigation des mécanismes

Deux avenues d'interprétation n'étant pas mutuellement exclusives ont été élaborées pour tenter d'expliquer la dissociation de performance observée pour le traitement de l'information visuelle de bas niveau dans l'autisme, soit des différences au niveau de mécanismes microscopiques (neuronaux) et macroscopiques (relation entre régions corticales).

Au niveau neuronal, les auteurs ont suggéré qu'une connectivité atypique au sein du système sous-tendant le traitement de l'orientation de stimuli visuels chez les autistes pourrait entraîner la dissociation de performance observée. Considérant que la capacité de détection de l'orientation au niveau de l'aire visuelle primaire (V1) est principalement dépendante des interactions (connections) entre les colonnes de neurones (Andrews, 1965), un changement dans ces interactions pourrait affecter cette capacité. Les auteurs suggèrent que l'inhibition latérale soit le processus impliqué dans une telle dissociation. Chez les autistes, l'idée a d'abord été suggérée par Gustafsson (1997) qui propose qu'une organisation atypique des circuits neuronaux, principalement liée à une inhibition latérale excessive, pourrait expliquer les capacités supérieures de discrimination ainsi que les réponses atypiques à certains stimuli sensoriels. De manière plus spécifique, il propose qu'une augmentation de l'inhibition latérale au sein de l'aire visuelle primaire dans l'autisme puisse définir de manière plus circonscrite la réponse de chacune des colonnes de neurones à une orientation donnée. Ainsi, les autistes montreraient une capacité supérieure pour détecter l'orientation d'un stimulus et pour discriminer des différences d'orientation entre deux stimuli.

Considérant que les colonnes d'orientation de V1 sont spécifiquement sensibles aux changements de luminance (premier ordre; Chubb & Sperling, 1988), la détection de l'orientation des réseaux de premier ordre, comme ceux utilisés dans l'étude de Bertone et al., (2005), peut être réalisée au sein d'une colonne de neurone répondant à une orientation donnée. Une inhibition latérale excessive dans l'autisme entraînerait une sélectivité plus précise des colonnes à une orientation spécifique et, donc, des performances supérieures pour discriminer l'orientation des stimuli définis par la luminance. Par contre, la présence de connections latérales atypiques au sein de V1 pourrait entraver la capacité de discrimination de l'orientation de stimuli de deuxième ordre (définis par la texture) dont l'analyse requière une deuxième étape de traitement à une échelle spatiale plus grossière (V2/V3), et donc un circuit de connections neuronales plus complexe (Chubb & Sperling, 1988). La détection de l'orientation de tels stimuli nécessite une intégration de l'information analysée par des colonnes de neurones adjacents (Field, Hayes, & Hess, 1993). Ce processus pourrait être plus difficile à mettre en place si la réponse des colonnes à une orientation donnée est très spécifique étant donné que l'information devra être intégrée à travers un plus grand ensemble de neurones. En somme, Bertone et al. (2005) suggèrent que le même mécanisme, une inhibition latérale excessive au niveau de neurones du cortex visuel primaire, sélectif à l'orientation de stimuli définis par la luminance, entraîne deux conséquences inverses : une meilleure discrimination de ce type de stimuli (premier ordre), ainsi qu'une entrave au traitement de stimuli plus complexes pour lesquels un réseau entre les aires primaires (V1) et non primaires (V2/V3) doit être mis en place. Récemment, des évidences empiriques supportant l'hypothèse de connections neuronales atypiques sous-tendant le traitement atypique de l'information visuelle de bas niveau ont été rapportées (Keita, Mottron, & Bertone, 2010; Vandenbroucke, Scholte, van Engeland, Lamme, & Kemner, 2008).

Au niveau du traitement cortical plus global, ou macroscopique, une des hypothèses de l'origine de la dissociation de performances rapportée par Bertone et al. (2005) stipule que les aires visuelles impliquées dans la réalisation de la tâche pourraient être plus efficaces en isolation qu'en synchronie. Selon cette hypothèse, les meilleures performances des autistes pour traiter les stimuli statiques de premier ordre pourraient s'expliquer par le fait que le traitement de ces stimuli n'implique que l'aire visuelle primaire V1. Inversement, les performances inférieures des autistes pour discriminer l'orientation des stimuli statiques de deuxième ordre pourraient provenir du fait que le traitement de ces stimuli implique des connections entre les régions visuelles primaire (V1) et non primaires (V2, V3). Une telle hypothèse est supportée par divers résultats démontrant une diminution de la connectivité fonctionnelle, par exemple entre les aires visuelles extra-striées (V3) et le sulcus temporal supérieur chez les autistes pendant la réalisation d'une tâche d'attribution d'états mentaux (« theory of mind ») bien que l'activation au niveau des aires visuelles extra-striées ne soit pas réduite (Castelli, Frith, Happe, & Frith, 2002). Les auteurs proposent que la région plus spécialisée pour la réalisation de la tâche (i.e. sulcus temporal supérieur) ne reçoive pas l'information nécessaire des régions corticales en amont (i.e. aires visuelles extra-striées) qui traitent les aspects les plus élémentaires des stimuli, ce qui expliquerait la réduction de l'activation au niveau plus spécialisé, mais l'activation typique des aires perceptives. Dans une autre étude, Just et ses collaborateurs (2004) rapportent que, chez les personnes autistes, il y a une réduction de la synchronie fonctionnelle (mesure de la corrélation entre le décours temporel de la réponse au sein des différentes régions cérébrales) entre des paires de régions impliquées dans le traitement syntaxique. Les auteurs ont donc suggéré une théorie proposant une baisse de la connectivité entre les différentes régions cérébrales dans l'autisme (« underconnectivity hypothesis »). Bien que les résultats soutenant cette hypothèse portent sur des processus cognitifs complexes (ex.

langage, attribution d'états mentaux), il est possible de penser que cette baisse de communication entre les régions puisse aussi se retrouver au sein des processus perceptifs de bas niveau.

1.5 À la recherche de l'analogue auditif

Un traitement perceptif atypique représente une caractéristique générale associée au phénotype autistique, les particularités perceptives étant rapportées tant pour la modalité visuelle qu'auditive. Étant donné les parallèles entre ces deux modalités sensorielles, il est possible que l'hypothèse spécifique à la complexité ait une portée multimodale et s'applique aussi en audition.

Au niveau empirique, les autistes démontrent une capacité de traitement de l'information perceptive visuelle et auditive supérieure à celles des individus non autistes. En vision, cette supériorité est, entre autres, rapportée au niveau du traitement de *bas niveau* et de niveau *intermédiaire*; par exemple pour des tâches de discrimination de l'orientation (Bertone et al., 2005), de détection de figures cachées (Jolliffe & Baron-Cohen, 1997), de recherche visuelle (Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009) ou encore pour la tâche du dessin avec blocs (Caron et al., 2006). En audition, les autistes obtiennent des performances supérieures à celles des individus non autistes principalement pour le traitement de *bas niveau*, c'est-à-dire pour discriminer les sons purs (Bonnel et al., 2010; Bonnel et al., 2003; Jones et al., 2009), et démontrent aussi des capacités supérieures aux non autistes pour traiter les notes de musique (Heaton, 2003; Miller, 1989).

Au niveau cortical, la présence d'un traitement fonctionnel hiérarchique caractérise le traitement de l'information sensorielle. Une organisation fonctionnelle hiérarchique caractérise l'analyse de l'information au niveau du cortex visuel (Bartels & Zeki, 1998; Moutoussis & Zeki, 1997; Van Essen, 2003). En audition, les études menées chez les primates décrivent une organisation corticale similaire; le décodage des sons purs étant principalement limité aux régions auditives primaires, tandis que les sons plus complexes comme les vocalisations requièrent l'implication des régions primaires et non primaires (Kaas & Hackett, 2000; Rauschecker & Scott, 2009; Recanzone & Cohen, 2010). Des études de neuroimagerie suggèrent que la hiérarchie représente aussi une caractéristique du traitement de l'information auditive chez l'humain (Okada et al., 2010; Wessinger et al., 2001). Enfin, les mécanismes proposés pour tenter d'expliquer la dissociation de performance observée pour le traitement de l'information visuelle de bas niveau dans l'autisme pourraient aussi possiblement sous-tendre une possible dissociation similaire en audition. À l'échelle neuronale, une des hypothèses candidate est la présence d'une inhibition latérale excessive au sein du cortex visuel primaire (V1; Bertone et al., 2005). Comme au niveau visuel où le processus d'inhibition latérale vise à augmenter la détection de l'orientation des stimuli, il existe, au niveau des aires auditives primaires (A1), un circuit d'inhibition latérale permettant d'affiner la courbe de réponses des neurones pour des fréquences spécifiques (Oswald et al., 2006). L'hypothèse d'une inhibition latérale excessive au sein des régions auditives spécialisées pour le traitement de la fréquence pourrait donc aussi, tel que proposé dans la modalité visuelle, être à la fois bénéfique pour le traitement de stimuli n'impliquant que ces régions et à la fois gênant pour la mise en place du réseau entre plusieurs aires du cortex auditif nécessaire au traitement de stimuli plus complexes. En effet, selon cette hypothèse, les réponses fréquentielles au niveau de l'aire auditive primaire seraient plus précises et spécifiques dans l'autisme. Ainsi, tel que proposé en vision, l'analyse de stimuli auditifs plus complexes pourrait être plus difficile étant donné la nécessité d'intégrer l'information à travers un plus grand réseau neuronal.

L'hypothèse d'une baisse de la connectivité entre régions corticales à la base de la dissociation comportementale en vision pourrait aussi s'appliquer en audition. En effet, il a été suggéré qu'une baisse de connectivité entre les différentes régions cérébrales représente une caractéristique globale du cerveau des autistes (Belmonte, Allen, et al., 2004). En réponse à des stimuli auditifs simples, une étude d'électrophysiologie a démontré la présence de connections neuronales atypiques au sein du cortex auditif chez des enfants autistes qui pourraient possiblement sous-tendre une baisse de connectivité dans cette région (Wilson, Rojas, Reite, Teale, & Rogers, 2007). De plus, des différences microstructurales au niveau des fibres de matière blanche permettant le transfert des influx nerveux ont été observées dans la région principalement impliquée dans le traitement auditif, le gyrus temporal supérieur (Lee et al., 2007), supportant ainsi l'hypothèse d'une connectivité corticale atypique impliquant les régions auditives dans l'autisme.

1.6 Objectifs et hypothèses

L'objectif de cette thèse est d'explorer si l'hypothèse spécifique à la complexité proposée pour expliquer certaines particularités du traitement de l'information visuelle dans l'autisme pourrait aussi caractériser le traitement de l'information auditive dans cette population.

Afin de valider cette proposition, il est d'abord nécessaire d'examiner la capacité de traitement de l'information auditive dans l'autisme. Une revue exhaustive de la littérature servira à vérifier si un parallèle peut être tracé entre la dissociation de performance observée en vision et certaines particularités du traitement de l'information auditive dans l'autisme. Possiblement, une relation inverse entre complexité et performance pourrait être mise en lumière en audition. Une telle dissociation constituerait une première évidence permettant de proposer une généralisation de l'hypothèse spécifique à la complexité à la modalité auditive.

Ensuite, l'analogie entre les modalités visuelle et auditive doit passer par une définition commune de la complexité. En vision, les stimuli de premier et deuxième ordre sont définis comme étant simples et complexes en regard de l'étendue du réseau d'aires corticales fonctionnelles requises pour les traiter. Donc, pour tenter de faire le pont vers la modalité auditive, il est nécessaire de trouver des stimuli pouvant aussi être dissociés selon l'étendue de leur traitement cortical. Une méta-analyse quantitative des études de neuroimagerie utilisant des stimuli auditifs chez le sujet non autiste permettra d'investiguer comment la complexité acoustique est représentée au niveau cortical. Ainsi, les stimuli auditifs dont le traitement est limité au niveau des aires auditives primaires seront considérés comme simples (analogues aux stimuli visuels de premier ordre) et ceux dont le traitement requiert l'implication d'aires corticales supplémentaires, comme complexes (analogues aux stimuli visuels de deuxième ordre).

Enfin, en analysant la réponse aux stimuli auditifs ayant été définis comme simples et complexes au niveau cortical, il sera possible de vérifier si les prédictions de l'hypothèse spécifique à la complexité pourraient aussi s'appliquer en audition chez les autistes. L'activité cérébrale associée au traitement de sons simples et complexes sera mesurée dans un groupe d'autistes et un groupe d'individus non autistes. En se basant sur l'hypothèse suggérant une intégration atypique de l'information entre les différentes régions cérébrales dans l'autisme, une baisse de l'activité des aires auditives non primaires à l'écoute de sons complexes devrait être observée chez les autistes en comparaison au groupe non autiste. De plus, les autistes pourraient parallèlement démontrer une augmentation de l'activité des aires primaires reflétant ainsi un biais vers les processus en amont lors de tâches perceptives, tel que prédit par le modèle EPF.

1.6.1 Méthode d'investigation

Dans cette thèse, la technique d'Imagerie par Résonance Magnétique fonctionnelle (IRMf) sera utilisée afin de mesurer la réponse corticale aux stimuli auditifs ayant été identifiés comme simples et complexes en regard du nombre de régions fonctionnelles impliquées dans leur traitement. La section suivante se veut un bref exposé des principes de bases de la technique ainsi que des considérations spécifiques de l'utilisation de cette méthode lors de l'étude du traitement de l'information auditive.

La technique de résonance magnétique nucléaire (RMN) utilise les propriétés de la matière et plus précisément les moments magnétiques, spins, des noyaux atomiques. Dans une expérience classique de RMN, un patient est introduit dans l'entrefer de l'aimant qui génère un champ magnétique environ 60 000 fois supérieur au champ magnétique terrestre, alors, les spins nucléaires des atomes d'hydrogènes de l'organisme s'orientent dans ce champ. Ensuite, le changement d'orientation des noyaux est forcé par une onde excitatrice vibrant à leur fréquence de résonance (fréquence de Larmor); ceci a pour effet de maximiser leur niveau énergétique et certains spins basculent à la réception de cette énergie. À l'arrêt de l'excitation, les spins ont tendance à retourner à leur état initial; on appelle ce phénomène relaxation. La RMN est une mesure des temps de relaxation. En effet, la libération d'énergie liée au changement d'état génère un voltage (signal RMN) qu'il est possible de mesurer à l'aide d'une antenne.

L'IRMf est une des méthodes d'imagerie basée sur les principes de RMN et elle repose sur la théorie proposant que chacune des régions anatomiques cérébrales puisse être associée à une ou plusieurs tâches fonctionnelles spécifiques. Pour réussir à acquérir des images sensibles aux fonctions cérébrales en IRMf, il était nécessaire d'identifier un phénomène biophysique associé au traitement cortical de l'information qui allait pouvoir être mesuré en RMN. Idéalement, il faut pouvoir capter des images sensibles à l'activité neuronale étant donné que le traitement de l'information au niveau cortical repose sur l'activité d'ensembles de neurones. Cependant, en IRMf, on ne capte pas directement des images reflétant l'activité neuronale, on acquiert plutôt des images de l'activité physiologique corrélée à l'activité neuronale.

Pour traiter l'information qui parvient au cerveau, l'activité au sein de certaines régions corticales augmente ce qui implique que les demandes énergétiques des neurones de ces régions augmentent. Pour atteindre les neurones, les sources d'énergie (oxygène et glucose) sont véhiculées via le système vasculaire. Le cerveau ne stocke que très peu de ressources énergétiques et une hausse de l'activité neuronale doit s'accompagner d'une augmentation du débit sanguin permettant un échange. L'apport sanguin permet à l'oxygène, lié aux molécules d'hémoglobine, de rejoindre les neurones. L'augmentation locale et transitoire du débit sanguin cérébral régional semble donc être une réflexion de l'activité neuronale de cette zone (Fox & Raichle, 1986; Sokoloff et al., 1977).

En IRMf, l'acquisition d'images repose sur l'effet BOLD (« Blood Oxygen Level Dependant »), principe physiologique qui lie les variations de débit sanguin régional et l'activité neuronale sous-jacente. Pour détecter cet effet, l'IRMf utilise la susceptibilité magnétique de l'hémoglobine. En effet, une fois liée à l'oxygène (oxyhémoglobine) elle est diamagnétique (faible perturbation du champ magnétique) tandis qu'elle est paramagnétique (forte perturbation du champ magnétique) sous la forme desoxyhémoglobine, c'est-à-dire lorsqu'elle a cédé ses ions oxygène (Pauling & Coryell, 1936). Le signal BOLD reflète les différences de susceptibilités magnétiques entre les compartiments intra et extra-vasculaires qui induisent la présence d'un champ perturbateur autour des vaisseaux lequel peut être détecté. Puisque le sang artériel est saturé, très peu de désoxyhémoglobine s'y trouvant, la susceptibilité magnétique en amont des zones d'échanges avoisine celle des tissus environnants et varie très peu en fonction de l'activité cérébrale. Au contraire, le sang veineux est moins saturé en oxygène au repos et cette saturation augmente légèrement pendant l'activité cérébrale. En effet, lorsqu'il y a une hausse locale de l'activité neuronale, le débit sanguin régional augmente considérablement, de l'ordre de 50 %, tandis que la consommation neuronale d'oxygène augmente proportionnellement plus faiblement, de l'ordre de 5 % (Fox & Raichle, 1986). Cette augmentation de la saturation en oxygène entraîne une baisse du taux de désoxyhémoglobine dans les territoires veineux en aval des régions activées. On trouve donc une diminution de la différence de susceptibilité entre les territoires intra et extra-vasculaires. L'amplitude de la perturbation du champ magnétique est réduite, ce qui entraîne une augmentation de l'intensité du signal, donc une réponse IRM positive. Les images acquises en IRMf ne représentent donc pas une mesure directe de l'activité neuronale liée aux différentes conditions expérimentales, mais reflètent plutôt, via l'effet BOLD, des variations régionales de débit sanguin cérébral qui, elles, sont corrélées à l'activité neuronale sous-jacente. Les images fonctionnelles sont ensuite superposées sur une image cérébrale anatomique. Ainsi, l'IRMf permet de visualiser des différences de localisation, de l'étendue ou de l'intensité des changements au niveau du débit sanguin régional corrélées à la réalisation de différentes tâches cognitives.

La haute résolution spatiale (de l'ordre du millimètre) de cette technique permet de localiser avec précision les régions montrant des variations d'activité. Considérant l'importance dans le présent projet de définir la complexité selon l'étendue du réseau de régions cérébrales fonctionnelles impliquées, l'IRMf représente une méthode adéquate pour mettre en lumière des différences associées à l'analyse de stimuli dont le traitement n'implique qu'une versus plusieurs régions cérébrales fonctionnelles. La méthode d'IRMf a donc été préférée aux techniques électrophysiologiques, comme l'électroencéphalographie ou la magnétoencéphalographie, qui offrent plutôt un avantage lorsque le décours temporel de la réponse corticale représente la variable d'intérêt considérant la haute résolution temporelle de ces techniques.

Cependant, en neurosciences de l'audition, la technique d'IRMf a longtemps été considérée comme inadéquate à cause du bruit intense généré par le scanner lors de l'acquisition d'image. L'utilisation de l'IRMf pour étudier le fonctionnement du système auditif nécessite donc des considérations méthodologiques particulières afin de s'assurer que le bruit généré par l'appareil n'interagisse pas avec les mesures de l'activité du cortex auditif associée à la tâche. En effet, on peut imaginer qu'un stimulus auditif présenté pendant l'acquisition d'images fonctionnelles soit partiellement ou complètement masqué par le bruit du scanner. Aussi, le bruit de l'appareil entraîne inévitablement une activation du cortex auditif et possiblement des phénomènes de saturation ou d'habituation de la réponse auditive (Bandettini, Jesmanowicz, Van Kylen, Birn, & Hyde, 1998; Robson, Dorosz, & Gore, 1998). De plus, la présentation de stimuli en présence du bruit de l'appareil implique nécessairement une activité cognitive supplémentaire permettant aux participant de distinguer les différentes sources sonores et maintenir leur attention sur les stimuli (« auditory streaming », Bregman, 1990). Ceci aurait des répercussions sur le profil d'activité corticale et possiblement sur les performances des participants.

Les études ayant tenté de développer des techniques d'imagerie visant à réduire ces effets ont montré que l'interaction entre les stimuli et le bruit de l'appareil pouvait être minimisée lorsque des moments de silence étaient inclus entre les acquisitions d'images cérébrales, en comparaison aux protocoles standards où l'acquisition est continue (Eden, Joseph, Brown, Brown, & Zeffiro, 1999; Edmister, Talavage, Ledden, & Weisskoff, 1999; Hall et al., 1999). Considérant que la réponse corticale (réponse hémodynamique) suivant la présentation d'un stimulus auditif est maximale après 3-4 secondes et retourne à la ligne de base après environ 6 secondes (Belin, Zatorre, Hoge, Evans, & Pike, 1999), il est possible d'espacer les acquisitions de manière à capter les images après la présentation des stimuli, au moment où l'activité auditive liée à la tâche est le plus intense. Cette technique d'acquisition, nommée « sparse sampling », permet d'optimiser la détection de l'activation cérébrale associée à la tâche étant donné que les images sont acquises au moment où les changements d'activité cérébrale associés au bruit de l'appareil sont minimum et ceux liés à l'écoute des stimuli sont maximum (voir Figure 2, Chapitre 4, page 127). De cette manière, la réponse corticale associée aux stimuli auditifs n'est pas masquée par la réponse associée au bruit de l'appareil et les stimuli peuvent être présentés sur un fond silencieux ce qui permet d'éviter l'addition d'une contrainte attentionnelle. Cette technique d'acquisition sera donc privilégiée dans le présent travail.

Chapitre 2. Can spectro-temporal complexity explain the autistic pattern of performance on auditory tasks?

Can spectro-temporal complexity explain the autistic pattern of performance on auditory tasks?

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Abstract

To test the hypothesis that level of neural complexity explains the relative level of performance and brain activity in autistic individuals, available behavioural, ERP and imaging findings related to the perception of increasingly complex auditory material under various processing tasks in autism were reviewed. Tasks involving simple material (pure tones) and/or low-level operations (detection, labelling, chord disembedding, and detection of pitch changes) show a superior level of performance and shorter ERP latencies. In contrast, tasks involving spectrally- and temporally-dynamic material and/or complex operations (evaluation, attention) are poorly performed by autistics, or generate inferior ERP activity or brain activation. Neural complexity required to perform auditory tasks may therefore explain pattern of performance and activation in autistic individuals during auditory tasks.

Keywords : Autism, audition, perception, complexity, local, global

Can spectro-temporal complexity explain the autistic pattern of performance on auditory tasks?

Autistic individuals present with atypical reactions in response to non-social and social auditory input, such as hypo-reactivity to both verbal and loud sounds, and hyper-reactivity for sounds of mild and low intensity (Grandin & Scariano, 1986). Whereas some autistic individuals do not make use of expressive language, others develop special talents in processing auditory information, such as absolute pitch (AP), and display outstanding musical memory and improvisation abilities (Heaton, 2003; Miller, 1999). These positive and negative signs that are linked to auditory perception are part of the diagnostic criteria of autism (Lord et al., 1997).

Notwithstanding the relative paucity of information on auditory processing, current models of atypical perception in autism are multi-modal, and emphasize either enhanced low-level and locally-oriented visual and auditory perception (Enhanced Perceptual Functioning model, Mottron & Burack, 2001), or diminished/intact processing of global visual and auditory information (Frith, 2003; Mottron, Burack, Iarocci, Belleville, & Enns, 2003; Mottron, Morasse, & Belleville, 2001; Plaisted et al., 2003). However, none of these models has provided an explanation based on the functional neuroanatomy of perception.

In studies of the neural bases of this contrasting pattern of performance in the visual modality, inferior performance in the processing of static and dynamic *second-order* stimuli, and intact or superior performance in the discrimination of *first-order* stimuli (Bertone & Faubert, 2003; Bertone, Mottron, Jelenic, & Faubert, 2005) are reported. V1 first stage filters extract first-order orientation or motion direction, whereas second-order orientation or motion information is detected at a second-stage of filtering, in areas V2/V3 (Bertone & Faubert, 2003; Chubb & Sperling, 1988). For this reason, first-order information can be considered to be “simple”, but second-order information is considered to be more “complex” since it recruits more extensive neural circuitry as well as additional processing prior to orientation identification.

Based on this evidence, Bertone et al. (2005) hypothesized that superior sensitivity for first-order information and inferior sensitivity for second-order information detection in autism are related to an atypical neural connectivity, resulting in greater lateral inhibition at the neural level. This hypothesis may be considered as a within-perception correspondent of Minshew, Goldstein, and Siegel's (1997) "complexity-deficit" hypothesis but adds specific predictions and explanations for superiority on simple perceptual tasks. According to Bertone et al.'s model, "complexity" is defined in terms of hierarchical neural organization, and has to be dissociated from the difficulty level of a task. For example, a task which is "simple" at the neural level, like first order texture discrimination, may be difficult to achieve.

Although Bertone et al.'s results are still limited to a laboratory setting and to the visual modality; their hypothesis represents a promising heuristic tool for the investigation of auditory perception in autism that could lead to a multi-modal model of autistic perceptual atypicalities. In order to evaluate whether Bertone et al.'s (2005) complexity hypothesis can be generalized to the auditory modality, we will review the available behavioural, electrophysiological, and brain imaging studies on auditory processing in autism. A particular emphasis will be given to the auditory findings relevant to locally-oriented, enhanced low-level, and simple versus complex dissociations.

Relevant dimensions and measures of auditory perception

Complexity of auditory stimuli

The distinction between simple and complex stimuli has a spectral and a temporal counterpart. A stimulus that contains energy at a single frequency (e.g., a pure tone) is simple, whereas a sound that contains several frequency components (e.g., a harmonic series, a chord) is spectrally complex. Temporally complex stimuli contain amplitude changes between onset and offset or contain sequences of sounds delimited by an onset and an offset. One aspect of temporal complexity is that auditory sequences (e.g., melodies) form gestalts whose emerging properties are different from those of their constituents (individual tones).

Temporal complexity is represented at various time scales. For example, dynamic frequency and spectral transformations at the time scale of hundreds of ms are the basic constituents of phonemes. At larger time scales, melodies or sentences consist of sequences of sounds. The spectral versus temporal distinction can be mapped on the local and global levels of auditory information, with spectral complexity being embedded in the temporal complexity (Jackendoff, 1987; Scott & Johnsrude, 2003). A local level stimulus (a note) is not necessarily simple as it can contain spectral or amplitude changes, but can be considered as simple when it is a part of a coherent whole (a melody). Vocal sounds are especially complex in this regard, as they include multiple sources of complexity (harmonics, formants, rapid sequences of speech sounds).

Organization of the cortical auditory system.

The primary auditory cortex or A1 (Brodmann Area (BA) 41) is located on Heschl's transverse gyrus, within the supra temporal plane of the superior temporal gyrus. This A1 region, called "core", is devoted mainly to pure-tone processing and has a tonotopic organisation. A1 is surrounded by a "belt" and a lateral "parabelt" (A2; BA 22, 42) which are responsive to sounds with complex spectro-temporal structure, such as spectrally dynamic sounds and frequency-modulated sounds. For example, the "voice" region (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000), is embedded in BA 22. Levels of tonotopia decrease from center to periphery: they are evident in the core, less clear in the belt, and are absent in the parabelt. According to Griffith (2003a), a simple versus complex hierarchy of analysis can be found in the auditory cortex, at least for pitch perception. Spectrally complex sounds require a larger neural complexity than pure tones (Scott & Johnsrude, 2003). Increased stimulus complexity results in increased activation in the auditory cortical core and in surrounding auditory regions, but activity resulting from simple tonal stimuli is mainly restricted to the core (Di-Salle et al., 2003; Hudspeth, 2000; Semple & Scott, 2003). As in vision, neural processing of auditory stimuli involves two distinct pathways. A predominantly "what" pathway is dedicated to the characterization of pitch and phonemes. A "where" pathway is implicated in sound localization, and its activity is modulated by the spectro-temporal complexity of sounds. However, these two pathways are heavily interconnected and present some functional overlapping (Belin & Zatorre, 2000). Technical difficulties in separating activation linked to encoding of auditory stimuli from that linked to the conscious operation of labelling, the increased individual variability of auditory cortex as compared to visual cortex, the acoustic noise of fMRI, and the intrinsically temporal nature of auditory information have slowed the achievement of typical auditory functional cartography (Griffith, 2003a; Zatorre, 2003).

Investigation of auditory processing at various levels of complexity

The most elementary behavioural assessment of cortical auditory processing is represented by categorisation, labelling, and discrimination tasks for isolated tones that can themselves be of increased spectral complexity (pure vs. complex tones). Although these tasks involve sensory and perceptual processing *per se*, they also require conscious access and comparison with information stored in memory. At a higher level of integration, the use of musical stimuli allows the investigation of hierarchical dimensions of temporal complexity –(i.e. local -note- and global -contour and temporal aspects of melodies). The discrimination of changes in the pitch of the notes of a melody, the detection of tones masked by noise, the detection of contour changes in single or simultaneous melodies are example of tasks that can be used to assess different levels of auditory complexity by behavioural methods. Linguistic auditory stimuli involve various levels of spectral and temporal complexity in addition to language-specific characteristics such as phonology, grammar, and discourse.

Neural bases of cortical auditory processes can be studied non–invasively using electroencephalography (EEG) and magnetoencephalography (MEG). Event–related potentials (ERPs) and magnetic brain field potentials are real time, trial by trial, measures of neuroelectric and neuromagnetic cortical signals, respectively, that are evoked by an external stimulus or emitted by the brain as a decision or response is initiated. These signals are produced by the synchronized activity of neural assemblies in the brain. While both techniques provide a millisecond time resolution of the sequence of processes involved during a task but with a relatively limited spatial resolution, MEG signals are less attenuated than EEG by cranial tissues and thus allow a better localisation of the active cortical sources. The peaks and dips that compose an ERP waveform are named by their polarity (P for positive and N for negative) and the time elapsed since the presentation of the stimulus. ERP cortical activity to auditory stimuli follows brainstem auditory evoked responses that correspond to signal transmission from the cochlea through the brainstem. The cortical ERP waves appearing 50 to 100 ms after the presentation of the stimulus are a reflection of the basic sensory analysis related to a specific modality and are modulated by the physical characteristics of the stimulus. The responses occurring 200 ms after stimulus presentation are considered long–latency responses, as they are thought to reflect higher level processing and are sensitive to the task instructions and manipulations (Hillyard, 1999).

The N1 (N1m in MEG) is the predominant auditory sensory response in adults. This component is present when the auditory supra–temporal areas are activated and is a reflection of cortical processing of the different attributes of auditory stimuli (Näätänen & Picton, 1987). It is composed of the fronto–centrally predominant N1b component (around 100 ms after stimulus–onset) and of the T–complex over bilateral temporal scalp sites (Wolpaw & Penry, 1975). This latter biphasic component consists of the N1a and N1c which peak around 75 ms and 130 ms, respectively, with the interpolated positivity (Ta). N1b mainly corresponds to activation of tangentially oriented sources in the supratemporal plane of the auditory cortex, and is modulated by changes in the physical properties of an auditory stimulus. The two negative comments of the T–complex, the N1a which indicates stimulus detection and N1b stimulus discrimination, are generated by radially oriented sources in the lateral supratemporal plane and lateral superior temporal gyrus (Picton*,* 1999; Scherg & Von Cramon, 1986). Maturational changes of the N1a are noted during infancy and childhood (e.g. Bruneau Roux, Adrien, & Barthélémy,1999). Bruneau et al., (1999) reported smaller and later fronto–central N1b and larger and later temporal N1c peaks when recorded in 4–8–year–old children than in adults (Bruneau et al., 1999). With increasing age, the N1b latency decreased but its amplitude did not change.

Mismatch negativity (MMN) in ERPs and its magnetic counterpart, the mismatch magnetic field (MMF), are auditory evoked potentials typically elicited by a discriminable change in an ongoing train of auditory stimuli. It is obtained by subtraction of ERP or magnetic field responses to standard sounds from those elicited by the deviants (Näätänen, 2000). In ERPs, this response takes the form of a negative–going component, and occurs approximately 100 to 250 ms after deviant stimulus onset. The MMN reflects automatic, preconscious change detection processes as the MMN is independent of voluntary attention.

MMN/MMF studies can be conducted using various types of auditory and speech stimuli (tone, vowels), and they do not require active subject participation. This latter feature underlying the MMN generation makes it well–suited as a measure of sound discrimination abilities, and can be conducted with very young children, and with autistic individuals without expressive language. On the basis of source modelling (Jemel, Achenbach, Müller, Röpcke, & Oades, 2002; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000), scalp current density mapping (Deouell et al., 1998; Giard, Perrin, Pernier & Bouchet, 1990), MEG data (Hari, 1984), and intra–cortical recordings (Kropotov, 2000), MMN appears to have mainly two main generators, one located on both supra–temporal planes of the auditory cortices (BA 41) which reflects auditory discrimination, and one in frontal cortex, reflecting involuntary attention to stimulus changes (Näätänen, 2003). The precise location of the temporal MMN was found to be partly dependent on the level of complexity of the sound (i.e., simple, complex, phonemic), the deviating feature (frequency, duration, intensity), and the feature parameters (Alho, 1995; Giard, 1995; Libenthal et al., 2003).

At a higher level, the longer latency P3 component indexes the attention and memory related to the processing of auditory stimuli of various complexity. The P3 component is a positive response occurring about 300 ms after stimulus presentation; it is elicited when a subject has to discriminate an infrequent stimulus from frequent standards (Polich, 2003). The subcomponent P3a is elicited for involuntarily attended-to stimuli, and P3b is elicited when participants are asked to respond (Polich, 2003). The P3a is interpreted as an indication of the involuntary orientation of attention toward salient events in the environment (Siegal & Blades, 2003) and of attention switching, whereas the P3b is related to high level parameters such as stimulus probability, meaningfulness, decision making, and task relevance. In sum, increased response time between the stimulation and the response are indicative of increasingly complex processes, from low level, “psychophysical” response to higher order evaluation. Therefore, these measures allow disentangling the activity of primary and associative auditory areas (N1, MMN) from their modulation by higher order cognitive operations (P300; Bomba & Pang, 2004).

The cerebral regions underlying sound processing can also be studied with neuroimaging methods such as single photon emission computed tomography (SPECT), which investigate cortical perfusion at rest, and functionally by positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). fMRI has the advantage of allowing the presentation of a large variety of auditory stimuli in a single experiment, and the acquisition of reliable statistical maps in individual subjects. fMRI studies comparing measures of blood oxygenation obtained during sound stimulation to those obtained during silence allow the delineation of cortical areas activated by sound, and the comparison, in individual subjects, of the activity induced by different types of sounds. fMRI measures the changes in blood oxygenation whereas PET uses a radioactive tracer and measures metabolic processes correlated with neuronal activity.

Auditory processing in autism at increasing levels of complexity

Rest studies of auditory cortex

Two studies of brain perfusion at rest found decreased perfusion of the associative auditory cortex, the superior temporal gyrus (BA 44⁄22) and the multimodal superior temporal sulcus (BA 21) among autistic children. In a SPECT study of 23 autistic participants (mean CA: 6.5, mean IQ: 48), who were compared to persons with mental retardation, decreased rCBF was identified in the bilateral insula (BA 52) and in the superior temporal gyri (BA 22), in addition to decreased perfusion of the middle frontal gyrus (BA 9) and a language-related region, the left inferior frontal gyrus (BA 45; Ohnishi et al., 2000). In a PET study with two distinct groups of 21 (mean CA of 8.4 years) and 12 (mean CA of 7.4 years) autistic participants with moderate to severe language impairment, hypoperfusion in the left superior temporal gyrus (Brodmann's area 22/42), in the right superior temporal gyrus (Brodmann's area 22/42), and in the right superior temporal sulcus (Brodmann's area 21) was observed (Zilbovicius et al., 2000). However, as the language experience of the comparison group likely exceeded that of the autistic group despite IQ matching, non-autistic participants of Zilbovicius et al. had a superior language level compared to the autistic group, and those of Ohnishi were older (language level not indicated) than their autistic group. In the absence of a similar type of study in high-functioning adult verbal individuals, the interpretation of temporal hypoperfusion as related to language experience or as an intrinsic characteristic of autism is not possible.

Simple auditory stimuli in autism

The most elementary behavioural measure of cortical auditory perception is the labelling of the pitch of pure tones presented in isolation. Absolute pitch (AP) is the capacity to identify the pitch of an isolated tone without reference to a standard. Superior pitch labelling represents the most replicated example of enhanced low-level perception in autism, extending from savant to non-savant and subclinical autistic populations. Absolute pitch is approximately 500 times more frequently among autistics (5%; Rimland & Fein, 1988) than among non autistics (1/10 000; Takeuchi & Hulse, 1993). Most musical savants possess AP, and most of them are autistics (Miller, 1989). Subclinical cognitive and social atypicalities characterizing autism occur more often in musicians with AP than those without AP (Brown et al., 2003). High functioning autistic adults (mean 17.91 years old) possess a superior ability to categorize pure tones, differing in frequency by 1% to 3 %, as high or low (Bonnel et al., 2003). Similarly, autistic children (CA: 7-13, IQ 55-127) had superior immediate and delayed (one week) recall of new pure tones / pictures associations than a comparison group (Heaton, Hermelin, & Pring, 1998)

ERP measures of auditory detection in autistic children present a discrepant picture that may reflect the heterogeneity in IQ level across participant groups, but also in the level of language experience among participants. For example, measurements of N1b produced in the past contradictory findings, attributed (Bomba & Pang, 2004) to the ignorance of its transformation across development. Taking these transformations into account, longer latency and smaller amplitude of the temporal auditory ERPs (N1b and N1 c) were reported in response to pure tones (Bruneau et al., 1999) in developmentally delayed, four to eight years old autistic children. The amplitudes of the auditory ERPs were correlated to the intensity of the stimulation bilaterally in non-autistic children with mental retardation and in typically developing children, but in the right hemisphere only among autistic children (Bruneau et al., 1999). However, similar abnormalities in ERP responses are also reported among children with severe impairment in language development (Tonnquist-Uhlen, 1996).This is consistent with the finding that a majority of children with and without autism (around 12 years of age) who also display language deficits elicited no identifiable M50/M100 peaks when listening to the second of a pair of tones (interval, 150 ms), whereas children with Asperger syndrome and typically developing individuals displayed that response (Oram–Cardy, Flagg, Roberts, Brian, & Roberts, 2005b). Children old enough to generate the N1 component reported no significant difference in amplitude or latency on this response (Kemner, Verbaten, Cuperus, Camfferman, & Van Engeland, 1995; Lincoln, Courchesne, Harms, & Allen, 1995). The interpretation of atypical N100 as a correlate of the level of language development, rather than a marker of autism *per se*, is consistent with Bruneau, Bonnet-Brilhault, Gomot, Adrien, and Barthélémy's (2003) findings that bilateral N1c produced by pure tones were of inferior amplitude among a group of 21 autistic children with mentally retardation and language delay and that typical bilateral intensity was only present in their right hemisphere. N1C amplitude was higher in children with better verbal (and non-verbal) abilities.

At a higher level of complexity, Bonnel et al. (2003) found a hyperdiscrimination of pure tones in high-functioning autistic adults (mean 17.91 years old). The autistic subjects showed better performance than the comparison participants in discriminating "same-different" pure tones (presented by pairs). Their superiority was more pronounced in the lowest level (identification) than in this discrimination task. In terms of neural activation, identification, the matching of *one* tone with its long term memory trace, relies on simpler neural network than discrimination, the comparison of *two* tones in short term memory. We explain this difference in relative difficulty by a "complexity" hypothesis, similar to the way Bertone et al. (2005) accounted for superior perception of first order texture. Enhanced perception of pure tones would make an identification task relatively easier for autistics, although discrimination is easier than identification in non-autistic individuals.

Among language delayed autistic children, Ceponiene et al. (2003) found an intact MMN for pure-tone stimuli. Two ERP studies conducted with low IQ individuals found diminished discrimination as indexed by the MMN or MMF responses. In an MEG study (Tecchio et al., 2003), low-functioning autistic individuals (8-32 years old) displayed reduced tone-MMF amplitude on an auditory oddball paradigm in which the stimuli were 100-ms pure tones. Oram-Cardy, Flagg, Roberts, and Roberts (2005a) found longer latency MMF responses to deviant pure tones in autistic children and teenagers with below average IQ compared to typically developing children. Delayed tone-MMN, mainly over the right hemisphere, was reported in children with Asperger syndrome (Jansson-Verkasalo et al., 2003). Jansson-Verkasalo et al. (2003)concluded that there is evidence for an auditory discrimination deficit in autism spectrum disorder. In contrast, evidence from studies with low-functioning, low verbal development autistic persons indicates shorter latency to MMN, and additional central and frontal sources for deviant sounds in a sequence of standards while participants were watching a silent movie (Gomot, Giard, Adrien, Barthélémy, & Bruneau, 2002). A group of 6-19 year old, mentally retarded (level unknown) autistic individuals presented a larger amplitude of the tone-MMN (Ferri et al., 2003). Considering that the change is detected more rapidly when the difference between the deviant and the standard is greater, this finding can be interpreted as an amplified perception of sounds or hypersensitivity to sound changes in this population (Bruneau & Gomot, 2005).

The analysis of P300 subcomponents reveals informative differences in cognitive strategies between autistics and non-autistics. For pure tones, a P3a-like wave following the MMN was found among autistic children (Gomot et al., 2002), whereas typically developing children displayed an MMN without P3a. This finding suggests that only autistic children switch attention automatically toward the deviant stimuli. Ceponiene et al. (2003) also reported that simple tone changes elicited a typical P3a, indicating that simple auditory tones successfully catch the attention of autistic children. An amplitude decrease of the P3b component in response to clicks (Novick, Vaughan, Kurtzberg, & Simson, 1980) and tones in autism (Ciesielski, Courchesne, & Elsemian, 1990; Courchesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989; Lincoln, Courchesnes, Harms, & Allen, 1993; Oades, Walker, Geffen, & Stern, 1988) were also reported among autistic persons. An amplitude reduction of the P3b could reflect a shut-off of later memory or attention evaluation of the discrepant stimuli analogous to the “optional” higher order processing, as is observed in the visual modality (Mottron et al., this issue).

Perception of spectral complexity in autism

In ecological situations, autistic individuals show aversive reactions to spectrally complex non-social (vacuum cleaners) or social (cafeterias) sounds (Goldfarb, 1961), but also behavioural evidence of the absence of reaction to voice as toddlers. This latter behaviour is included in diagnostic scales for autism (Lord et al., 1997). However, contrary to a common cliché, familiar voices and faces matching, familiar voice recognition, and unfamiliar voice discrimination are normal even among mentally retarded autistics (Boucher, Lewis, & Collins, 2000).

Current empirical knowledge of *s*pectral complexity processing by autistics presents a dichotomous picture. An enhanced ability in chord disembedding, identifying whether a tone is or is not present in a chord formed of several tones, is often found in savant syndrome (Miller, 1989; Mottron, Peretz, Belleville, & Rouleau, 1999), but also in non-savant populations. Autistic children aged 7 to 15 of typical measured intelligence are superior to a comparison group in memorizing the association of a tone and its label, and in identifying a missing tone from a chord composed of the tones that had been presented in the first part of the task (Heaton, 2003). However, they perform at a standard level when asked to decide if a tone is part of the chord composed of tones to which they had not been exposed before. These results may be interpreted in the light of the relation between superior search and disembedding in the visual modality (O'Riordan, 2001, 2004). It is possible that the demonstrated superior processing of simple tones produces an advantage in auditory disembedding, but this is inconsistent with Plaisted et al.'s (2003) findings that the auditory filters of high-functioning autistic individuals and Asperger syndrome (13-28 years old) are broader than those of typically developing individuals. Their study measured the threshold of a 2 kHz pure tone in the presence of a notched noise; the notch was centered at the frequency of the tone and the notch bandwidth was varied. Plaisted et al. concluded that poorer frequency selectivity may explain the impaired performance in the recognition of speech in noise. Although Plaisted et al.'s findings are discrepant with findings that high-functioning autistic persons have superior perceptual abilities in simple perceptual tasks, their small sample size and the fact that five out of eight participants had normal auditory filter bandwidths necessitates caution in the interpretation of the findings.

Ceponiene et al., (2003) assessed ERPs to non-linguistic (complex tones composed of four sinusoidal tones) and linguistic (vowel) stimuli in a MMN paradigm among autistic participants whose language levels ranged from nearly absent to concordant with chronological age. They found identical MMN amplitude in both groups for both types of stimuli, indicating that high-functioning autistic children were able to *discriminate* changes in frequency as well as the control group. Similarly, Kemner et al. (1995) presented complex vocal stimuli in an oddball paradigm and found similar MMN amplitude between autistic children (6.8-13 years, IQ 80) and typically developing children. In an MEG oddball paradigm, Oram-Cardy et al. (2005b) found normal MMN amplitude, but with delayed latency, to simple tones and a synthesized vowels sequence among linguistically delayed autistic children. These findings suggest that the complexity and speechness quality of the stimuli does not interfere with the sensory discrimination of the deviant sound. However, delayed syllable-MMN over the right hemisphere, although with greater amplitude, was reported among children with Asperger syndrome (Jansson-Verkasalo et al., 2003). In the analysis of the long-latency P3 components, Ceponiene et al. reported a group effect on the P3a amplitude, with vowels only, indicating that the vowel changes do not catch the attention of autistic participants. The difference in P3a between the autistic and non-autistic groups, indicating the absence of automatic attention for a certain category of stimuli, increased as stimuli increased in complexity since there was: i) no group difference for pure tones, ii) a trend for a group difference for complex tones, and iii) a significant P3a group difference for vowels (Ceponiene et al., 2003).

In an fMRI study, Gervais et al. (2004) reported that autistic participants of normal intelligence failed to activate voice-related areas in the superior temporal sulcus when listening to voice stimuli. This lack of activation of the "voice areas" was interpreted as a showing that autistics "may be unable to process voice stimuli using the selective mechanisms activated by vocal sounds in normal controls" (p. 802). These findings need to be interpreted with caution since the participants were verbal, and therefore, the absence of voice activation cannot indicate a deficit in voice recognition that is anyway not evident in autism (Boucher et al., 2000). Indeed, a tentative replication with four adult autistic participants using a paradigm similar to that of Gervais et al. revealed a typical activation of the STS (Pelletier et al., 2005). The "catch-22" issue in brain-imaging studies on language processing in autism is that, if conducted with non-verbal individuals, differences in activation may be attributed either to the autistic syndrome or to impaired language development and diminished expertise, whereas if conducted with verbal individuals, these differences cannot be used to explain a language deficit. Moreover, the experience gained with conflicting findings on fusiform face area activation during face processing (Jemel et al., this issue) suggests that task dependent interpretations should be carefully examined before concluding that there is a deficit in a localised brain function.

Perception of auditory temporal complexity in autism

There are multiple indications that speech and musical production are not problematic for autistic individuals, even for long sequences of sounds (Applebaum, Egel, Koegel, & Imhoff, 1979; Miller, 1989; Mottron et al., 1999). However, the ability to reproduce a sequence is poorly informative on the level of processing allowing this reproduction. For example, a "chaining" encoding strategy (local by local associations) can allow the same level of performance as the standard perception of their global auditory properties (Happé & Frith, this issue; Mottron, Peretz, & Ménard, 2000;).

The evidence from the initial studies of perception of the holistic auditory properties of sequences of pure tones indicates a similar pattern of performance as in visual hierarchical perception (enhanced local processing, intact global perception, superior disembedding ability). Autistics are superior in the discrimination of the direction of interval changes, even for relatively small (4 semitones) pitch intervals (Heaton, Pring, & Hermelin, 1999). In Mottron et al.'s (2000) study, the local level was defined as the pitch of the individual notes of a short melody and the global level as the pattern of rises and falls in pitch in this melody (contour). Two holistic musical properties, the detection of modification in pitch contour and transposition ability, were found to be unremarkable in high-functioning autistic individuals. However, autistic participants were superior in the detection of local pitch changes, suggesting an enhanced performance in pitch perception at the local level of auditory gestalts. A typical detection of global contour modification was also found by Heaton et al. (1999).

Foxton et al. (2003) investigated the effect of global structure (defined as the combination of contour, and timing) on the processing of pitch changes within sequences of five tones in a study in which participants needed to determine whether a subsequent probe sequence was the same as a standard sequence that was presented earlier. There was no difference between groups of persons with and without autism on conditions in which participants had to discriminate an identical probe from a probe that differed from the standard in contour ("no interference", NOi condition) or in the local pitch of one of the notes ("local pitch interference", LPi condition). In the "local pitch and timing interference" (LPTi) condition, the "same" sequence had the same overall pattern of rise-and-fall (or fall-and-rise) in pitch as the standard sequence, but the actual timing of the change in pitch direction was not the same between the standard and the "same" probe. In this condition there was no significant difference between the groups, although the absolute score of the autistic group was higher than that of the control group. Unlike the autistic group, performance by control participants was worse in the LPTi than in the NOi condition. Foxton and her colleagues interpreted the latter finding as evidence that the autistic listeners were better able to ignore the effects of the interference of global structure in a task that required a match between the general direction of pitch changes. However, the lack of a significant difference between groups in the LPTi condition means that these findings should be interpreted with caution. If replicated, these results would suggest that autistic individuals are able to focus on a simple feature of a sequence of tones (the direction of pitch change) while ignoring a complex combination of contour, absolute pitch and timing.

Perception of combined spectro-temporal complexity

One of the most complex auditory tasks is the recognition of speech in speech-like noise, which combines the spectro-temporal complexity of both signals. Adult highly verbal autistics and individuals with Asperger syndrome did not differ from control listeners in speech recognition when noise was a spectrally modulated speech-like sound, but had inferior speech recognition in the presence of noise with temporal and temporal - spectral dips (Alcantara et al, 2004). If replicated, this finding reveals a difficulty in auditory segregation (figure – ground phenomenon) with speech stimuli.

Aiming to determine the capacity of discrimination of prosody in adults (mean 33 years old) with Asperger Syndrome (AS), Kujala, Lepistö, Nieminen-vonWendt, Näätänen, & Näätänen, (2005) asked eight patients to identify, in a sequence of utterances with an emotional content, an utterance with deviant emotional connotations while their cortical evoked potentials were measured. MMN responses to the deviant connotations was delayed over the right hemisphere in AS compared to the control group (mean 32 years old), possibly reflecting impaired discrimination of prosody in Asperger syndrome.

Another type of spectral and temporal complexity is produced by changes occurring at the level of the phonological structure of human language. The brain activation produced by speech-like dynamic stimuli ("spectral motion") was investigated by Boddaert et al. (2003) in a PET study, in one non-verbal and four verbal autistic adults (average IQ 64). The stimuli consisted of central 200-ms steady-state formant-like spectral peaks surrounded by initial and final changes similar to formant transitions. In non-autistic individuals, these stimuli induced bilateral activation of secondary auditory areas (lateral belt of the auditory cortex). "Spectral motion" has been considered as an auditory equivalent of visual motion (Thivard, Belin, Zilbovicius, Poline, Samson, 2000). Autistic participants displayed a typical activation of the primary auditory cortex, but an atypical right hemispheric dominance in the auditory temporal cortex and a reduced activation of the posterior part of the left middle temporal gyrus, a region that is involved in word processing. The same experiment was replicated with 11 autistic children (IQ 43, 4 verbal; the remaining 7 had possibly no expressive language), compared to a group with higher IQ (64) and possessing possibly a different language experience (Boddaert et al., 2004). Results were comparable to those obtained in adults: the left middle temporal gyrus BA 21 and 39) and the precentral frontal gyrus (BA 43/6) were significantly less activated in autistic children than in non-autistic control children. The interpretation of these data in relation to the distinctive features of autism is unclear until similar data with high-functioning verbal individuals have been obtained.

Lastly, the extreme paucity of brain imaging data available on brain activation during auditory language processing in autism has to be underlined. There is currently no fMRI data on activation produced by auditorily conveyed speech production and reception in autism. One PET study (Müller et al., 1999), conducted with 5 autistic adults showed the typical blood flow increase in the perisylvian cortex when listening to short sentences, but without the leftward inferior frontal and perisylvian asymmetry seen in a comparison group. However, normal activation patterns were observed during speech production.

Conclusion

Perception of visual information by autistics individuals presents a well established dissociation between enhanced detection and discrimination of simple visual elements, locally oriented processing, preserved global processing, and deficits in discrimination of neurally-defined complex (e.g. second order, dynamic) stimuli. This dissociation maps the hierarchical organisation of the visual cortex, with increasingly complex processing following a hierarchical, postero-anterior gradient (Bertone et al, 2005). In the auditory modality, the tonotopic organisation of simple pitch detection, with increasingly large neural networks required for complex spectro-temporal structure, shares similarities with the organisation of the visual cortex. From this similarity, a simple (enhanced) vs. complex (spared or impaired) dissociation within perceptual processes may be predicted in the auditory modality.

To examine the support for this hypothesis, available findings related to the perception of auditory material of increasing complexity (pure tones, spectrally modulated, temporally modulated) and operations (detection, discrimination, evaluation) in autism were reviewed. This review revealed a simple vs. complex within-perception dissociation consistent with this hypothesis. Tasks that combine simple material (pure tones) and low-level operations (detection, labelling) show a superior level of performance. This is the case for spontaneously occurring special abilities in savants (absolute pitch) and empirically observed capacities for non-savants (superior pitch discrimination, shorter detection latency and increased N1c amplitude for single tone detection, and automatic attention to simple tones). Superior pitch processing allows chord disembodying in well-defined, spectrally complex sounds (chords). In contrast, spectrally complex language-like sounds do not yield automatic attention.

For sequences composed of simple sounds (melodies), superior local processing produces an enhanced detection of local changes. In contrast, tasks combining spectrally and temporally dynamic, complex material, with complex operations (e.g. auditory streaming for language) display a deficit. Brain imaging findings showing hypoperfusion in the auditory associative cortex at rest and during the presentation of complex spectral-temporal sounds, may suggest an optional use or a deficit of higher order auditory processing, both consistent with this hypothesis. However, the interpretation of imaging findings is dependent on their replication in high functioning autistic individuals, and the use of comparison groups of similar language expertise.

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Chapitre 3. Stimulus complexity and categorical effects in human auditory cortex: an Activation Likelihood Estimation meta-analysis

Stimulus complexity and categorical effects in human auditory cortex: an Activation Likelihood Estimation meta-analysis

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Abstract

Investigations of the functional organization of human auditory cortex typically examine responses to different sound categories. An alternative approach is to characterize sounds with respect to their amount of variation in the time and frequency domains (i.e. spectral and temporal complexity). Although the vast majority of published studies examine contrasts between discrete sound categories, an alternative complexity-based taxonomy can be evaluated through meta-analysis. In a quantitative meta-analysis of 58 auditory neuroimaging studies, we examined the evidence supporting current models of functional specialization for auditory processing using grouping criteria based on either categories or spectro-temporal complexity. Consistent with current models, analyses based on typical sound categories revealed hierarchical auditory organization and left-lateralized responses to speech sounds, with high speech sensitivity in the left anterior superior temporal cortex. Classification of contrasts based on spectro-temporal complexity, on the other hand, revealed a striking within-hemisphere dissociation in which caudo-lateral temporal regions in auditory cortex showed greater sensitivity to spectral changes, while anterior superior temporal cortical areas were more sensitive to temporal variation, consistent with recent findings in animal models. The meta-analysis thus suggests that spectro-temporal acoustic complexity represents a useful alternative taxonomy to investigate the functional organization of human auditory cortex.

Keywords: fMRI, sound category, time, frequency, hierarchy

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Introduction

Current accounts of the functional organization of auditory cortex, mostly based on response specificity to different sound categories, describe an organizational structure that is both hierarchical and hemispherically specialized (Hackett, 2008; Rauschecker, 1998; Rauschecker & Scott, 2009; Recanzone & Cohen, 2010; Woods & Alain, 2009; Zatorre, Belin, & Penhune, 2002).

Characterizing responses to stimuli from typical auditory categories such as music, voices, animal or environmental sounds have provided important information about the cortical specialization for auditory processing. However, this classification may not fully account for the range of stimulus variability encountered across neuroimaging studies, as most stimuli do not fit neatly into one auditory category. For instance, an amplitude modulated tone can vary in ways that cannot be adequately characterized using typical categories. However, its characteristics can easily be described in terms of variations in time (temporal dimension) and frequency (spectral dimension), suggesting an alternative approach to stimulus classification. Accordingly, any auditory stimulus can be described with respect to its sound complexity characteristics specified with respect to changes in time and frequency. This approach represents a comprehensive characterization of sounds that is not limited to specific categories. Therefore, complexity might represent an alternative organizing principle along which to represent auditory cortical response specialization. In this conceptualization, a single frequency sinusoidal wave (pure tone), constant over time, can be classified as simple, and a sound containing multiple components can be classified as complex with respect to frequency. Examples of sounds with high spectral complexity are musical notes or sustained vowels. Similarly, a sound with acoustical structure varying over time can be classified as complex with respect to the time domain. Examples of stimuli with high temporal complexity are frequency or amplitude modulated sounds or sound sequences. Natural sounds can be complex with regards to both their frequency composition and temporal variation. Phonemes, the basic units of speech, contain multiple frequency components, called formants, which may be combined over time to produce syllables and words. Similarly, musical sequences are composed of complex changes in fundamental frequency and harmonic structure that unfold over time. Additionally, speech processing is mainly dependent on temporal information (Shannon, Zeng, Kamath, Wygonski, & Ekelid, 1995), while spectral composition is most relevant for music perception (Warrier & Zatorre, 2002). Hence, acoustic complexity is not independent of sound categories and the two classification methods explored here should not be considered as mutually exclusive.

As previously proposed, an auditory stimulus can be categorized in more than one way; either based on a priori knowledge about the characterizing features of the sound source or on the basis of a sound's acoustic pattern in the frequency and time domain (Griffiths & Warren, 2004). Additionally, some studies suggest that auditory cortex activation to sounds of a given category could reflect a specialized response to the acoustic components characterizing sounds within this category (Lewis, Brefczynski, Phinney, Janik, & DeYoe, 2005; Lewis, et al., 2009). This suggests a certain level of interaction between the cortical processes involved in the analysis of acoustic features and those showing sensitivity to sound categories. However, recently Leaver and Rauschecker (2010) demonstrated categorical effects of speech and music stimuli even when controlling for changes in spectral and temporal dimensions. The two classification approaches are therefore not mutually exclusive and both methods seem relevant and can complement each other in revealing different aspects of cortical auditory specialization. In vision, cortical representation of stimulus complexity has been described with simple (first-order) information being analyzed within primary visual cortex (V1) and complex (second-order) information processing involving both primary and non-primary visual cortex (V2/V3) (Chubb & Sperling, 1988; Larsson, Landy, & Heeger, 2006). Given that parallels have often been drawn between visual and auditory cortical functional organization (Rauschecker & Tian, 2000), we were interested in examining how well characterization of sounds by their acoustic complexity might reflects new insights into regional functional specialization.

Given that auditory neuroimaging studies exhibit a high degree of stimulus and task heterogeneity, their individual cortical activity patterns are not easily integrated to obtain an unambiguous picture of typical human auditory cortical organization. Neuroimaging meta-analysis offers a potential solution to this problem as it estimates the consistency of regional brain activity across similar stimuli and tasks, providing a quantitative summary of the state of research in a specific cognitive domain (Fox, Parsons, & Lancaster, 1998), estimating the replicability of effects across different scanners, tasks, stimuli and research groups. By revealing consistently activated voxels across a set of experiments, meta-analysis can characterize the cortical response specificity associated with a particular type of task or stimulus (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009). Activation Likelihood Estimation (ALE) is a voxel-wise meta-analysis method that provides a quantitative summary of task-related activity consistency across neuroimaging studies (Turkeltaub, Eden, Jones, & Zeffiro, 2002 .

In the current study, we use quantitative ALE meta-analysis to examine the spatial consistency of human auditory processing, classified using either conventional sound categories or acoustic complexity. Given the focus of our study on stimulus complexity effects, we excluded studies of spatial auditory processes including localization, and inter-aural delay, as well as those including complex tasks.

First, we classified sounds using typical auditory *categories* to examine the evidence supporting hierarchically and hemispherically lateralized functional organization for auditory cortical processing. Hierarchical auditory processing has been described as sensitivity to stimulus complexity increasing from primary to non-primary auditory cortex, with simpler perceptual features represented at primary levels (Hall, et al., 2002; Scott & Johnsrude, 2003; Wessinger, et al., 2001). Relative hemispheric specialization is reflected by predominantly left-hemisphere processing for speech sounds and stronger right-hemisphere responses to music (for a review see Zatorre, Belin, et al., 2002). We used typical sound *categories,* such as pure tones, noise, music and vocal sounds, to classify auditory material to see if simple sound processing is associated with activity in primary auditory cortex while complex sound processing is associated with activity including both primary and non-primary auditory cortex. We were also interested in examining whether there was meta-analytic evidence for distinctive patterns of hemispheric specialization for music, vocal sounds and speech.

Next, we more closely examined vocal stimuli and a particular subcategory of vocal sounds: intelligible speech. Vocalizations constitute an ecologically central sound category that includes all sounds with a vocal quality irrespective of phonetic or lexical content.

Examples include speech in various languages, non-speech affective vocalizations (e.g., laughter), and laboratory-engineered sounds, such as time-reversed speech, that exhibit distinctly vocal qualities. Vocal sounds include, but are not limited to, intelligible speech. Based on previous findings, we expected to observe bilateral superior temporal gyrus (STG) and the superior temporal sulcus (STS) activity related to vocal sounds (Belin, Zatorre, & Ahad, 2002; Belin, Zatorre, Lafaille, Ahad, & Pike, 2000; Kriegstein & Giraud, 2004), and anterior STG and STS activity on the left related to speech intelligibility (Benson, Richardson, Whalen, & Lai, 2006; Uppenkamp, Johnsrude, Norris, Marslen-Wilson, & Patterson, 2006).

Finally, we examined whether *acoustic complexity*, estimated from variations in time (temporal) and frequency (spectral) dimensions, represents a relevant organizing principle for functional response specificity in human auditory cortex. In terms of spectral composition, stimuli can have single or multiple frequency components. In the temporal dimension, stimuli can be characterized as unchanging or, for those containing temporal changes, having either regular or as irregular changes. Using this classification, we characterized the cortical response related to each level of acoustic complexity, including single unchanging, single regular change, or multiple unchanging classes. Then, by comparing the “multiple” to the “single” categories, independent of the temporal changes, and the “changing” to the “unchanging” categories, independent of the frequency composition, we isolated the cortical activity related to variations in the frequency and time dimensions, respectively.

Materials and methods

Inclusion of studies

A preliminary list of articles was identified using several Medline database searches including both articles published prior to March 2010 (keywords: positron emission tomography (PET), functional magnetic resonance imaging (fMRI), auditory, sound, hear*, speech, and music) and lists of citations within those articles. Studies were included if they fulfilled specific inclusion criteria: (1) the study was published in a peer-reviewed journal; (2) the study involved a group of healthy typical adult participants with no history of hearing, psychiatric, neurological or other medical disorders, (3) the subjects were not trained musicians; (4) the auditory stimuli were delivered binaurally, with no inter-aural delay because of our focus on non-spatial auditory processing; (5) the task-related activity coordinates were reported in standardized anatomical space; (6) the study used whole-brain imaging and voxel-wise analysis. As our main goal was to determine the spatial distribution within auditory cortical regions, the few studies using incomplete brain coverage, but that included the temporal cortex were not excluded (Belin, Zatorre, Hoge, Evans, & Pike, 1999; Binder, et al., 2000; Binder, Frost, Hammeke, Rao, & Cox, 1996; Celsis, et al., 1999; Hugdahl, Thomsen, Ersland, Rimol, & Niemi, 2003; Schonwiesner, Rubsamen, & von Cramon, 2005; Stevens, 2004; Zaehle, et al., 2007). Additionally, some studies specifically included subcortical structures (Griffiths, Buchel, Frackowiak, & Patterson, 1998; Hwang, Li, Wu, Chen, & Liu, 2007; Mutschler, et al., 2010) and (7) the study had to include passive listening or a simple response task, such as a button press at the end of each sound to assess the participants' attentive state, task characteristics that tended to minimize the inclusion of activity related to top-down processes or task difficulty (Dehaene-Lambertz, et al., 2005; Dufor, Serniclaes, Sprenger-Charolles, & Demonet, 2007; Sabri, et al., 2008).

Of over 7000 articles retrieved, 58 (19 PET & 39 fMRI) satisfied all inclusion criteria and were included in the analysis (Table 1). Several studies reported activity from multiple task and control conditions. For our analysis, only conditions incorporating either no overt task or a simple task used to maintain attention were considered. To maintain consistency among the control conditions, only task contrasts with a low-level baseline (silence, tone or noise) were included. For some studies, more than one contrast satisfied our criteria and all were included in the analysis. This procedure was employed to maximize the sensitivity of the analysis, but could potentially bias the results towards samples for which more than one contrast was included.

Table 1. Neuroimaging studies included in the meta-analysis

Reference	Table/Figure	Category	Frequency composition	Changes over time	Stimuli of interest	Baseline	Foci
Belin et al., 1998	Table 1, p. 537	--	Multiple	Irregular	Rapid formant transition	Silence	3
		--	Multiple	Irregular	Extended formant transition	Silence	2
Belin et al., 1999	Text, p. 422-423	--	Multiple	Unchanging	Harmonic complex sound	Silence	4
Benson et al., 2001	Table 1, p.372	Music	--	--	Note/Chord/Chord progression	Rest	27
	Table 2, p. 373	Vocal	Multiple	Irregular	Vowel/Consonant-Vowels/Syllables	Rest	24
Binder et al., 1996	Table 1, p. 1244	Vocal	Multiple	Irregular	Words	Tones sequence	1
Binder et al., 2000	Table 2, p. 518	--	Multiple	Regular	Sequence of tones	Noise	11
		Vocal	Multiple	Irregular	Words	Sequence of tones	8
		Vocal	Multiple	Irregular	Pseudowords	Sequence of tones	8
		Vocal	Multiple	Irregular	Reversed words	Sequence of tones	7
Binder et al., 2008	Appendix	Vocal	Multiple	Irregular	Words	Rest	12
		Vocal	Multiple	Irregular	Words	Tones	2
Blood et al., 1999	Table 2, p. 384	Music	--	--	Melodies	Noise	3
		Music	--	--	Melodies	Noise	3
Brown et al., 2004	Table 1, p. 2035	Music	Multiple	Irregular	Music	Rest	21
Burton et al., 2000	Table 2, p. 682	Vocal	Multiple	Irregular	Words	Tone	3
		Vocal	Multiple	Irregular	Words	Tone	6
Burton & Small, 2006	Table 2, p. 647	Vocal	Multiple	Irregular	Words	Tone	4
Celsis et al., 1999	Table 1, p. 138	Tone	Single	Unchanging	Tone	Rest	1
		Tone	Single	Unchanging	Tone	Rest	1
		Vocal	Multiple	Irregular	Syllable	Rest	3
		Tone	Single	Unchanging	Tone	Rest	3
		--	Multiple	Unchanging	Square wave tone	Rest	3
		Vocal	Multiple	Irregular	Syllable	Rest	3
Chen et al., 2008	Table 2, p. 2849	Music	Multiple	Irregular	Musical rhythms	Silence	9

Dalla Barba et al., 1998	Table 1, p. 552	Vocal	Multiple	Irregular	Words	Rest	5
De Nil et al., 2008	Table 2, p.119	Vocal	Multiple	Irregular	Words	Silence	1
Démonet et al., 1992	Table 4, p. 1758	Vocal	Multiple	Irregular	Phonemes (3 or 4 syllables non words)	Tones	7
		Vocal	Multiple	Irregular	Words	Tones	14
Engelien et al., 2006	Table 1, p. 603	--	Multiple	Irregular	Meaningful non-verbal sounds	Rest	8
		--	Multiple	Irregular	Meaningless non-verbal sounds	Rest	14
Fernandes et al., 2008	Table 2, p.887	Vocal	Multiple	Irregular	Narrative sentences	Silence	2
Gaab et al., 2007a	Table 1, p. 710	Vocal	Multiple	Irregular	Words	Silence	7
		Vocal	Multiple	Irregular	Words	Silence	9
Gaab et al., 2007b	Table 1, p. 727	Vocal	Multiple	Irregular	Words	Silence	5
		--	Multiple	Irregular	Recorded scanner noise	Silence	2
Giraud et al., 2004	Table 1, p 250	Vocal	--	--	Speech (sentences)	Temporally matched complex noise	5
Griffiths et al., 1998	Table 1, p. 424	Music	--	--	Melodies	Sequence of tones	4
Hall et al., 2000	Table 1, p. 114	--	Single	Regular	Amplitude and frequency modulated tone	Static tone	2
Hall et al., 2002	Table 2, p. 144	--	Multiple	Unchanging	Harmonic complex tone	Single tone	5
		--	Single	Regular	Frequency modulated tone	Static tone	10
Hart et al., 2003	Text, p. 778	--	Single	Regular	Amplitude and frequency modulated tone	Unmodulated tone	2
Hart et al., 2004	Table 1, p. 182	Tone	Single	Unchanging	Tone	Silence	4
		--	Single	Regular	Frequency modulated tone	Silence	6
Hertrich et al., 2010	Table S1	Vocal	Multiple	Irregular	Syllables	Silence	10
		--	Single	Regular	Single formants sweep	Silence	8
Hugdahl et al., 2003	Table 3, p. 43	Vocal	Multiple	Irregular	Vowel	Silence	4
	Table 4, p. 43	Vocal	Multiple	Irregular	Pseudowords	Silence	3
	Table 5, P. 43	Vocal	Multiple	Irregular	Words	Silence	2
Hwang et al., 2007	Table2, p.289	Vocal	Multiple	Irregular	Sentences	Quiet	7
Jäncke et al., 1998	Table 1, p. 878	Vocal	Multiple	Irregular	Syllables	Silence	9
		Vocal	Multiple	Irregular	Syllables	Silence	9

		Vocal	Multiple	Irregular	Syllables	Silence	9
	Table 2, p.878	--	Multiple	Regular	Tone sequence	Silence	4
		--	Multiple	Regular	Tone sequence	Silence	6
		--	Multiple	Regular	Tone sequence	Silence	6
Lillywhite et al., 2010	Table 1, p. 875	Vocal	Multiple	Irregular	Story listening	White noise	2
Müller et al., 1999	Table 3, p.24	--	Multiple	Regular	Sequence of tones	Rest	6
		Vocal	Multiple	Irregular	Sentences	Rest	5
Mummery et al., 1999	Table 1, p. 452	Vocal	--	--	Speech (words)	Signal correlated noise	7
Mutschler et al., 2010	Supp. Material	Music	Multiple	Irregular	Melodies	Rest	94
O'Learly et al., 1996	Table 2, p. 27	Vocal	Multiple	Irregular	Words	Tone	2
		--	Multiple	Irregular	Environmental sounds	Tone	2
Obleser et al., 2006	Table 2, p.566	Vocal	Multiple	Irregular	Vowel	Band-pass noise	4
Paulesu et al., 1995	Table 2, p. 667	Vocal	Multiple	Irregular	Words	Tones	5
Peretz et al., 2009	Table 1, p.263	Music	--	--	Melodies	Random tone sequence	8
Petersen et al., 1988	Table 2, p. 585	Vocal	Multiple	Irregular	Words	Silence (fixation point)	6
Price et al., 1992	Figure 1, p. 180	Vocal	Multiple	Irregular	Nouns	Rest	6
Reynolds et al., 2009	Table 1, p.374	Vocal	Multiple	Irregular	Story listening	Rest	3
Rimol et al., 2005	Table 1, p. 1063	Vocal	Multiple	Irregular	Consonant	Rest	8
		Vocal	Multiple	Irregular	Syllables	Rest	6
		Noise	Multiple	Unchanging	Noise (white, brown, pink)	Rest	12
		Noise	Multiple	Unchanging	Noise (white, brown, pink)	Rest	8
	Table 2, p. 1064	Vocal	Multiple	Irregular	Consonant	Noise	1
		Vocal	Multiple	Irregular	Syllable	Noise	3
Schwarzbauer et al., 2006	Table 1, p. 779	Vocal	--	--	Sentences	Signal correlated noise	12
		Vocal	--	--	Sentences	Signal correlated noise	6
Schönwiesner et al., 2005	Text, p. 1523-25	--	Single	Regular	Parametric increase in temporal rate change	Silence	2
		--	Multiple	Unchanging	Parametric increase in spectral components	Silence	2
Specht & Reul, 2003	Table 1, p.1950	Tone	Single	Unchanging	Tones	Rest	5

		--	Multiple	Irregular	Sounds of animal and instruments	Rest	9
		Vocal	Multiple	Irregular	Words	Rest	18
	Table 2, p.1951	--	Multiple	Irregular	Sounds of animal and instruments	Tones	7
		Vocal	Multiple	Irregular	Words	Tones	12
Steinbrink et al., 2009	Table 1, p.2406	Vocal	Multiple	Irregular	Increase rate of syllable presentation	Silence	7
		--	Multiple	Regular	Increase rate of click sequence	Silence	8
Stevens, 2004	Table 1, p.166	Vocal	Multiple	Irregular	Voice	Tone	13
		Vocal	Multiple	Irregular	Words	Tone	5
Thivard, et al., 2000	Table 1, p.2971	--	Multiple	Unchanging	Static complex sound	Silence	6
		--	Multiple	Irregular	Complex sound modulated (motion)	Silence	6
		--	Single	Irregular	Complex sound modulated (motion)	Static complex sound	4
Vouloumanos et al., 2001	Table 1, p.998	Vocal	Multiple	Irregular	Words	Tones	8
		--	Multiple	Irregular	Non speech complex sinewave sounds	Tones	5
Warren & Griffiths, 2003	Table 1, p.5802	Music	--	--	Changing pitch sequences	Fixed pitch sequences	4
Warrier et al., 2009	Table 2, p.65	--	Single	Regular	Parametric increase in temporal rate change	Silence	6
		--	Multiple	Unchanging	Parametric increase in spectral components	Silence	6
Wise et al., 1991	Table 2, p.1808	Vocal	Multiple	Irregular	Nouns	Rest	6
Zaehle et al., 2007	Table 1, p. 1201	Vocal	Multiple	Irregular	Sentences	Silence	2
		Vocal	Multiple	Irregular	Sentences	Silence	2
		Tone	Single	Unchanging	Tones	Silence	2
		Tone	Single	Unchanging	Tones	Silence	2
		Vocal	Multiple	Irregular	Sentences	Tones	2
		Vocal	Multiple	Irregular	Sentences	Tones	2
	Table 2, p. 1201	Vocal	Multiple	Irregular	Sentences	Silence	2
		Vocal	Multiple	Irregular	Sentences	Silence	2
		Tone	Single	Unchanging	Tones	Silence	2
		Tone	Single	Unchanging	Tones	Silence	2
		Vocal	Multiple	Irregular	Sentences	Tones	2

		Vocal	Multiple	Irregular	Sentences	Tones	2
Zatorre et al., 1992	Table 2, p.847	Noise	Multiple	Unchanging	White noise bursts	Silence	8
		Vocal	Multiple	Irregular	Syllables	Noise	6
Zatorre et al., 1994	Table 2, p.1911	Music	--	--	Melodies	Noise	2
Zatorre et al., 1996	Table 6, p. 26	Vocal	Multiple	Irregular	Syllables	Noise	6
Zatorre et al., 2002	Table 1, p. 907	Noise	Multiple	Irregular	Noise (reversed environmental sounds)	Silence	3
Zatorre & Belin, 2001	Table 1, p. 948	--	Single	Regular	Tone sequence with increasing rate of presentation	Silence	2
		--	Multiple	Unchanging	Tone sequence with increasing number of spectral elements	Silence	3
Zevin & McCandliss, 2005	Table 1	Vocal	Multiple	Irregular	Syllables	Silence	8

Contrast classification procedure

One hundred seventeen contrasts, including 768 foci, met the inclusion criteria. These contrasts were classified first by typical sound *categories* and then according to their variation along either the frequency or time dimension (Table 1).

For the first method, each contrast was classified with respect to one of the typical sound categories: simple sounds or pure tones (9 contrasts, 22 foci), noise (4 contrasts, 31 foci), music (10 contrasts, 175 foci) and vocal sounds (62 contrasts, 370 foci). The pure tones category included only contrasts of single tones versus silence; the noise category included white, pink and brown noise (Rimol, Specht, Weis, Savoy, & Hugdahl, 2005), noise bursts (Zatorre, Evans, Meyer, & Gjedde, 1992) and the combination of multiple reversed environmental sounds (Zatorre, Bouffard, Ahad, & Belin, 2002). Melodies, notes, chords and chord progressions were classified as music. Finally, all sounds with a vocal quality (syllables, words, voices, reversed words, or pseudowords) were included in the vocal sounds category. Ideally, we would have included other commonly used sound categories such as animal or environmental sounds; however the number of contrasts falling into these categories was not sufficient for quantitative meta-analysis, with only one contrast presenting environmental sounds and only two falling into the animal sound category. The remaining contrasts (30/118) were not included in this analysis because they did not neatly fit into one sound category, including modulated tones, frequency sweep, harmonic tone, or recorded scanner noise.

For the second method, we classified the stimuli with respect to their acoustic features. Two levels of complexity were defined using the frequency dimension (single and multiple frequency components) and three levels in the time domain (unchanging, regular periodic change or irregular change). Therefore, task contrasts were classified in one of six complexity levels depending on their frequency- and time-related acoustic features (Table 1 & Figure 5A): (1) ‘single, unchanging’ (single tone; 9 contrasts, 22 foci), (2) ‘single, regular change’ (frequency or amplitude modulated tone, single formant frequency sweep, parametric variation of modulation rate or rate of presentation; 8 contrasts, 38 foci), (3) ‘single, irregular change’ (1 contrast, 4 foci)), (4) ‘multiple, unchanging’ (harmonic tone, square wave tone, vowel, noise, or parametrically increasing spectral component numbers; 10 contrasts, 57 foci), (5) ‘multiple, regular change’ (tone sequences and increasing click rate sequences; 6 contrasts, 41 foci) or (6) ‘multiple, irregular change’ (vocal sounds, music, or environmental sounds; 70 contrasts, 517 foci). Each task contrast was classified using the stimulus description in the study methods section. Contrasts resulting from covariate effects of a parameter of interest were classified according to parameter complexity. For instance, effects related to parametric increases in temporal modulation rate were assigned to the ‘single, regular change’ complexity level (Schonwiesner, et al., 2005). Ambiguous contrasts were excluded from analysis. For example, we did not classify contrasts that used comparison stimuli that had acoustic complexity comparable to the stimuli of interest (Blood, Zatorre, Bermudez, & Evans, 1999; Giraud, et al., 2004; Griffiths, et al., 1998; Mummery, Ashburner, Scott, & Wise, 1999; Peretz, et al., 2009; Schwarzbauer, Davis, Rodd, & Johnsrude, 2006; Warren & Griffiths, 2003; Zatorre, Evans, & Meyer, 1994) nor those using stimuli that could be assigned to more than one complexity level, such as notes, chords, or chord progressions (i.e stimuli including note/chord/chord progression Benson, et al., 2001).

ALE meta-analysis

After the task-related activity maxima were classified, Activation Likelihood Estimate (ALE) maps (Turkeltaub, et al., 2002) were computed using GingerALE 1.1 (Laird, et al., 2005). Coordinates reported in MNI space were converted to Talairach space using the Lancaster transform icbm2tal (Lancaster, et al., 2007). ALE models uncertainty in localization of each activation focus as a Gaussian probability distribution, yielding a statistical map in which each voxel value represents an estimate of the likelihood of activity at that location, utilizing a fixed effects model for which inferences should be limited to the studies under examination. Critical thresholds for the ALE maps were determined using a Monte Carlo style permutation analysis of sets of randomly distributed foci. A FWHM of 10 mm was selected for the estimated Gaussian probability distributions. Critical thresholds were determined using 5,000 permutations, corrected for multiple comparisons ($p < 0.01$

False Discovery Rate (FDR) Laird, et al., 2005) with a cluster extent of greater than 250 mm^3. In order to present results in the format most commonly used in the current literature, the ALE coordinate results were transformed into MNI standard space using the Lancaster transform (Lancaster, et al., 2007), while ALE maps were transformed by applying spatial normalization parameters obtained from mapping from Talairach to MNI space.

Analysis using classification by typical auditory categories

First, ALE maps were computed for each of the four typical auditory categories: pure tones, noise, music and vocal sounds. Each resulting map shows regions exhibiting consistent activity across studies for each sound category. For example, the 'music' map shows the voxel-wise probability of activity for all 'musical stimuli vs. baseline' contrasts.

Next, we examined hemispheric specialization effects by directly comparing the 'music' and 'vocal' sound categories. We directly compared a random subsample of the 'vocal' sounds category (20 contrasts, 156 foci) to the 'music' category (10 contrasts, 175 foci). This procedure ensured that the resulting ALE maps would reflect activity differences between studies rather than the imbalance in coordinate numbers between those categories (Laird, et al., 2005). Then, as lateralization effects are reported for intelligible speech rather than vocal sounds, only contrasts using intelligible speech with semantic content, such as words or sentences, were included. The 'music' and the 'speech' categories were directly compared to investigate the expected lateralization effects. Given that many contrasts fell into the intelligible speech category, we selected only one contrast per study, including a total of 27 contrasts (166 foci).

Finally, we assessed cortical auditory specialization for processing intelligible speech. Given that specialized auditory processes can be more easily isolated when the contrasting stimuli are as close as possible to the stimuli of interest in terms of acoustic complexity (Binder, et al., 2000; Uppenkamp, et al., 2006), contrasts containing unintelligible spectrally and temporally complex sounds were used as for comparison. Thirteen contrasts (76 foci) selected included reversed words, pseudowords, recorded scanner noise, single formant, environmental sounds, and modulated complex sounds. We directly compared the intelligible speech and complex non-speech sound categories.

Analysis using classification by auditory complexity

To investigate the relevance of acoustic complexity as a stimulus property predicting functional auditory specialization, we computed ALE maps for each level of complexity. Given that only one contrast fell into the 'single, irregular change' dimension, this analysis was not conducted. Moreover, as most of the contrasts were classified as 'multiple frequencies, irregular modulation', (70 contrasts, 517 foci) a randomly selected subsample of 10 contrasts (70 foci) were selected from this level of complexity to facilitate comparison of activity extent between levels.

Next, we examined effects related to auditory complexity. For the frequency domain, all contrasts falling in the 'multiple' level (26 contrasts, 168 foci) were directly compared to those in the 'single' level (18 contrasts, 64 foci), independent of their variation over time, (Figure 5A, bottom row vs. top row, green arrow). For the time dimension, comparisons were made between the contrasts including stimulus changes over time (regular and irregular; 25 experiments, 153 foci) and those who did not (unchanging; 19 contrasts, 79 foci), independent of their frequency composition (Figure 5A, middle and right column vs. left column, blue arrow).

Results

Stimulus Classification Using Typical Auditory Categories

We observed different patterns of activity corresponding to the typical sound categories of pure tones, noise, music and vocal sounds (Figure 1 and Table 2). For all the categories, the strongest effects were found in auditory cortex (Brodmann areas 41, 42 and 22). For the pure tone map, high ALE values were found bilaterally in medial Heschl's gyri (HG). The noise map revealed effects in right medial HG and bilaterally in STG posterior and lateral to HG. Effects related to music were seen in HG, anterior and posterior STG. Finally, vocal sounds elicited large bilateral clusters of activity in HG as well as anterior, posterior and lateral aspects of the STG. While pure tone effects were restricted to auditory cortex, effects outside temporal cortex were observed for the other categories. Additional activity was seen in frontal cortex for noise (BA 6, 9), music (BA 4, 6, 44, 45, 46), and vocal sounds (BA 45). Effects were observed in cerebellum for noise and music as well as in the anterior cingulate gyrus for vocal sounds.

Table 2. Category classification. MNI coordinates of the locations of significant ALE maxima for each sound category ($p < 0.01$, k= 250 voxels)

Region			Coordinates				
		BA	x	y	z	Volume (mm^3)	ALE ($X10^{-3}$)
Pure tones							
Temporal	Heschl's gyrus	41	53	-17	1	3864	26.00
	Heschl's gyrus	41	-51	-20	1	2600	16.85
Noise							
Temporal	Superior temporal gyrus	22	68	-23	5	1544	12.98
	Superior temporal gyrus	42	-50	-29	15	1384	15.58
	Superior temporal gyrus	22	51	-24	-1	648	11.30
Frontal	Precentral gyrus	9	-46	12	38	664	8.67
	Superior frontal gyrus	6	13	14	57	552	11.36
	Inferior frontal gyrus	9	45	14	20	496	10.28
Sub cortical	Cerebellum		33	-65	-28	360	7.83
Music							
Temporal lobe	Superior temporal gyrus	22	53	-11	2	6744	21.07
	Superior temporal gyrus	22	-51	-12	-7	4848	28.52
	Superior temporal gyrus	22	55	12	-9	1096	18.21
	Superior temporal gyrus	22	-49	3	-13	256	11.58
Frontal lobe	Inferior frontal gyrus	45	51	34	18	1264	14.91
	Inferior frontal gyrus	45	-42	24	12	1240	14.04
	Precentral gyrus	44	-57	17	4	360	12.41
	Medial frontal gyrus	6	-2	-3	67	352	14.39
	Precentral gyrus	4	54	-2	51	280	12.31
Sub cortical	Cerebellum		-31	-62	-20	912	14.10
Vocal sounds							
Temporal	Superior temporal gyrus	22	-59	-12	-5	22648	134.64
	Superior temporal gyrus	22	62	-13	-4	18088	101.69
Frontal	Inferior frontal gyrus	45	-48	17	26	2112	21.16
Limbic	Cingulate gyrus	24	-5	13	46	584	18.72

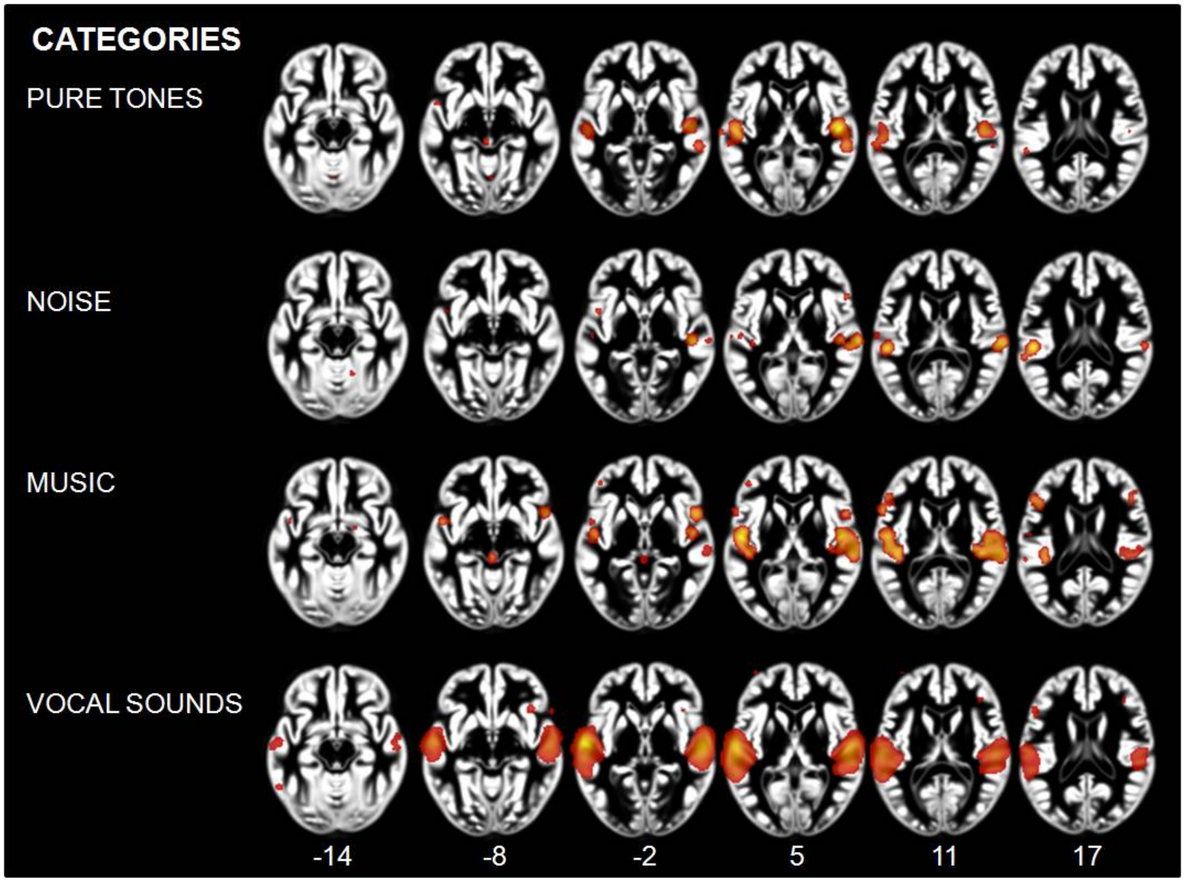


Figure 1. ALE maps showing clusters of activity related to sound categories: pure tones, noise, music and vocal sounds. Maps are superimposed on an anatomical template in MNI space. Axial images are shown using the neurological convention with MNI z-coordinate labels ($p_{FDR} < 0.01$)

Effects related to typical sound categories were lateralized. Qualitative examination revealed larger clusters in right auditory cortex for music and in left auditory cortex for vocal sounds (Table 2). The direct comparisons between the musical and vocal sounds and between the musical and speech sounds yielded similar findings (Figure 2 and Table 3). Greater activity related to music was observed bilaterally in posterior and anterolateral HG, the planum polare and the most anterior parts of the right STG. We also observed effects related to music processing outside the temporal lobe, in inferior frontal gyrus (BA 45), the middle frontal gyrus (BA 6) and the left cerebellum (lobule IV). On the other hand, the reverse comparisons revealed stronger activity for vocal sounds as well as for speech in lateral HG, extending to lateral and anterior STG. For the vocal sounds, the extent of auditory activity was greater on the left (10,312 voxels) than on the right (4,952 voxels), however the ALE values were similar on the left (45.66×10^{-3}) and on the right (42.24×10^{-3}). As for the speech sounds, both the volume of activity and the corresponding ALE were greater on the left (11,112 voxels, 61.39×10^{-3}) than the right (5,736 voxels, 38.21×10^{-3}) hemisphere.

Table 3. Lateralization effects. MNI coordinates of the locations of significant ALE maxima resulting from the comparison between speech and music ($p < 0.01$, k= 250 voxels)

Region		BA	Coordinates x	y	z	Volume (mm^3)	ALE (X10^{-3})
Music > Voices							
Temporal	Heschl's gyrus	41	-49	-11	4	920	22.64
	Heschl's gyrus	41	-40	-30	10	800	15.25
	Heschl's gyrus	41	51	-9	0	680	17.15
	Superior temporal gyrus	22	53	12	-9	584	16.18
	Heschl's gyrus	41	42	-27	11	336	13.18
Frontal	Inferior frontal gyrus	45	51	34	18	776	14.75
	Inferior frontal gyrus	45	-40	27	14	384	13.00
	Midle frontal gyrus	6	-2	-3	67	376	14.39
Subcortical	Cerebellum		-31	-65	-20	392	13.04
Voices> Music							
Temporal	Superior temporal gyrus	22	-59	-10	-5	10312	45.66
	Superior temporal gyrus	22	59	-19	-1	4952	42.24
	Middle frontal gyrus	9	-48	19	26	1032	17.67
Music > Speech							
Temporal	Superior temporal gyrus	22	55	12	-9	728	17.31
	Heschl's gyrus	41	-49	-9	4	696	20.77
	Heschl's gyrus	41	-38	-28	8	480	12.75
	Heschl's gyrus	41	51	-9	2	408	14.44
	Heschl's gyrus	41	45	-27	11	336	15.08
Frontal	Inferior frontal gyrus	45	-40	27	14	1048	13.32
	Inferior frontal gyrus	45	51	34	18	560	14.37
	Middle frontal gyrus	6	-2	-5	68	304	14.33
Subcortical	Cerebellum		-31	-62	-20	728	14.09
Speech > Music							
Temporal	Superior temporal gyrus	22	-59	-12	-5	11112	61.39
	Superior temporal gyrus	22	62	-13	-4	5736	38.21
Frontal	Medial frontal gyrus	8	-16	37	37	336	14.13

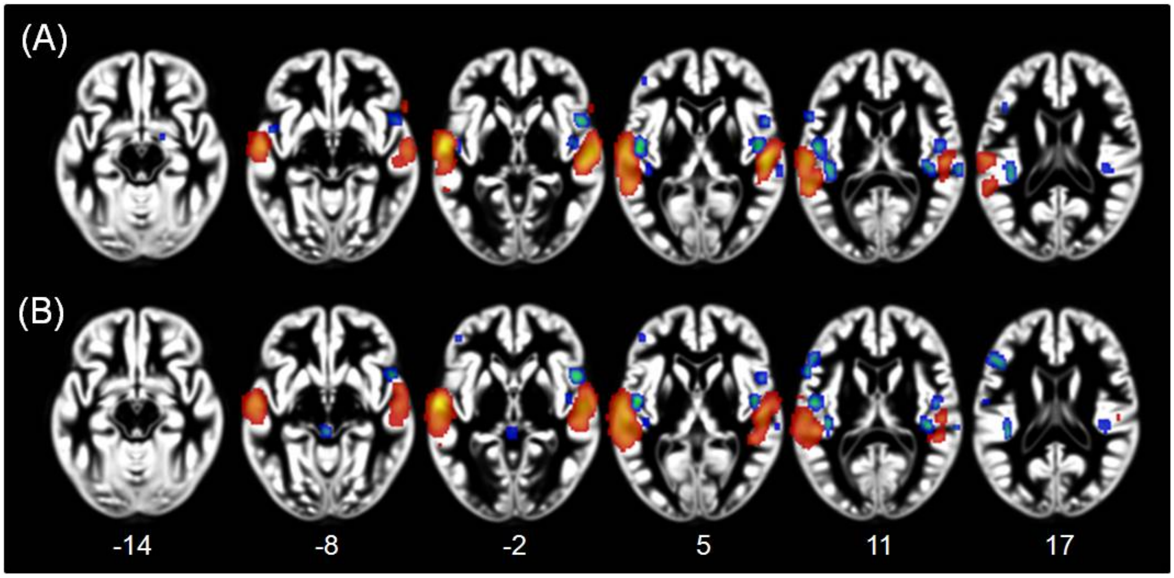


Figure 2. ALE maps showing lateralization effects for voices > music (RED-YELLOW) and music > voices (BLUE-GREEN) comparisons (A) and for speech > music (RED-YELLOW) and music > speech (BLUE-GREEN) comparisons (B). Maps are superimposed on an anatomical template in MNI space. Axial images are shown using the neurological convention with MNI z-coordinate labels ($p_{FDR} < 0.01$)

We observed specialization for speech processing in auditory cortex. The comparison between intelligible speech and complex non-speech sounds, including vocal sounds without intelligible content, is shown in Table 4 and Figure 3A. Speech was associated with greater activity in non-primary (BA 22) and associative (BA 39) auditory areas, lateral STG, bilateral anterior and middle STS, and the planum temporale (PT). These clusters were larger and had higher ALE values in the left hemisphere. We also observed stronger left prefrontal cortical activity (BA 8) for speech sounds. The reverse comparison yielded stronger activity related to complex non-speech sounds in the right PT (x = 68, y = -27, z = 8, 128 voxels; Figure 3A). The ALE maps associated with speech intelligibility had overlap with the vocal sound category maps (Figure 3B). While large bilateral clusters were observed along the STG and STS for the vocal sounds, there was specific sensitivity to speech intelligibility in the left anterior STG.

Table 4. Functional specialization for speech sounds. MNI coordinates of the locations of significant ALE maxima resulting from the comparison between speech and complex non speech contrasts ($p < 0.01$, k= 250 vx).

Region			Coordinates				
		BA	x	y	z	Volume (mm^3)	ALE (X10^{-3})
Intelligible speech > Complex non speech							
Temporal	Superior temporal gyrus	22	-59	-10	-5	8760	39.48
	Superior temporal gyrus	22	59	-11	-5	4416	28.91
	Superior temporal gyrus	39	-48	-53	37	272	13.40
Frontal	Medial frontal gyrus	8	-16	37	37	424	14.21
Complex non speech > Intelligible speech							
	No suprathreshold voxels						

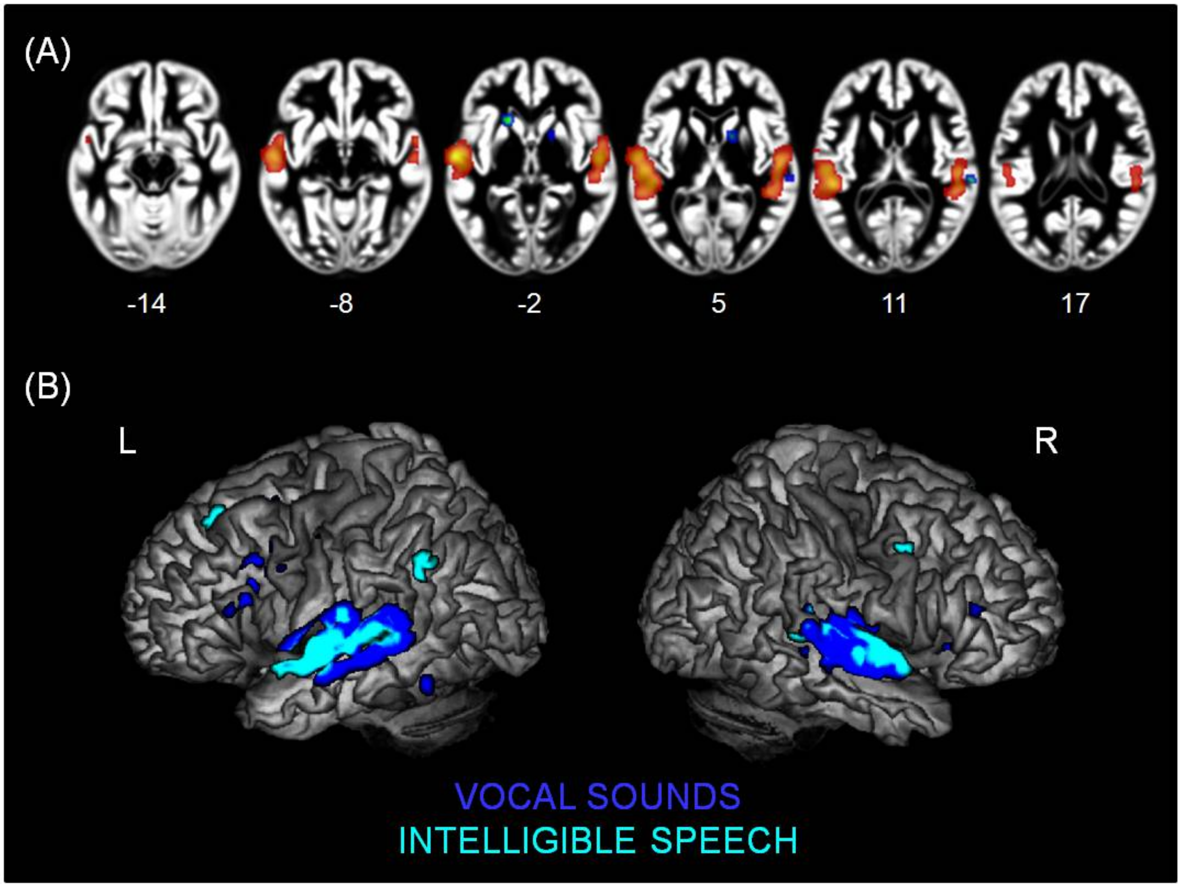


Figure 3. ALE maps showing clusters of activity related to (A) intelligible speech > complex non-speech sounds (RED-YELLOW) and to intelligible speech < complex non-speech (BLUE-GREEN). Axial images are shown using the neurological convention with MNI z-coordinate labels. (B) Rendering of ALE maps related to vocal sound category (dark blue) and to speech intelligibility (pale blue). The maps are superimposed on anatomical templates in MNI space. ($p_{FDR} < 0.01$)

Stimulus Classification Using Auditory Complexity

Classification of sounds with respect to their spectral and temporal complexity revealed effects in the temporal lobe (Table 5 and Figure 4). The ‘single, unchanging’ stimulus class was associated with two clusters centered on medial HG (BA 41). The ‘single, regular change’ stimulus class was associated with two large bilateral clusters of activity in medial and lateral HG, extending around HG into the anterolateral STG. On the left, we observed one additional peak of activity in posterior STG. For the ‘multiple, unchanging’ stimulus class, temporal lobe activity was centered on medial HG and posterior STG. Effects for the ‘multiple, regular change’ stimulus class were observed in HG, extending to the posterolateral STG. Finally, the ‘multiple, irregular change’ stimulus class was associated with large bilateral effects in, and posterior to, HG. The complexity level maps revealed effects outside the temporal lobe, in frontal cortex areas BA 6, 9, 36, and 47 for the ‘multiple, unchanging and ‘multiple, regular change’ stimulus classes. We also observed effects in the cerebellum for the ‘single, regular change’ and ‘multiple, irregular change’ stimulus classes.

Effects related to stimulus spectral and temporal variations were identified by comparing, respectively, the multiple to the single stimulus classes (independent of changes over time; Figure 5B GREEN) and the changing to the unchanging stimulus classes (independent of the number of frequency components; Figure 5B BLUE). The coordinates of the effects related to increasing auditory complexity are reported in Table 5. Overlapping sensitivity to spectral and temporal effects was observed in the lateral portion of HG. Increasing numbers of frequency components were associated with greater effects in posterior and lateral non-primary auditory fields, specifically bilateral posterolateral STG and PT. Modulatory effects were also seen in inferior frontal gyrus (BA 45, 47). In contrast, the effects related to temporal modulations compared to their absence were observed in HG, anterior STG, anterior STS, inferior frontal cortex (BA 46, 47) and right cerebellum (lobule IV).

Table 5. Complexity classification. MNI coordinates of the locations of significant ALE maxima for each level of acoustic complexity and comparison ($p < 0.01$, k= 250 voxels)

Region		BA	Coordinates			Volume	ALE
			x	y	z	(mm^3)	($X10^{-3}$)
Complexity levels							
Single unchanging							
Temporal	Heschl's gyrus	41	53	-17	1	3880	26.00
	Heschl's gyrus	41	-51	-18	0	2488	16.85
Single regular change							
Temporal	Superior temporal gyrus	22	57	-11	2	7448	35.23
	Superior temporal gyrus	22	-55	-15	5	5160	24.64
	Superior temp. sulcus	21	-66	-43	5	600	12.27
Sub cortical	Cerebellum		25	-62	-21	304	7.98
Multiple unchanging							
Temporal	Heschl's gyrus	41	-40	-27	10	7240	18.91
	Heschl's gyrus	41	53	-21	1	6104	17.69
Frontal	Inferior frontal gyrus	9	-46	12	38	480	8.67
	Superior frontal gyrus	6	13	14	57	448	11.36
	Inferior frontal gyrus	9	45	15	20	408	10.28
Multiple regular change							
Temporal	Superior temporal gyrus	42	66	-21	5	6256	22.56
	Superior temporal gyrus	42	-59	-21	12	6096	21.90
Frontal	Inferior frontal gyrus	46	62	35	7	848	15.86
	Inferior frontal gyrus	47	-42	27	-4	688	12.63
Multiple irregular change							
Temporal	Superior temporal gyrus	22	57	-19	1	8344	24.12
	Superior temp. sulcus	22	-57	-14	-2	6040	23.61
Subcortical	Cerebellum		18	-58	-24	672	12.44
			-31	-64	-18	552	10.27
Comparisons between complexity levels							
Multiple > Single							
Temporal	Superior temporal gyrus	22	-59	-23	10	7920	33.16
	Superior temporal gyrus	22	68	-21	5	7760	42.48
Frontal	Inferior frontal gyrus	46	62	35	7	440	15.86
	Inferior frontal gyrus	47	-42	27	-4	320	13.50
Subcortical	Cerebellum		29	-56	-27	840	14.98
Changing > Unchanging							
Temporal	Superior temporal gyrus	22	62	-13	0	9680	34.68
	Superior temporal gyrus	22	-57	-9	-3	5872	33.42
	Superior temp. sulcus	22	-66	-43	5	632	16.15
Frontal	Inferior frontal gyrus	46	62	35	7	472	15.85
	Inferior frontal gyrus	47	-42	27	-4	368	13.50
Subcortical	Cerebellum		23	-58	-24	968	17.21

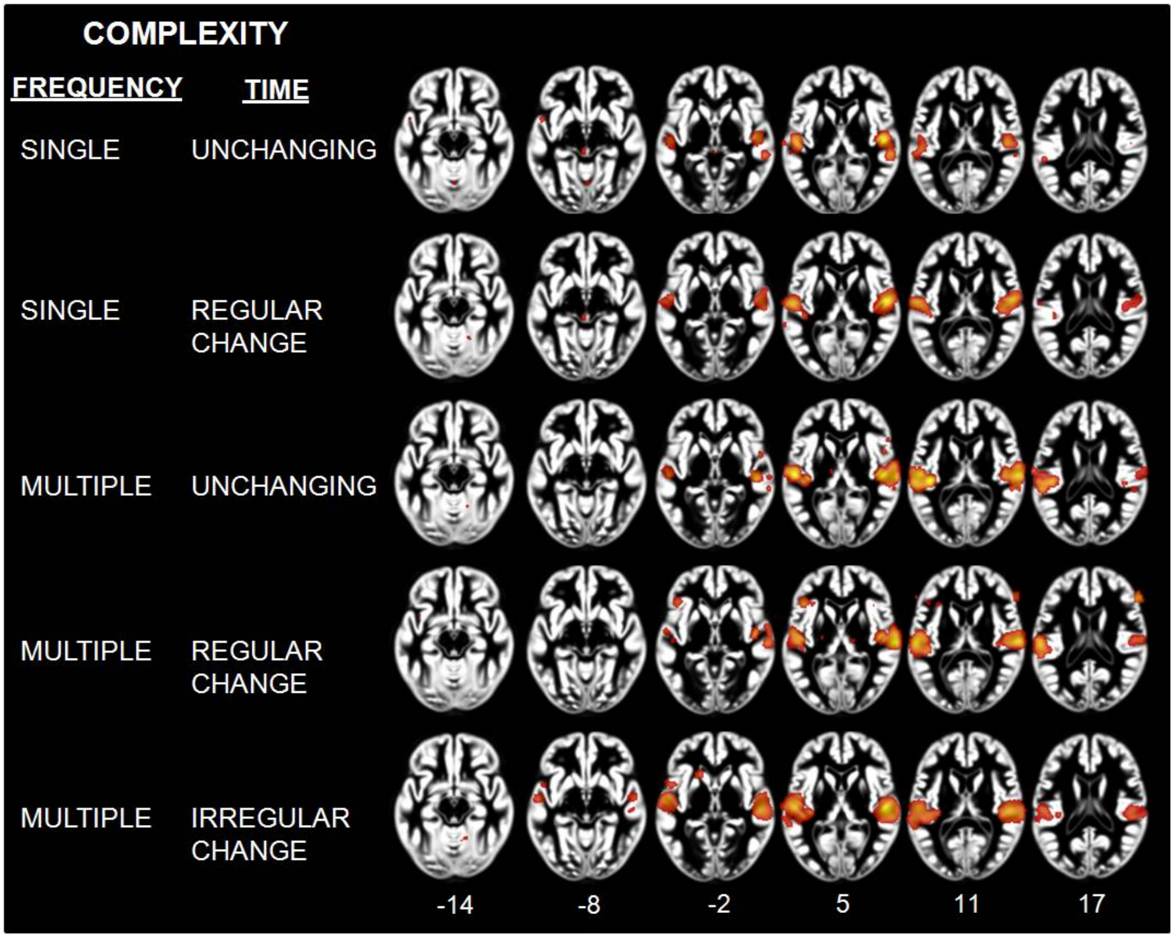
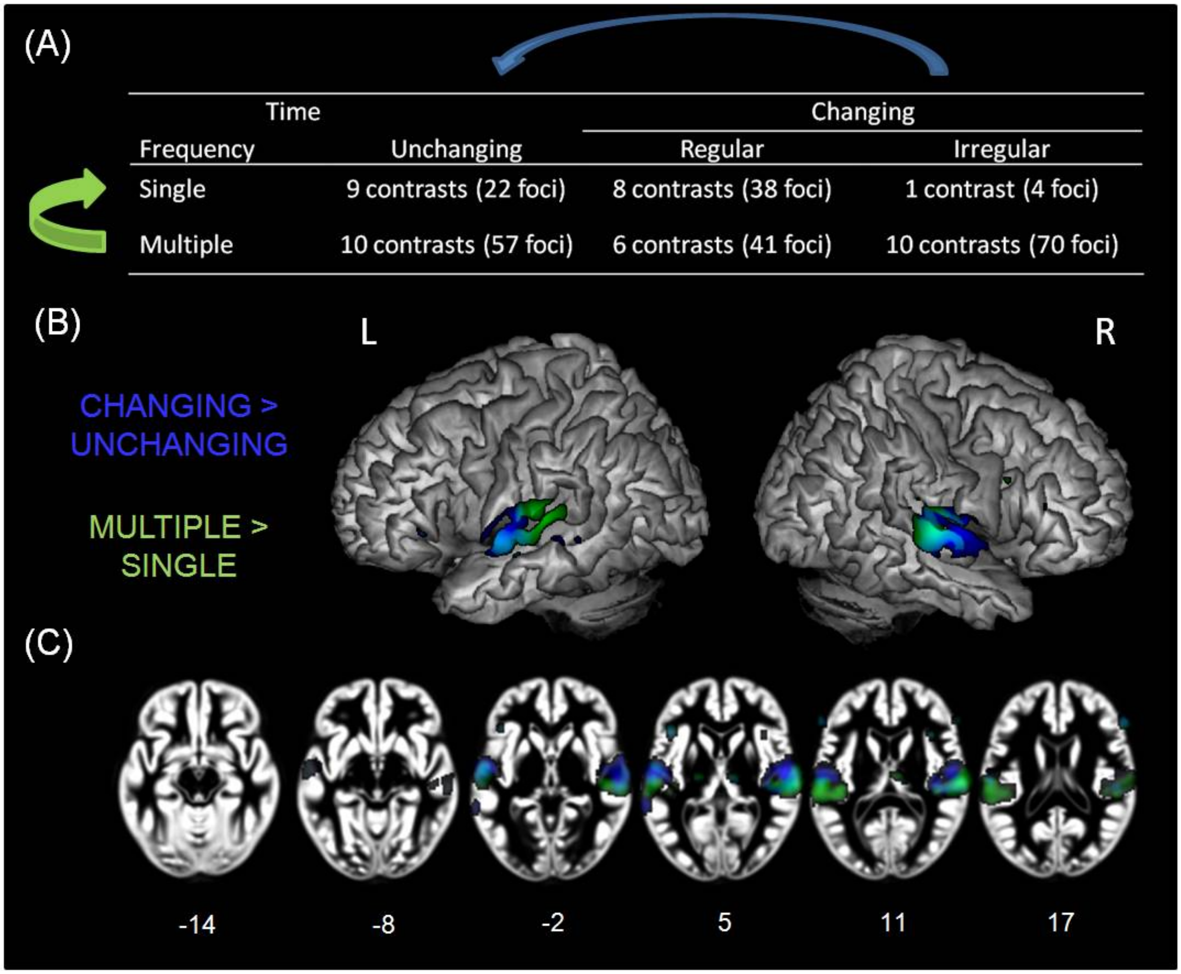


Figure 4. ALE maps showing effects related to each level of complexity: Single unchanging, single regular change, multiple unchanging, multiple regular change and Multiple irregular change. Maps are superimposed on an anatomical template in MNI space. Axial images are shown using the neurological convention with MNI z-coordinate labels ($p_{FDR} < 0.01$)



Time		Changing	
Frequency	Unchanging	Regular	Irregular
Single	9 contrasts (22 foci)	8 contrasts (38 foci)	1 contrast (4 foci)
Multiple	10 contrasts (57 foci)	6 contrasts (41 foci)	10 contrasts (70 foci)

Figure 5. Table of complexity levels and corresponding number of contrasts (A). Rendering (B) and axial overlay (C) of the ALE maps reflecting the effects related to frequency (GREEN) and time (BLUE) complexity axis. Maps are superimposed on an anatomical template in MNI space. Axial images are shown using the neurological convention with MNI z-coordinate labels ($p_{FDR} < 0.01$)

Discussion

Summary of findings

In a quantitative meta-analysis of 59 neuroimaging studies, we examined the functional specialization of human auditory cortex using two different strategies for classifying sounds. The first strategy employed typical categories, such as pure tones, noise, music and vocal sounds. The second strategy categorized sounds according to their acoustical (spectral and temporal) complexity.

ALE maps computed for each typical sound category included simple (pure tones) and complex (noise, voices, and music) sounds. This analysis gave results consistent with models describing hierarchical functional organization of the human auditory cortex, with simple sounds eliciting activity in the primary auditory cortex and complex sound processing engaging additional activity in non-primary fields. We observed an expected leftward hemispheric specialization for intelligible speech, while right hemisphere specialization for music was less evident. Additionally, the comparison of intelligible speech to complex non-speech stimuli yielded bilateral effects along the STG and STS, with higher sensitivity to speech intelligibility in the left anterior STG.

Examining an alternative classification based on stimulus variation along spectral and temporal dimensions, we observed a within-hemisphere functional segregation, with spectral effects strongest in posterior STG and temporal modulations strongest in anterior temporal STG. We suggest that acoustic complexity might represent a valid alternative classificatory scheme to describe a novel within-hemisphere dichotomy regarding the functional organization for auditory processing in temporal cortex.

Hierarchically and hemispherically specialized architectures for auditory processing

Originally elaborated on the basis of non-human primate studies, the hierarchical functional organization scheme in auditory cortex incorporates three levels of processing: core (primary area), belt and parabelt (non-primary areas). Simple sound processing is thought to solely recruit the core region whereas complex sounds are believed to elicit activity in core, belt and parabelt areas. While belt region responses are thought to be sensitive to acoustic feature variations, the parabelt, and more anterior temporal regions, show greater sensitivity to complex sounds such as vocalizations (Hackett, 2008; Rauschecker, 1998; Rauschecker & Scott, 2009; Woods & Alain, 2009). Our quantitative meta-analysis using typical sound classes confirmed that hierarchical processing is a feature that can adequately describe human auditory cortical organization.

Using an ALE analysis of pure tone processing to investigate the correspondence between the core region and activity related to simple sound processing, we observed ALE extrema values bilaterally in medial HG, the putative location of primary auditory cortex. This finding is consistent with previous electrophysiological (Hackett, Preuss, & Kaas, 2001), cytoarchitectural (Sweet, Dorph-Petersen, & Lewis, 2005) and functional imaging (Bilecen, Scheffler, Schmid, Tschopp, & Seelig, 1998; Lauter, Herscovitch, Formby, & Raichle, 1985; Lockwood, et al., 1999; Wessinger, et al., 2001) studies of the human auditory cortex that have localized the core region to medial HG. Our findings confirm the existence of functional specialization for simple sound processing in the human core homologue. Consequently, the statistical probability maps used here could serve to functionally define primary auditory cortex in a region of interest analysis of functional neuroimaging data.

In contrast, we expected ALE analyses of the complex sound categories to show activity in all three levels of the processing hierarchy. We observed overlapping activity among the complex sound maps in medial HG (core) as well as stronger activity related to complex sound processing in regions surrounding medial HG, corresponding to the areas described as the auditory belt/parabelt in primates (Kaas & Hackett, 2000; Rauschecker, 1998; Rauschecker & Scott, 2009; Recanzone & Cohen, 2010) and humans (Rivier & Clarke, 1997; Sweet, et al., 2005; Wallace, Johnston, & Palmer, 2002). The fact that the complex sound maps showed effects in medial HG activity supports the notion that primary auditory regions participate in the early stages of processing upon which further complex processing is built.

Outside primary auditory cortex, noise elicited activity in posterior temporal non-primary fields such as planum temporale (PT). The spatial pattern was similar to that observed in relation to broadband noise, stimuli that have been used to demonstrate the hierarchical organization of human auditory cortex (Wessinger, et al., 2001). The PT is generally believed to be involved in complex sound analysis and participate in both language and other cognitive functions (Griffiths & Warren, 2002).

For music, in addition to primary auditory cortex activity, we observed activity in non-primary auditory fields along the superior temporal gyrus bilaterally. This result is consistent with the idea that simple extraction and low-level ordering of pitch information involves processes within primary auditory fields, while higher-level processing for tone patterns and melodies involve non-primary auditory fields and association cortex (Zatorre, Belin, et al., 2002). Moreover, non-primary regions in anterior and posterior STG are thought to process melody pitch intervals (Patterson, Uppenkamp, Johnsrude, & Griffiths, 2002; Tramo, Shah, & Braida, 2002; Warren & Griffiths, 2003). Music also elicited strong inferior frontal cortex activity, a region thought to process musical syntax (Koelsch, et al., 2002; Maess, Koelsch, Gunter, & Friederici, 2001; Zatorre, et al., 1994).

For vocal sounds, we observed strong bilateral temporal lobe activity in anterior and posterior parts of dorsal STG and the STS, findings consistent with earlier studies (Belin, 2006; Binder, et al., 1994). STG activity in response to vocal sounds has previously been interpreted as a neural correlate of the rapid and efficient processing of the complex frequency patterns and temporal variations characterizing speech. The human STG is thought to subserve complex auditory processing, such as vocalizations, as is the STG in non-human primates (Rauschecker, Tian, & Hauser, 1995). Belin and colleagues (Belin, et al., 2002; Belin, et al., 2000; Fecteau, Armony, Joanette, & Belin, 2004) reported cortical responses to voices along the upper bank of the middle and anterior STS. The anterior STS is selectively responsive to human vocal sounds (Belin, et al., 2000). Response specificity to vocal sounds and their rich identity and affective information content is of crucial importance, as it reflects a set of high-level auditory cognitive abilities that can be directly compared between human and non-human primates. The regions described as "Temporal Voice Areas" in humans (Belin, et al., 2000) are thought to be functionally homologous to the temporal voice regions recently described in macaques (Petkov, et al., 2008). Our meta-analysis using typical sound categories demonstrates that, in humans, simple sound processing elicits activity limited to the core area while complex sounds elicit effects in all three cortical processing levels.

In addition to the hierarchical organization of auditory cortex, we expected hemispheric asymmetries for music and speech, and observed the expected left lateralization of auditory cortex responses to vocal sounds and intelligible speech. For vocal sounds, lateralization effects were observed only as a larger volume of auditory activity on the left while, for the speech sounds, the left auditory cortical responses were larger and stronger (higher ALE values) than the right hemisphere responses. Greater lateralization effects for intelligible speech is in agreement with previous independent imaging studies, not included in this meta-analysis, reporting that intelligible speech sounds elicit strong activity in left STG and STS (e.g. Liebenthal, Binder, Spitzer, Possing, & Medler, 2005; Obleser, Zimmermann, Van Meter, & Rauschecker, 2007; Scott, Blank, Rosen, & Wise, 2000). Conversely, we did not see the expected right response lateralization related to music. Possibly, the small number of experiments included in the music category limited the power of this analysis and could have prevented us from observing the expected rightward auditory response. ALE maps derived from small samples are more sensitive to between-study cohort heterogeneity that could limit the detection of hemispheric effects. It is also possible that the right hemisphere is sensitive to particular features of musical stimuli such as fine pitch changes (Hyde, Peretz, & Zatorre, 2008) or to specific task demands like contextual pitch judgment (i.e. contextual pitch judgment Warrier & Zatorre, 2004) which were not present in our sample.

Response specificity to speech intelligibility

Within the general category of vocal sounds, a human-specific category of intelligible speech can be further distinguished. Response specificity to speech intelligibility is an important part of understanding the human-specific neural network underlying speech comprehension, and ultimately human language and communication.

In order to identify speech-specific processes, we directly compared intelligible speech to complex non-speech contrasts that included unintelligible spectro-temporally complex sounds. This comparison yielded stronger speech-related activity in lateral non-primary superior temporal regions, specifically in posterior STG, and anterior and middle STS. The effects were stronger and larger in the left hemisphere. Similar effects have been reported in independent studies examining specialization for processing speech sound that did not fulfill our inclusion criteria for this analysis (Davis & Johnsrude, 2003; Liebenthal, et al., 2005; Narain, et al., 2003; Scott, et al., 2000; Thierry, Giraud, & Price, 2003). Consistent with the present finding, these previous reports emphasized that speech-specific STS responses are more left-lateralized.

Beyond the auditory cortex, we observed activity in left inferior frontal and prefrontal cortex. These findings support an expanded hierarchical model of speech processing that originates in primary auditory areas and extends to non-auditory regions, mainly within frontal cortex, in a range of motor, premotor, and prefrontal regions (Davis & Johnsrude, 2007; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009). In non-human primates, based on reports of high level of connection between the auditory and frontal cortex, it has been proposed that frontal regions responsive to auditory material should be considered as part of the auditory system (Hackett, Stepniewska, & Kaas, 1999; Kaas, Hackett, & Tramo, 1999; Romanski, et al., 1999).

Functional specialization of the auditory cortex response: acoustic complexity effects

As an alternative to the classical division of auditory stimuli into typical categories like pure tones, noise, voices and music, we explored how acoustic variations along the temporal and spectral dimensions were represented at the cortical level. This approach for defining auditory material is an efficient and comprehensive characterization of sounds that can be considered as a complement to the more typically studied categorical effects. Possibly, certain aspects of human auditory processes might be better characterized in terms of their capacity to analyze acoustic features rather than having differential sensitivity to typical sound categories. In a meta-analysis Rivier & Clarke (1997) found no clear functional specialization in non-primary auditory fields for a range of complex sound categories, showing that processing sounds of different categories such as noise, words and music, elicited activity in multiple non-primary fields around HG with no emergence of a specific organizational pattern. Similarly, Griffiths & Warren (2002) reported that activity within the PT, an auditory association region, is not spatially organized according to sound categories such as music, speech or environmental sounds.

By classifying sounds according to their variations in time and frequency, we isolated different levels of auditory complexity, suggesting a within-hemisphere functional segregation with anterior STG and STS more sensitive to changes in the temporal domain and posterior regions (PT and posterolateral STG) more sensitive to changes in along the spectral dimension. Interestingly, a partial overlap was observed between regions sensitive to temporal and spectral changes in lateral HG, suggesting great sensitivity to variations in acoustic properties within this region, consistent with a recent report of strongest sensitivity to stimulus acoustic features within HG (Okada, et al., 2010).

Our observation of differential sensitivity to temporal and spectral features can be interpreted in the light of previous findings. First, in the animal literature, a within-hemisphere model of spectral and temporal processing in the auditory cortex has been proposed (Bendor & Wang, 2008). This scheme suggests two streams of processing originating from primary auditory cortex; an anterior pathway sensitive to temporal changes and a lateral pathway responsive to spectral changes. More precise temporal coding is seen as one progresses from primary to anterior auditory regions in primates (Bendor & Wang, 2007) and greater sensitivity to temporal modulations in anterior non-primary auditory fields is also observed in cats (Tian & Rauschecker, 1994). Possibly, a longer integration window in anterior auditory fields could underlie complex temporal processing (Bendor & Wang, 2008). As regards spectral processing, increasing sensitivity to broadband spectrum noise compared to single tones has been observed in lateral and posterior auditory fields in non human primates (Petkov, Kayser, Augath, & Logothetis, 2006; Rauschecker & Tian, 2004). Furthermore, given that the neurons within these regions show strong tuning to bandwidth and frequency, some have suggested their involvement in the early stages of spectral analysis of complex sounds (Rauschecker & Tian, 2004). In our study, sensitivity to temporal changes was observed in anterior temporal regions, while, in response to changes along the spectral dimension, we mainly observed response selectivity in postero-lateral auditory fields. Our results therefore seem to be consistent with previous animal studies.

Second, cortical response specificity to spectral and temporal processing has also been studies in humans. Whereas some studies reported no clear functional segregation between responses to spectral and temporal cues (Hall, et al., 2002) or observed neuronal populations tuned to specific combinations of spectro-temporal cues (Schonwiesner & Zatorre, 2009), other studies found the sorts of specific sensitivity to spectral vs. temporal features in human auditory cortex we observed in our meta-analysis. For instance, lateral HG and anterolateral PT activity have been reported in association with fine spectral structure analysis (Warren, Jennings, & Griffiths, 2005) and change detection of complex harmonic tones involved the posterior STG and lateral PT (Schonwiesner, et al., 2007). Additionally, recent studies examining effective connectivity effects among auditory regions reported that spectral envelope analysis follows a serial pathway from HG to PT and then to the STS (Griffiths, et al., 2007; Kumar, Stephan, Warren, Friston, & Griffiths, 2007). Conversely for temporal complexity effects, a stream of processing from primary auditory cortex to anterior STG has been observed for auditory pattern analysis such as dynamic pitch variation (Griffiths, et al., 1998). Similarly, significant effects of temporal modulation have been reported in anterior non-primary auditory fields (Hall, et al., 2000).

Some studies therefore report patterns of activity consistent with the current findings, albeit separately for spectral and temporal features.

A more frequently observed feature of spectral versus temporal processing is between-hemisphere functional specialization. Most studies observed slight but significant lateralization effects with a left-lateralized response to temporal information and right-lateralized activity to spectral information (Jamison, Watkins, Bishop, & Matthews, 2006; Obleser, Eisner, & Kotz, 2008; Schonwiesner, et al., 2005; Zatorre & Belin, 2001). In the current study, lateralization effects were not seen with regard to complexity. However, at higher processing levels, leftward lateralization for speech was observed. Others studies failing to demonstrate the expected lateralization proposed that early stages of processing involve bilateral auditory cortex and that higher cognitive functions, such as speech processing, also rely on these regions but involve more extensive regions in the dominant hemisphere (Langers, Backes, & van Dijk, 2003). Alternatively, Tervaniemi & Hugdahl (2003) reviewed studies showing that response lateralization within the auditory cortex is dependent on sound structure as well as acoustic background they are presented in. For instance, reduced or absent hemispheric specialization for speech sounds has been reported when the amount of formant structure is not sufficient to establish phoneme categorization (Rinne, et al., 1999) or when sounds are presented in noise (Shtyrov, et al., 1998). Stimulus heterogeneity among the different experiments included in our meta-analysis could explain why we did not observe asymmetrical hemispheric effects.

To summarize, our meta-analysis demonstrates a clear within-hemisphere functional segregation related to spectral and temporal processing in human auditory cortex, consistent with the known organization of non-human primate auditory system. That such clear spectral vs. temporal complexity gradients are observed (Figure 5), while very few of the included studies have explicitly addressed this issue, illustrates the power of the meta-analysis approach for human neuroimaging studies. Based on the observed regional functional segregation, we argue that acoustic complexity could well represent a relevant stimulus dimension upon which to identify response segregation within the auditory system. Complexity and categorical effects could therefore be considered as two complementary approaches to more fully characterizing the underlying nature of auditory regional functional specialization.

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Chapitre 4. Atypical processing of auditory temporal complexity in autistics

Atypical processing of auditory temporal complexity in autistics

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Abstract

Autistics exhibit a contrasting combination of auditory behavior, with enhanced pitch processing abilities often coexisting with reduced orienting towards complex speech sounds. Based on an analogous dissociation observed in vision, we expected that autistics' auditory behavior with respect to complex sound processing may result from atypical activity in non-primary auditory cortex. We employed fMRI to explore the neural basis of complex non-social sound processing in 15 autistic and 13 non-autistics, using a factorial design in which auditory stimuli varied in spectral and temporal complexity. Spectral complexity was modulated by varying the harmonic content, whereas temporal complexity was modulated by varying frequency modulation depth. The detection task was performed similarly by autistics and non-autistics. In both groups, increasing spectral or temporal complexity was associated with activity increases in primary (Heschl's gyrus) and non-primary (anterolateral and posterior superior temporal gyrus) auditory cortex. Activity was right-lateralized for spectral and left-lateralized for temporal complexity. Increasing temporal complexity was associated with greater activity in anterolateral superior temporal gyrus in non-autistics and greater effects in Heschl's gyrus in autistics. While we observed similar hierarchical functional organization for auditory processing in both groups, autistics exhibited diminished activity in non-primary auditory cortex and increased activity in primary auditory cortex in response to the presentation of temporally, but not of spectrally complex sounds. Greater temporal complexity effects in regions sensitive to acoustic features and reduced temporal complexity effects in regions sensitive to more abstract sound features could represent a greater focus towards perceptual aspects of speech sounds in autism.

Keywords: Auditory cortex, enhanced perceptual functioning model, functional magnetic resonance imaging

Atypical processing of auditory temporal complexity in autistics

Introduction

Behavioral evidence indicates that the cognitive architecture of visual and auditory perceptual processing may be differently organized in autism (Behrmann, Thomas, & Humphreys, 2006; Dakin & Frith, 2005; Mottron, Dawson, Soulieres, Hubert, & Burack, 2006; Samson, Mottron, Jemel, Belin, & Ciocca, 2006). The diagnostic criteria for autism (Lord, et al., 1997) include signs related to both hypo- and hyper-reactivity to sounds (Grandin & Scariano, 1986; Metz, 1967; Novick, Vaughan, Kurtzberg, & Simson, 1980). While autistics[2] may display apparent disinterest in speech sounds, and aversive reactions to vacuum cleaner and crowd noises (Goldfarb, 1961), they may also have heightened musical interests, and enhanced auditory abilities such as superior pitch memory and pure tone discrimination (Bonnel, et al., 2003; Heaton, 2003).

Auditory processing atypicalities in autism have been interpreted in two frameworks. Weak central coherence theory (Frith & Happe, 1994) hypothesizes that autistics have difficulty integrating local auditory features into larger ensembles at the global level (Kellerman, Fan, & Gorman, 2005; Nieto Del Rincon, 2008). However, reports of intact global auditory processing in autism challenge this hypothesis (Heaton, 2005; Mottron, Peretz, Belleville, & Rouleau, 1999; Mottron, Peretz, & Menard, 2000). The enhanced perceptual functioning model (EPF) (Mottron, et al., 2006) describes both the superiorities of processing local features and the intact global contour processing within hierarchical auditory patterns(e.g. melody). Moreover, this model emphasizes the link between the bias towards local elements in hierarchical auditory patterns and superior pitch detection for pure tones (Heaton, 2003; Mottron, et al., 2000). However, the EPF predictions regarding the processing of psychophysically complex sounds are essentially derived from evidence reported from visual studies investigating early visual processing that have demonstrated superior processing abilities in autistics for simple, luminance-

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[2] The term ‘‘autistic’’ rather than ‘‘person with autism’’ is used in a respectful manner (see Sinclair, 1999).

defined information, extracted by mechanisms operating within primary (V1) visual cortex (Bertone, Mottron, Jelenic, & Faubert, 2005; Plaisted, O'Riordan, & Baron-Cohen, 1998), and lower performance for tasks involving more complex visual processing requiring involvement of both primary (V1) and non-primary (V2, V3) regions of visual cortex (Bertone, Mottron, Jelenic, & Faubert, 2003; Bertone, et al., 2005; Blake, Turner, Smoski, Pozdol, & Stone, 2003; Milne, et al., 2002; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005; Vandenbroucke, Scholte, van Engeland, Lamme, & Kemner, 2009). Atypical integration between primary and non-primary regions of the visual cortex could underlie this dissociation (Bertone, et al., 2005). This heuristic was recently extended to audition, resulting in predictions of differential processing by autistics for simple, compared to complex, auditory stimuli (Samson, et al., 2006). In support of this idea, enhanced pitch processing has been documented in numerous behavioral (Bonnel, et al., 2010; Bonnel, et al., 2003; Heaton, 2003, 2005; Jones, et al., 2009; O'Riordan & Passetti, 2006) and electrophysiological studies of autistics (Ferri, et al., 2003; Gomot, Giard, Adrien, Barthelemy, & Bruneau, 2002; Lepisto, et al., 2008; Lepisto, et al., 2005). In some cases, the behavioral advantage reaches outstanding levels, extending beyond four and five standard deviations above the mean of the control group (Heaton, Davis, & Happe, 2008). Moreover, superior processing of individual sound components might underlie enhanced chord disembodying (Heaton, 2003; Miller, 1989; Mottron, et al., 1999) or the unimpaired discrimination of non-social complex sounds in autistics if they were to achieve successful processing though the decomposition of complex sounds (Bonnel, et al., 2010)

The relevance of studying auditory perception in autism is not limited to the peaks of ability, as most studies report diminished abilities in processing social auditory information in this population. This is the case for speech recognition in noise (Alcantara, Weisblatt, Moore, & Bolton, 2004; Groen, et al., 2009) or prosody perception (Kujala, Lepisto, Nieminen-von Wendt, Naatanen, & Naatanen, 2005; Peppe, McCann, Gibbon, O'Hare, & Rutherford, 2007). However, typical voice processing abilities in autistics have been reported (Boucher, Lewis, & Collis, 2000). Event-related potential studies have shown reduced cortical responses to complex speech-like sounds, including vowels (Ceponiene, et al., 2003; Lepisto, et al., 2005; Lepisto, et al., 2006; Whitehouse & Bishop, 2008) and consonant-vowel syllables (Jansson-Verkasalo, et al., 2003; Russo, Zecker, Trommer, Chen, & Kraus, 2009). Finally, reduced activation of the "voice area" in the superior temporal sulcus (STS) has been reported in autistic adults (Gervais, et al., 2004), and a reduced leftward asymmetry has been observed for speech processing (Boddaert, et al., 2003; Boddaert, et al., 2004; Lepisto, et al., 2005; Lepisto, et al., 2006; Minagawa-Kawai, et al., 2009). It is therefore plausible that atypical processing of psychophysical properties of complex sounds plays a role in the apparent disinterest for speech, evident in most autistics, at least in their early years.

As in the visual system (Grill-Spector & Malach, 2004), auditory cortical analysis is organized hierarchically, with simple feature extraction at the primary level providing input to non-primary fields that subsequently extract more complex features. This functional organization scheme receives empirical support from both animal and human studies. In non-human primates and cats, the primary or 'core' auditory region, located in Heschl's gyrus (HG), is more tonotopically organized by frequency, has sharper frequency tuning and shows lower thresholds to pure tones as compared to non-primary auditory fields (Merzenich & Brugge, 1973; Morel, Garraghty, & Kaas, 1993; Rauschecker, Tian, & Hauser, 1995; Schreiner & Cynader, 1984). The non-primary neurons within the superior temporal gyrus (STG), labeled as 'belt' and 'parabelt' auditory regions, show broader individual frequency tuning, collectively respond to a broader range of frequencies and are selectively responsive to more complex stimuli such as band-passed noise (Rauschecker, et al., 1995; Recanzone, 2000). These physiological findings combined with the known anatomical connections among primary and associative auditory regions (Hackett, Stepniewska, & Kaas, 1998) lend support to hierarchical organizational accounts of information flow in non-human auditory cortex (Kaas & Hackett, 1998, 2000; Rauschecker, 1998). Similarly organizational plans are evident in human auditory cortex. An fMRI study reported that pure tone presentation resulted in activity increases in primary auditory cortex

(HG), whereas complex band-passed noise elicited activity increases extending to the surrounding non-primary auditory fields in the anterolateral aspect of HG and STG (Wessinger, et al., 2001), consistent with the location of the belt region in macaques (Rauschecker, 1998). Similarly, imaging studies have consistently revealed that *spectrally* complex sounds, with multiple harmonic components, and *temporally* complex sounds, with varying frequency or amplitude in time, elicit activity increases extending to non-primary auditory areas in anterior, lateral and posterior STG, corresponding to the belt and parabelt regions (Binder, et al., 2000; Giraud, et al., 2000; Hall, et al., 2002; Hart, Palmer, & Hall, 2003; Schonwiesner, Rubsamen, & von Cramon, 2005a; Schonwiesner & Zatorre, 2009; Thivard, Belin, Zilbovicius, Poline, & Samson, 2000; Zatorre & Belin, 2001). Moreover, while primary areas (HG) are sensitive to acoustic variations in speech sounds, non-primary areas within anterior and posterior superior temporal regions are more responsive to abstract sound features like intelligibility than to acoustic signal variations (Okada, et al., 2010), supporting the role of these non-primary fields in the processing of more complex auditory information (Rauschecker & Scott, 2009). In addition to a within-hemisphere hierarchical architecture, auditory processing models also incorporate lateralization features (Zatorre, Belin, & Penhune, 2002) mainly, a leftward asymmetry of the auditory cortical response to temporal sound variation (Belin, et al., 1998; Jamison, Watkins, Bishop, & Matthews, 2006; Schonwiesner, et al., 2005a; Zaehle, Wustenberg, Meyer, & Jancke, 2004; Zatorre & Belin, 2001) and rightward to spectral sound variation (Jamison, et al., 2006; Patterson, Uppenkamp, Johnsrude, & Griffiths, 2002; Schonwiesner, Rubsamen, & von Cramon, 2005b; Zatorre & Belin, 2001).

We used fMRI to examine differential auditory cortical responses to stimuli of varying spectral and temporal complexity in autism. Before being able to account for differential behavioural performances in naturalistic situations, and specifically for atypical autistic performance in music, language and voice processing, a preliminary study exploring the effects of variation in fundamental sound properties is required. For this purpose, we exposed our participants to simple and controlled stimuli, that is pure tones, in addition to spectrally and temporally complex sounds. Although spectral and temporal acoustic features are important characteristics of more complex sounds like speech, it is important to note that the stimuli used here do not represent actual features of speech and remain very simple in comparison to components like vowels, consonants or the structure of formants.

We define sounds as *spectrally complex* when they include more than one frequency component or harmonic. Similar stimuli have been used to investigate cortical auditory spectral complexity processing (Hall, et al., 2002; Hart, et al., 2003). We define *temporally complex* sounds as having frequency variation over time. Similar frequency-modulated sounds have been used in imaging studies (Hall, et al., 2002; Hart, et al., 2003). Our experiment is novel in this regard, as we use a parametric design with three levels of temporal complexity with increasing frequency modulation depth while maintaining constant modulation rate.

On the basis of previous work in typical individuals, we predicted that sounds of higher spectral and temporal complexity would induce increased activity in primary (HG) and non-primary auditory cortex, mainly with spatial extension to anterolateral STG (Hall, et al., 2002; Hart, et al., 2003). Based on hypothesized reduced integration among auditory cortical regions (Bertone, et al., 2005; Samson, et al., 2006), autistics should exhibit reduced activity in response to complex auditory material in non-primary auditory areas, with higher sensitivity to complex sound features. Between-group effects would possibly be more important in response to temporal complexity, which is specifically important for speech recognition, particularly low modulation rates as the one used here (Houtgast & Steeneken, 1985; Tallal, Miller, & Fitch, 1993). In terms of response lateralization, we expected a rightward asymmetry associated with spectral complexity and leftward for temporal complexity.

Material and methods

Participants

Thirteen typical (TYP) and 15 autistics (AUT) participants were included in this study. There were no significant differences in mean chronological age, Wechsler IQ scored with Canadian Norms (Wechsler, 1991, 1997), Raven's Progressive Matrices scored with norms for North America (Burke, 1985) or manual preference (Table 1). All but one participant in each group were right-handed. All had normal hearing as measured by pure-tone audiometry and no formal musical training. TYP participants were screened for any personal or familial neurological or medical conditions known to affect brain function. One AUT participant was medicated (lorazepam) at the time of testing. Informed written consent was obtained from all participants, and from the parents for minors, in accordance with the Regroupement Neuroimagerie Québec IRB approved protocol #2006-0204. All participants were compensated.

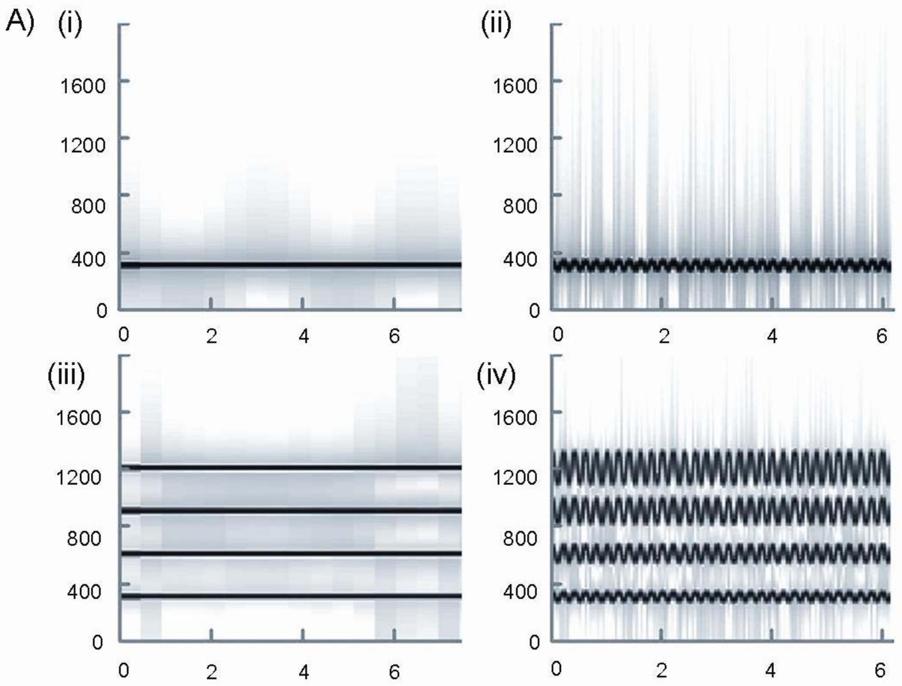
All participants were recruited from the database of the Pervasive Developmental Disorders specialized clinic of the Rivière-des-Prairies Hospital (Montréal, Canada). Exclusion criteria included a personal or family history of psychiatric or neurological disorders other than autism. The AUT participants were characterized using a combination of standard instruments including the Autism Diagnostic Interview Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994), the Autistic Diagnostic Observation Schedule (ADOS-G module 3 or 4) (Lord, et al., 1989) and clinical evaluation based on DSM-IV criteria.

Table 1. Participant Characteristics. Groups were matched on sex, age, IQ, Raven Progressive Matrices percentile scores and manual preference, which is reported as the Edinburgh score with -100 corresponding to completely left-handed and +100 to completely right-handed. ADI is the Autism Diagnostic Interview. Group differences were assessed using independent sample *t*-tests.

	TYP	AUT	*p*
Sample size (sex)	13 (2 F, 11 M)	15 (2 F, 13 M)	
Age (y:m)			
Mean (SD)	23:6 (7:5)	24:4 (6:3)	0.74
Range	16 - 39	14 – 35	
Full-scale IQ			
Mean (SD)	109.6 (10.8)	100.3 (13.9)	0.07
Range	92 - 131	78 – 126	
Performance IQ			
Mean (SD)	106.3 (13.0)	100.3 (11.8)	0.22
Range	87 - 133	86 – 117	
Verbal IQ			
Mean (SD)	111.1 (10.7)	100.4 (16.4)	0.06
Range	93 - 127	72 - 121	
Raven			
Mean (SD)	72.3 (23.2)	70.4 (31.5)	0.86
Range	19 - 98	6 - 100	
Handedness			
Mean (SD)	+61.2 (41.1)	+71.9 (49.0)	0.62
Range	-45 - +100	-100 - +100	
ADI Score Mean (cut-off)			
Social		24.1(10)	
Communication		18.2(8)	
Behavior		7.0(3)	
ADI Score Mean (cut-off)			
Social		11.0 (6)	
Communication		6.0 (3)	
Behavior		16.7 (10)	

Stimuli

The stimuli were synthesized at 44.1KHz with 16 bit resolution using MITSYN (Henke, 1976). Sounds were presented continuously for 6.24s, including raised cosine ramps (50ms). Eight stimulus classes were created by crossing two types of carrier signals (single- and multi-tone) with four levels of frequency modulation (FM) (0% (static), 25%, 50%, 100%). The carrier signal was either a 300Hz pure tone or a harmonic tone with a 300Hz fundamental and components of equal amplitude at 300, 600, 900, 1200Hz. The 300Hz pure tone stimulus was generated using a sine wave oscillator. The harmonically complex tones were generated using a waveform oscillator generating the first four harmonics of a 300Hz fundamental. A second oscillator was used to modulate the frequency of the carrier oscillator. The frequency of the FM sounds varied at a rate of 5Hz and the modulation depth differed across FM conditions (0%, 25%, 50% and 100%). Specifically, the depth of modulation defined the limits between which the frequency of the second tone oscillator warbled (+/- % of FM). For instance, the 300Hz component varied from 250 to 350Hz at 100% FM (+/-50Hz), while the warble was (+/-12.5Hz) at 25% and (+/-25Hz) at 50%. We used two spectral (single tone and harmonic) and four temporal (FM0, FM25, FM50, FM100) levels of complexity (Figure 1). A ninth silence condition was added as a baseline.



B)

Carrier Signals	Static (FM0)	FM25	FM50	FM100
Non-harmonic (single tone)	Condition 1	Condition 2	Condition 3	Condition 4
Harmonic (multi-tone)	Condition 5	Condition 6	Condition 7	Condition 8

Figure 1. The auditory stimuli were varied in both spectral and temporal complexity. (A) Spectrogram (decomposition of acoustic energy along time and frequency) of the stimuli. Frequency is shown in the vertical axis and time is represented in the horizontal axis. The energy level is represented by the greyscale (white (0) – black (96) dB). The four extreme conditions are represented here: (i) Unmodulated pure tone (condition 1), (ii) 100% modulated pure tone (condition 4), (iii) Unmodulated harmonic tone (condition 5) and (iv) 100% modulated harmonic tone (condition 8). (B) Table of the 8 conditions.

Task

Subjects listened to the stimuli and indicated, by pressing a button, if the sound was modulated or not. This controlled listening task was used to maintain the participants' attention and elicit more reliable activation (Hall, et al., 2000). Subjects heard stimuli outside the scanner to make certain that they understood the difference between modulated and unmodulated sounds. Stimuli were presented binaurally through MRI-compatible earphones (www.mrconfon.de) at a mean of 85-90dB sound pressure level (SPL).

On each trial, either one of the eight auditory stimuli or a silence condition was presented. Each run consisted of 72 trials: 64 sound trials (eight for each condition) and eight silence trials, with three runs per subject. The run order was counter-balanced across subjects and trials were presented in pseudo-randomized order within each run using E-Prime 1.1 (*Psychology Software Tools).* In the fMRI acquisition protocol, each 6.24s trial occurred prior to image acquisition periods lasting 2.76s, using a sparse sampling imaging protocol with an effective TR=9 s (Figure 2). This technique allowed minimizing interference from magnetic gradient noise (Eden, Joseph, Brown, Brown, & Zeffiro, 1999) and improving detection of auditory cortex activity (Belin, Zatorre, Hoge, Evans, & Pike, 1999; Edmister, Talavage, Ledden, & Weisskoff, 1999; Hall, et al., 1999).

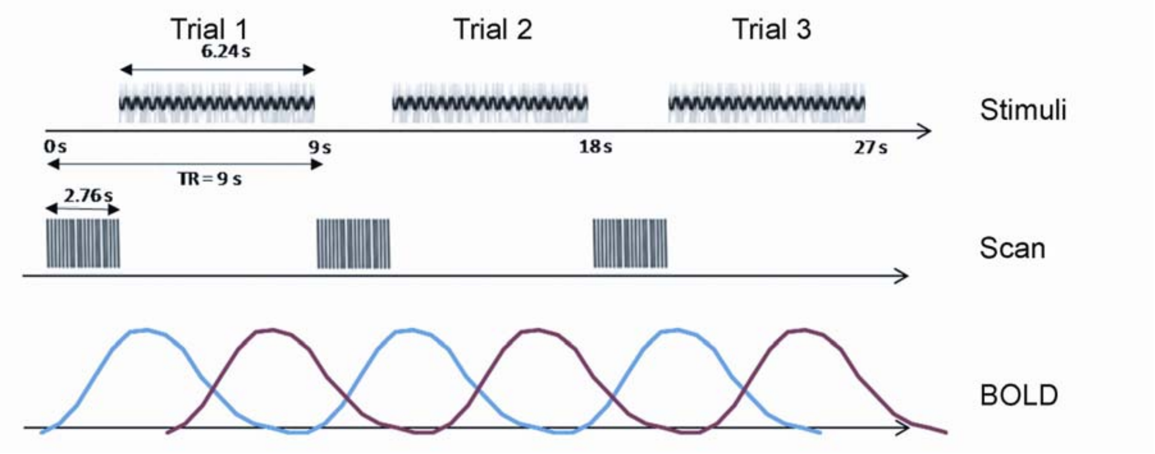


Figure 2. Stimulus presentation and imaging were interleaved to avoid acoustic noise interference with the task. The stimulus presentation, scan acquisition and hypothetical BOLD-contrast response to scanner noise (blue) and to the stimulus (red) are shown.

Image Acquisition

Images were acquired on a 3.0T TRIO MRI system at the «Unité de Neuroimagerie Fonctionnelle» (University of Montreal). The subject's head was immobilized with foam pads and a vacuum cushion, which helped to stabilize the headphones.

The acquisition began with an anatomical T1-weighted high-resolution image using an MPRAGE sequence (176 slices, voxel size=1mm^3, 256mm^2, TR=9.7ms, TE=4ms, flip=12°). Gradient echo phase and magnitude field maps were then acquired (voxel size=3mm^3, 64x64, TR=300ms, TE short=5.71ms, TE long=8.17ms, Flip=55°) to correct image distortions and improve the coregistration accuracy (Hutton, et al., 2002). Echoplanar images were acquired during three 10.8min runs of 72 scans (TE=30ms, voxel size=3.4mm^3, 46 slices, flip angle=90°).

Behavioral Analyses

Group x Task ANOVAs examining effects of group, spectral and temporal complexity were carried out on reaction time (RT) and accuracy (ACC) using a critical threshold of $p<0.01$. Statistical analysis was restricted to the 11 TYP and 13 AUT participants from the fMRI sample for which behavioral data were available.

Image Analyses

SPM5 was used for preprocessing and statistical modeling. Images were realigned, unwarped, spatially transformed to the ICBM152 (MNI) space (Collins, Neelin, Peters, & Evans, 1994) and spatially smoothed using a 3D Gaussian filtering kernel of 9mm FWHM.

First level analyses were conducted for each subject, using a design matrix including the eight stimulus conditions, along with six head motion estimates and a constant term included as covariates of no interest. We modeled the task regressors with a finite impulse response function of 2.76s bin width, selected to match the single volume acquisition time. A high-pass filter cutoff of 128s was used to remove low-frequency noise. At the second level, the first-level contrasts for each condition contrasted with the silence baseline were entered in a mixed effects model with three factors: Subject (28 levels), Group (2 levels) and Condition (8 levels). Cortical activity peaks were located using a brain atlas (Duvernoy & Cabanis, 1991).

Within-group contrasts. In each group, weighted contrasts ($p_{FWE\ corrected}<0.05$) across various condition combinations were used to identify areas showing linear effects with respect to complexity. To isolate the effects of spectral complexity, we contrasted the multi-tone (harmonic) conditions to the single tone conditions. For temporal complexity, the linear effect of the four frequency modulation levels was estimated with a parametric contrast. The resulting positive and negative effects reflected the respective increases and decreases in signal associated with increasing temporal complexity.

Conjunctions. To identify the regions exhibiting similar effects among groups, the contrasts computed in the within-group analysis were used to generate multi-group conjunction maps ($p_{FWE\ corrected}<0.05$). The harmonic vs. single tone contrast for each group was used to compute a conjunction of activity related to spectral complexity. The same procedure was employed to identify common activity increases and decreases related to increasing temporal complexity.

Between-group contrasts. Linear contrasts were used to identify the regions where the task-related activity varied between the groups. Since we had hypotheses concerning sensitivity differences to complex stimuli in cortical auditory areas, we restricted the analyses by using an inclusive mask of the conjunction of the respective complexity effects in each group. Additionally, we used an uncorrected threshold ($p_{uncorrected}<0.001$), because of the expected weaker strength of between-group effects. To investigate between-group differences in spectral complexity, we used a mask of the multi-group conjunction of activity related to harmonic multi-tone vs. single-tone conditions. To investigate temporal complexity effects, we used a mask of regions showing linear activity increases associated with increasing temporal complexity across groups.

Between-group comparisons of mean signal change in regions of interest (ROI).

To investigate effects in the auditory regions responsive to pure tone stimulation, we extracted the changes in activity associated with spectral and temporal complexity within functionally defined ROIs. These ROIs were derived from an independent meta-analysis of pure tone vs. silence contrasts in typical adult samples yielding bilateral activity centered on medial HG, the putative location of the primary auditory fields (Samson, Zeffiro, Toussaint, & Belin, 2011). They will be referred to as primary auditory cortex (PAC) ROIs, although caution should be taken as they actually correspond to functionally defined areas showing effects related to simple, pure tone, processing rather than a cytoarchitectonic map of the PAC. Considering that sound related activity in the initial analysis was observed in auditory cortex and the inferior frontal gyrus (IFG), both regions were selected as ROIs. The IFG ROIs were anatomical masks obtained from WFU PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). The IFG is known to be involved, among other things, in processing complex auditory features (Joanisse & Gati, 2003; Zaehle, Geiser, Alter, Jancke, & Meyer, 2008). Both ROIs are included to investigate the specificity of the auditory response, which could be argued for if the effect is seen only in the PAC ROI, but not in the IFG ROI. Mean signal changes within these ROIs for each of the eight sounds vs. silence contrasts were extracted for each subject using the REX toolbox (http://web.mit.edu/swg/software.htm). Linear mixed effect models investigating Group x ROI x Task effects were computed with the subject factor treated as a random effect.

Hemispheric specialization. Laterality indices (LI) were computed with the LI Toolbox (Wilke & Lidzba, 2007) using both voxel count and voxel value as measures. LI were calculated as: LI = (Σ Left – Σ Right) / (Σ Left + Σ Right), yielding values that ranged between left (+1) and right lateralization (-1). Signs of the reported LIs were inverted (-1: left, +1: right) for consistency with the MNI coordinate system. We computed activity asymmetries in STG and IFG using anatomically defined masks taken from the WFUPickAtlas (Maldjian, et al., 2003), using a contrast and subject specific adaptive threshold.

Results

Behavior

We observed no group performance differences on the sound modulation detection task (Table S1). A Group x Spectral Complexity (Non-harmonic, Harmonic) ANOVA on RT revealed no main effect of spectral complexity ($F(1, 22) = 2.894$, $p = 0.103$) and no main effect of Group ($F(1, 22) = 1.295$, $p = 0.267$). Similarly, the Group x Spectral Complexity ANOVA on ACC did not detect significant main effects or interactions ($F < 1$).

Second, a Group x Temporal Complexity (FM0, FM25, FM50, FM100) ANOVA on RT revealed a main effect of Temporal Complexity, $F(3, 66) = 26.887$, $p < 0.001$, with the RT being on average 35.5% shorter in the FM100 (fastest) conditions than in the FM25 (slowest) conditions. However, there was no main effect of group ($F(1, 22) = 1.295$, $p = 0.267$). The same ANOVA on ACC revealed a main effect of Temporal Complexity $F(3, 66) = 17.909$, $p < 0.001$, with, on average, 32.4% less accurate response in the FM25 conditions than in the FM100 conditions (most accurate). There was no main effect of Group for ACC ($F < 1$).

Imaging

Spectral Complexity

Within-group contrasts. We found right auditory cortex sensitivity to spectral complexity in both groups (Table 2), with peak activity in the lateral aspect of HG, 4mm more medially on the x axis in the AUT group. Figure 3 (i) shows that, using an uncorrected threshold ($p<0.001$), both groups showed bilateral activity centered on HG that extended along the anterolateral STG, mainly on the right. No groups exhibited negative spectral complexity effects.

Conjunction. A conjunction of multi-tone harmonic vs. single tone non-harmonic condition contrasts (Table S2, Figure S1) revealed that spectral complexity activity increases common to both groups were centered on HG bilaterally and extended to its lateral portion, mostly on the right.

Between-group contrasts. The comparisons revealed no suprathreshold voxels for the TYP>AUT and AUT>TYP contrasts, suggesting that spectral complexity processing did not differ between the groups.

Between-group comparisons of mean signal change in ROI. A mixed model of Group x ROI x Spectral level on mean ROI signal change values revealed a trend for a Group X ROI X Task interaction, $t(863) = -1.86, p = .063$. The bar plots in Figure 3 (ii) show that activity in PAC ROI tends to be greater in the AUT group.

Table 2. Within-group activity associated with auditory complexity. The coordinates are in MNI space. The critical threshold was *t* = 4.58, *p*<0.05 FWE-corrected. (d=Cohen's effect size; k = number of voxels)

		Left						Right					
Region	BA	x	y	z	*t*	D	k	x	y	z	*t*	d	k
Higher Spectral Complexity													
TYP													
Heschl's gyrus	41							60	-8	4	6.07	0.90	96
AUT													
Heschl's gyrus	41							54	-10	2	4.83	0.72	4
Negative Spectral Complexity													
no significant loci													
Increasing Temporal Complexity													
TYP													
Temporal													
Sup. temp. gyrus	41/22	-48	-20	8	13.79	2.04	2218	60	-8	4	16.41	2.43	2192
Frontal													
Middle frontal gyrus	8	-24	28	46	6.24	0.93	257	30	28	48	6.16	0.92	143
Superior frontal gyrus	9	-14	44	38	5.27	0.78	32						
Precentral gyrus	4							46	-12	38	5.02	0.74	16
Superior medial gyrus	10							4	54	10	4.89	0.72	35
Parietal													
Angular gyrus	39	-46	-64	46	4.89	0.72	550	42	-76	38	5.60	0.83	41
	39	-52	-68	32	5.57	0.83	340	54	-66	26	4.89	0.72	16
Precuneus	7	-8	-52	66	5.07	0.75	18	10	-58	50	5.00	0.74	30
Limbic lobe													
Anterior Cingulate	24	-6	36	-10	5.52	0.82	255						
AUT													
Temporal													
Sup. temp. gyrus	41/22	-48	-18	6	13.30	1.97	1133	56	-10	2	13.47	2.00	1303
Middle temp. gyrus	21	-66	-18	-14	4.82	0.71	3						
Decreasing Temporal Complexity													
TYP													
Frontal													
Inferior frontal gyrus	45	-32	24	-4	5.12	0.76	40	44	22	2	6.60	0.98	389
Inferior frontal gyrus	44							40	10	26	5.38	0.80	41
Superior frontal gyrus	6							4	14	52	5.12	0.77	33
AUT													
Frontal													
Inferior frontal gyrus	45							54	18	24	5.20	0.77	65

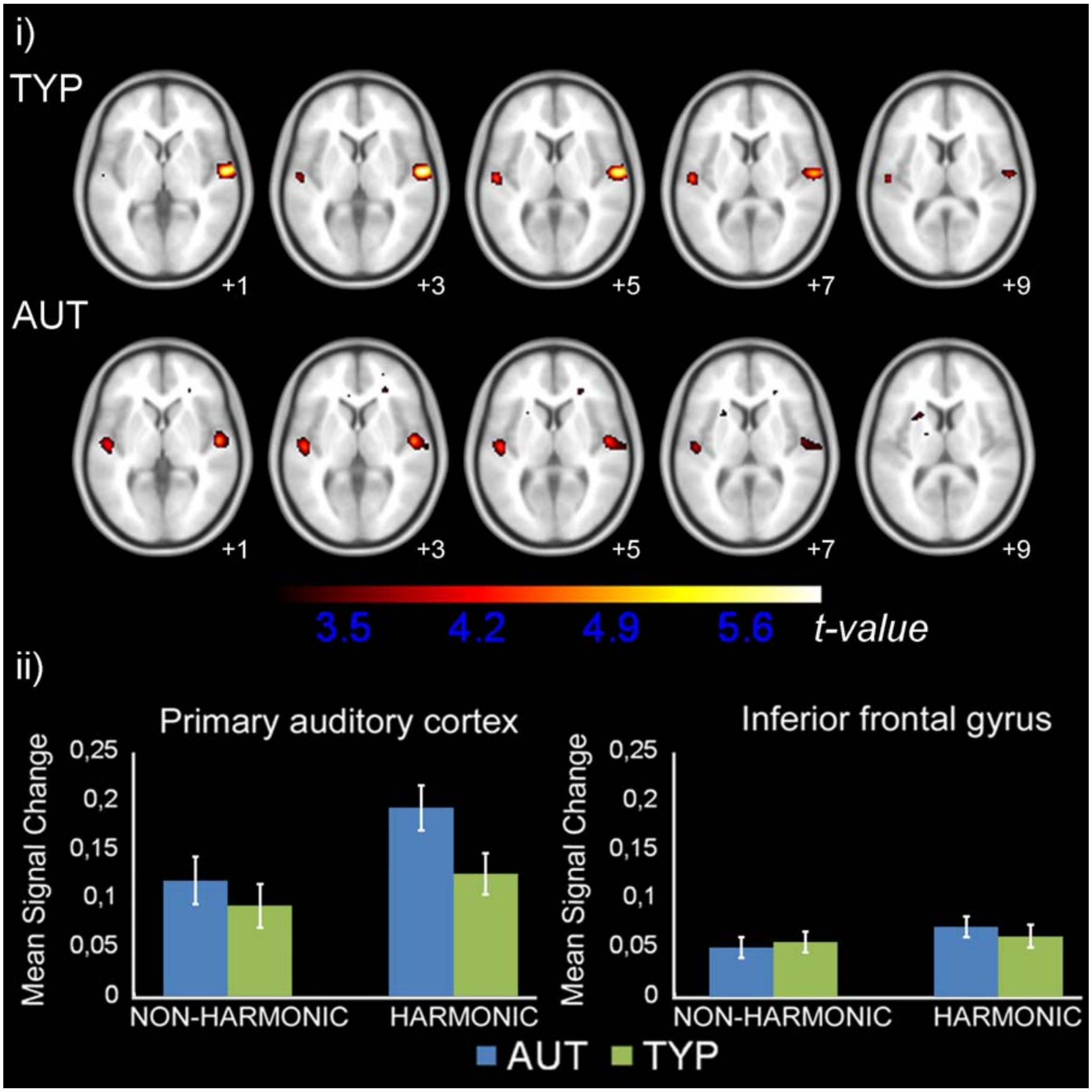


Figure 3. Spectral complexity is associated with higher activity in primary auditory cortex in AUT. (i) BOLD-contrast activity maps associated with spectral complexity effects in both groups. *T*-statistical maps, using an uncorrected critical threshold of p <.001, are superimposed on the SPM5 T1 template. Axial images are shown in the neurological convention with MNI z-coordinate labels. (ii) Mean signal change in primary auditory cortex (left) and the inferior frontal gyrus (right) for non-harmonic and harmonic conditions. Errors bars represent standard errors.

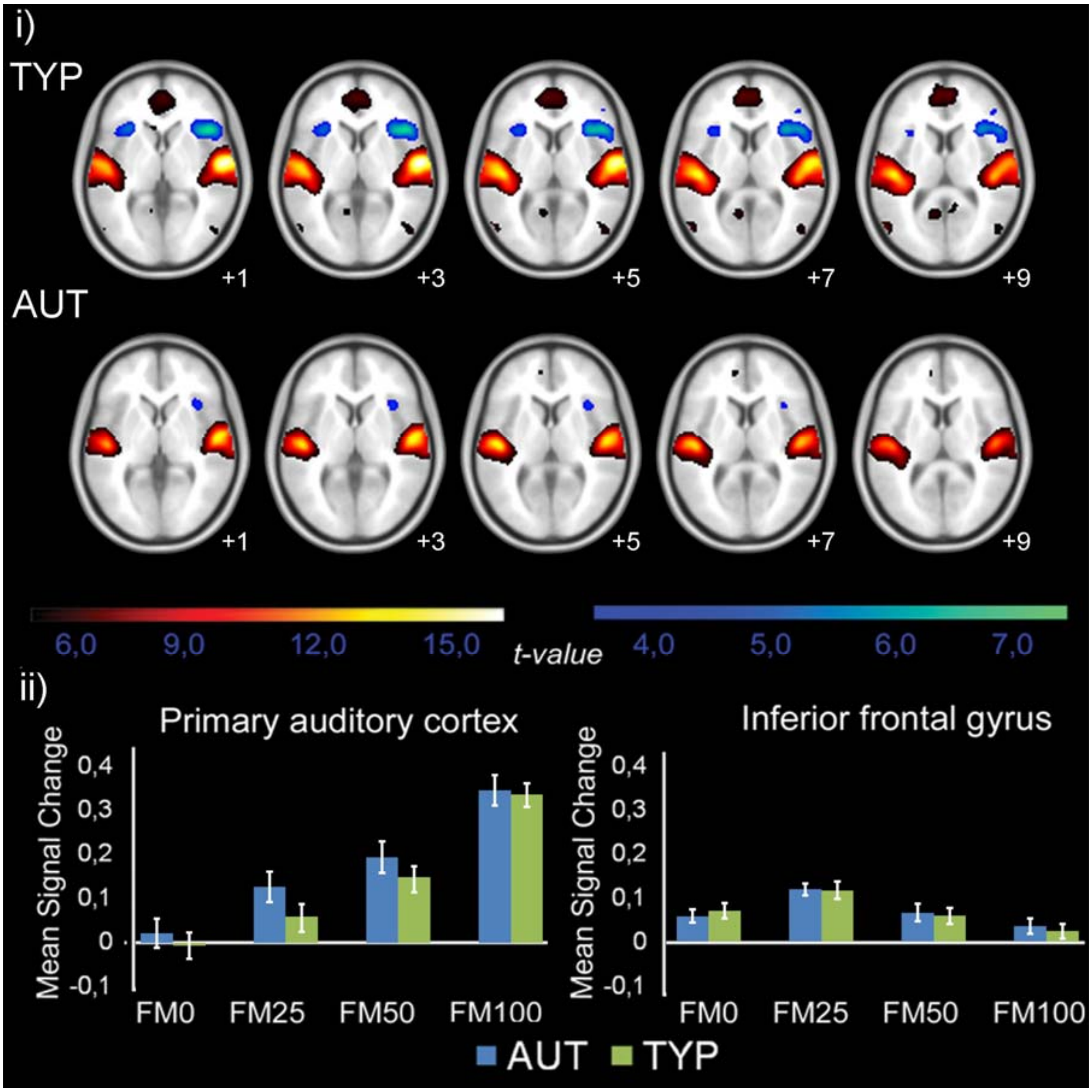


Figure 4. Increasing temporal complexity is associated with higher activity in primary auditory cortex in AUT. (i) BOLD-contrast activity maps showing temporal complexity effects in both groups. BOLD activity increases (red) and decreases (blue) associated with increasing temporal complexity. *T*-statistical maps, using an uncorrected critical threshold of *p* <.001, are superimposed on the SPM5 T1 template. Axial images are shown using the neurological convention with MNI z-coordinate labels. (ii) Mean signal change in primary auditory cortex (left) and inferior frontal gyrus (right) for FM0, FM25, FM50 and FM200 conditions. Errors bars represent standard errors.

Temporal Complexity

Within-group contrasts. To investigate activity related to increasing temporal complexity, the parametric effect of modulation depth levels was computed ($p_{unc}<0.001$). These analyses (Table 2, Figure 4 (i)) revealed bilateral clusters encompassing HG and surrounding posterior, lateral and anterior portions of the STG with activity peaks in medial HG in both groups. In TYP, this contrast also revealed activity in frontal and parietal lobes.

Signal decreases associated with increasing temporal complexity (Figure 4 (i), Table 2) revealed significant activity decreases in IFG bilateral in the TYP group and on the right only for AUT.

Conjunction. Common signal increases related to increasing temporal complexity revealed bilateral activity centered on HG extending towards the STG, mostly in its anterolateral portion (Table S2). Figure S2 reveals that the conjunction analysis also identified activity in the left angular gyrus and that the right insula and IFG commonly showed signal decrease.

Between-group contrasts. As shown in Figure 5 (Table 3), the TYP group showed greater signal increase related to increasing temporal complexity in auditory cortex ($p_{unc}<0.001$). Specifically, the TYP>AUT contrast revealed bilateral effects in posteromedial HG and in anterolateral STG. The reverse contrast (AUT>TYP) showed no significant effects indicating that no areas were more strongly associated with increasing temporal complexity in AUT. Between-group temporal complexity effects were studied separately for the single tone and harmonic carrier signals (Figure 5). For the non-harmonic conditions, one region in right anterolateral STG was more sensitive to temporal complexity increases in the TYP group. The same analysis for the harmonic conditions revealed foci in posteromedial HG and anterolateral STG bilaterally. The comparison of between-group (TYP>AUT) changes associated with harmonic vs. single tone signals revealed stronger sensitivity to increasing temporal complexity in the STG ($p= 0.008$ on the right; p= 0.019 on the left) and in posteromedial HG (p= 0.039 on the right; p= 0.023 on the left).

Between-group comparisons of mean signal change in ROI. A mixed model of Group X ROI X Temporal levels on mean ROI signal change values revealed a significant Group X ROI X Task interaction, $t(863) =-8.91, p <.001$. The plots in Figure 4 (ii) show that activity in PAC ROI in greater in the AUT group. This Group X Temporal effect in PAC ROI was confirmed by examining the simple effect, $t(418) =-2.16, p =.031$.

Hemispheric specialization. The LI computations (Table S3) for spectral complexity revealed right lateralization for both masks and both groups. Conversely, the LI values computed for temporal complexity revealed left lateralization in both groups for the STG and IFG. No significant between-group differences were observed ($p > 0.05$).

Table 3. Activity associated with group differences in spectral and temporal complexity effects. Temporal complexity is shown for both carrier signals (pure and harmonic tones), pure carrier alone and harmonic carrier alone. The coordinates are in MNI space. The critical threshold was *t* = 3.16, *p*<0.001 uncorrected. (d = Cohen's effect size; k = number of voxels)

	Left							Right					
Region	BA	x	y	z	*t*	d	k	x	y	z	*t*	d	k
Spectral Complexity													
TYP > AUT													
no significant loci													
AUT > TYP													
no significant loci													
Temporal Complexity													
TYP>AUT													
Superior temp. area	22	-64	-8	4	3.93	0.58	47	68	-10	4	4.62	0.69	98
Postero-medial HG	41	-48	-22	14	3.81	0.56	72	46	-26	8	3.76	0.56	23
AUT > TYP													
no significant loci													
Temporal Complexity (Pure Carrier Tone)													
TYP>AUT													
Superior temp. area	22							68	-10	4	3.23	0.48	2
AUT>TYP													
no significant loci													
Temporal Complexity (Harmonic Carrier Tone)													
TYP>AUT													
Superior temp. area	22	-62	-6	4	3.56	0.53	32	68	-10	4	3.95	0.58	94
		-68	-22	4	3.43	0.51	6						
Postero-medial HG	41	-42	-32	6	3.61	0.53	17	44	-28	6	3.23	0.48	2
AUT>TYP													
no significant loci													

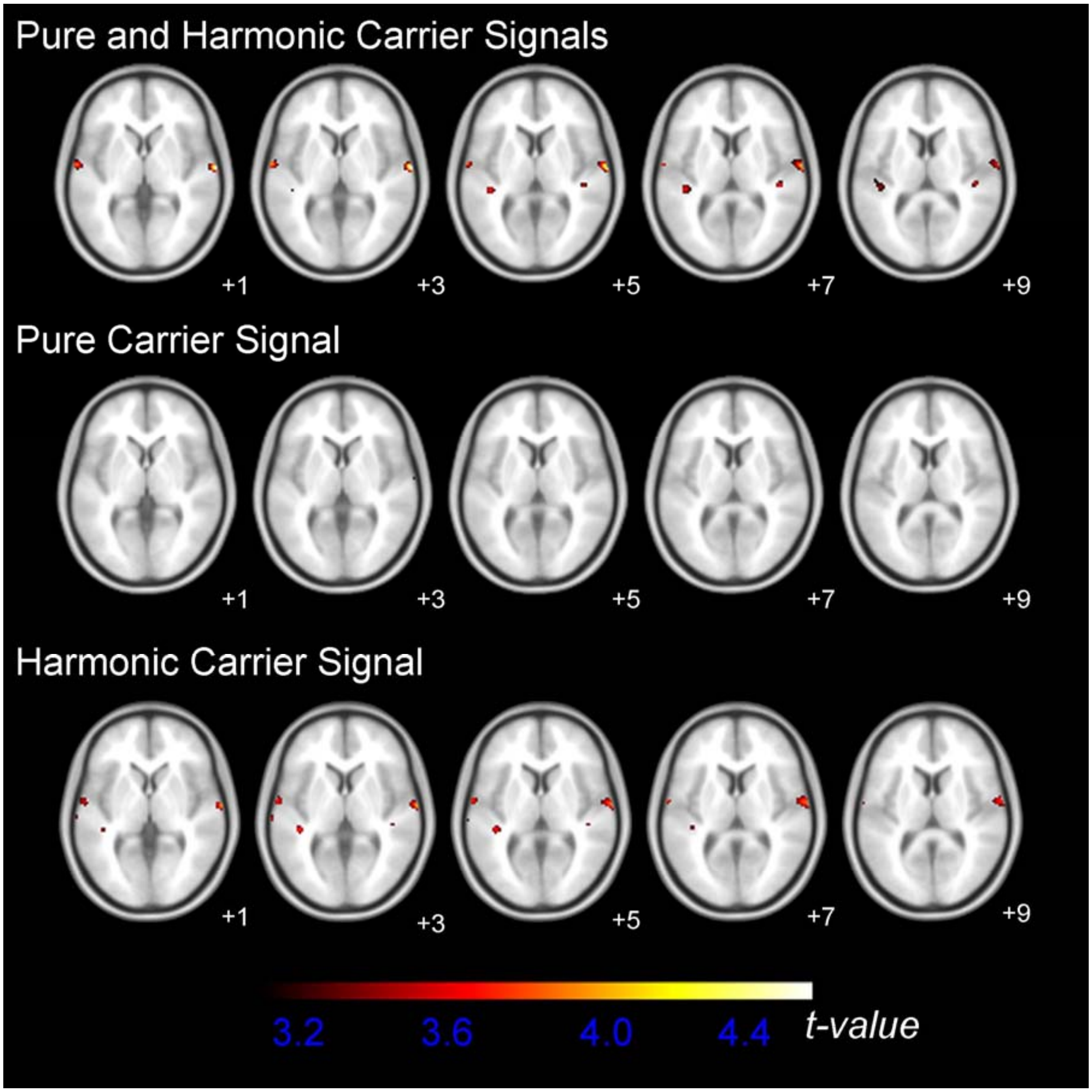


Figure 5. Activity maps associated with between-group differences in temporal complexity effects. Temporal complexity effects are shown averaged across pure and harmonic carrier signals and separately for pure and harmonic carrier signals. The *t*-statistical map, using an uncorrected critical threshold of *p* <.001, is superimposed on the SPM5 T1 template. Axial images are shown using the neurological convention with MNI z-coordinate labels.

DISCUSSION

Functional organization of auditory complexity processing

The contrast between harmonic and single tone conditions revealed bilateral activity in HG, the location of the primary auditory cortex, with an anterolateral extension of the activity along the STG, mainly on the right. Previous studies comparing harmonic to non-harmonic tones reported either activity in both HG and lateral STG (Hall, et al., 2002) or no significant activity (Hart, et al., 2003). We report an anterolateral activity extension intermediate between these two studies. Similar patterns have been observed in studies of spectral complexity processing using pure tone sequences varying in frequency, with activity seen in bilateral STG and right STS (Jamison, et al., 2006; Zatorre & Belin, 2001) or in right planum temporale (Hyde, Peretz, & Zatorre, 2008). In sum, the present results with respect to spectral modulation are generally in accord with previous imaging studies of non-autistics.

Increasing temporal complexity was associated with bilateral activity clusters centered on HG and extending to postero- and anterolateral STG. Previous studies that used the same 5Hz modulation rate to compare frequency modulated to unmodulated tones revealed an overlapping pattern (Hall, et al., 2002; Hart, et al., 2003) while investigation of frequency modulated speech-like sounds resulted in a comparable pattern (Thivard, et al., 2000). Others studies used increasing rates of pure tone alternation within a sequence (Jamison, et al., 2006; Zatorre & Belin, 2001) and reported changes limited to HG. Parametric increases in modulation rate of random spectrogram sounds have revealed HG and left anterolateral STG activity (Schonwiesner, et al., 2005b), effects also observed for amplitude modulated sounds, albeit with greater response in posterior STG (Giraud, et al., 2000; Hart, et al., 2003). The convergence between our findings and previous studies indicates that modulation depth is a reliable probe for studying temporal complexity. Lastly, we found similar response lateralization in the two groups: rightward for spectral and leftward for temporal complexity, consistent with previous evidence (Zatorre, et al., 2002). In sum, we report a pattern of activity in response to complex versus simple auditory material demonstrating the hierarchical organization of auditory processing, suggesting that autistics do not differ strongly from controls with respect to this basic architecture. Moreover, the absence of between-group differences and the spatial concordance of activity between groups suggest that the task was performed similarly by all. The task served as an attentional control and was designed for accuracy to be fairly high in all participants; therefore no between-group differences were expected.

Contribution to current models of auditory processing abilities in autism

On the basis of the visual complexity hypothesis (Bertone, et al., 2005), the difference in autistic auditory performance related to simple versus complex processing (Samson, et al., 2006), and the hierarchical organization of the auditory system (Wessinger, et al., 2001), we expected to observe between-group processing differences in non-primary auditory fields located along the STG. Specifically, autistics should exhibit reduced activity in auditory areas specifically recruited for processing complex auditory stimuli. The current results are consistent with this prediction as autistics showed decreased levels of activity related to temporal complexity in non-primary auditory regions within the STG that are recruited for processing temporally complex sounds in controls (Hall, et al., 2002; Hashimoto, Homae, Nakajima, Miyashita, & Sakai, 2000; Talavage, Ledden, Benson, Rosen, & Melcher, 2000).

In contrast, no significant between-group differences related to spectral complexity were seen, supporting the idea that autistics process spectral complexity in a typical fashion. The visual complexity hypothesis suggests that autistics will display reduced non-primary activity related to complex auditory processing. However, this model does not allow predictions specific to the spectral or temporal dimensions. On the other hand, behavioral results largely predict typical spectral complexity processing in autism e.g. intact speech in speech-like noise detection for spectrally but not for temporally modulated noise (Alcantara, et al., 2004; Groen, et al., 2009), strong musical abilities (e.g. Miller, 1989) and enhanced chord disembodying (Heaton, 2003; Mottron, et al., 1999).

As for temporal complexity, the neural activity differences reported here might be related to specific impaired speech discrimination in temporally modulated noise (Alcantara, et al., 2004; Groen, et al., 2009). However intact temporally complex non-social sound processing has also been observed (Bonnel, et al., 2010). This indicates that the atypical pattern of activity reported here may be related to unimpaired processing of complex non-social sounds in autism. However, this might not be the case for complex social sound processing. Considering that adequate music perception relies mostly on spectral processing (Warrier & Zatorre, 2002) and that temporal information is crucial for speech recognition (Shannon, Zeng, Kamath, Wygonski, & Ekelid, 1995; Tallal, et al., 1993), the dissociation between typical spectral and atypical temporal cortical effects we observed in autistics could explain the dissociation between heighted musical and atypical behavioral and cortical responses related to speech-like or speech sound processing in autistics (e.g. Alcantara, et al., 2004; Boddaert, et al., 2004; Ceponiene, et al., 2003; Lepisto, et al., 2005). Although our stimuli were non-linguistic and represent only basic acoustic features, they shared some characteristics of speech such as low frequency modulation rates which are thought to be essential for speech recognition (Houtgast & Steeneken, 1985).

Interestingly, we found stronger between-group differences related to temporal complexity in anterolateral STG for the harmonic compared to the pure carrier signal, when spectral and temporal axes of complexity are combined. This suggests larger between-group effects for more complex auditory material which are expected to elicit more extensive non-primary activity than sounds varying exclusively along spectral or temporal complexity axes (Hall, et al., 2002; Hart, et al., 2003). This is in line with the visual complexity hypothesis that asserts that differences between groups should emerge for processing information recruiting more extensive neural resources (Bertone, et al., 2005).

Are group differences limited to non-primary regions?

We found greater primary auditory signal change in autistics related to complex auditory processing, more for temporal than spectral dimensions, indicating that autistics rely more on primary areas, compared to non-autistics, when processing complex sounds. A greater reliance on primary auditory processes in autism could be related to previous demonstrations of greater orientation toward the low-level, perceptual information in speech (i.e. pitch) in autism (Heaton, Hudry, Ludlow, & Hill, 2008; Jarvinen-Pasley, Wallace, Ramus, Happe, & Heaton, 2008). Moreover, the reduced level of activity in auditory STG regions specifically sensitive to the non-acoustic features of speech stimuli, and increased activity within the HG region, more sensitive to acoustic variations in sounds (Okada, et al., 2010), might represent the correlate of a more perceptually-based processing style for speech sounds in autism (Heaton, Hudry, et al., 2008; Jarvinen-Pasley, et al., 2008). As emphasized by the EPF model (Mottron, et al., 2006), analysis within a processing hierarchy is biased towards lower-levels in autism (Soulieres, et al., 2009). Furthermore, the EPF model would predict a stronger engagement of primary regions for processing simple tones, as enhanced pitch processing abilities in autism is the most replicated and robust finding related to atypical auditory processing (e.g. Bonnel, et al., 2003; Heaton, 2003; Lepisto, et al., 2008; O'Riordan & Passetti, 2006). However, our study was insufficiently powered to detect between-group differences in pure tone processing and a direct investigation of this prediction remains to be conducted. The findings of diminished non-primary and increased primary auditory sensitivity for complex sounds suggest that, as in vision (Bertone, et al., 2005), complexity is a relevant variable in characterizing auditory processing mechanisms in autism.

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Supplementary material

Table S1. We observed no group performance differences. Accuracy (percent) and RT (ms) performance measures are shown for each sound condition. Group differences were assessed using independent sample *t*-tests. Values are reported as mean and standard deviation - *M* (*SD*).

	TYP	AUT	*p*
Stimulus Conditions			
Pure FM0			
Accuracy	89.39(12.69)	93.91(9.41)	0.328
RT	2187.76(863.49)	1685.99(587.80)	0.106
Pure FM25			
Accuracy	78.03(18.29)	67.95(27.40)	0.399
RT	2468.41(660.34)	2229.45(819.41)	0.448
Pure FM50			
Accuracy	89.77(18.29)	92.95(10.26)	0.598
RT	2040.76(814.99)	1807.26(822.10)	0.494
Pure FM100			
Accuracy	93.53(12.82)	94.87(6.84)	0.822
RT	1719.47(579.56)	1406.33(594.53)	0.207
Harmonic FM0			
Accuracy	90.53(14.80)	95.19(6.10)	0.310
RT	2034.92(694.73)	1479.24(488.21)	0.032
Harmonic FM25			
Accuracy	75.76(29.51)	65.06(24.33)	0.341
RT	2386.26(646.37)	2325.10(907.67)	0.854
Harmonic FM50			
Accuracy	90.53(17.98)	92.95(10.26)	0.684
RT	2039.44(738.46)	1717.36(871.10)	0.344
Harmonic FM100			
Accuracy	90.53(17.980	95.51(6.69)	0.363
RT	1614.00(455.85)	1443.20(598.43)	0.447

Table S2. Conjunction analyses. BOLD-contrast activity commonly associated with spectral and temporal complexity changes across groups. The coordinates are in MNI space. The critical threshold was *t* = 4.58, *p*<0.05 FWE-corrected. (d = Cohen's effect size; k = number of voxels)

	Left							Right					
Region	BA	x	y	z	*t*	d	k	x	y	z	*t*	d	k
Higher Spectral Complexity													
Heschl's gyrus	41							54	-10	4	4.60*	0.70	175
Increasing Temporal Complexity													
Heschl's gyrus	41	-50	-18	6	13.10*	1.94	1969	56	-10	2	13.47*	2.00	2081
Decreasing Temporal Complexity													
	no significant loci												

Table S3**.** Laterality indices are shown for spectral and temporal complexity modulation with regards to both voxel count and value for both groups for Superior Temporal Gyrus (STG), and Inferior Frontal Gyrus (IFG) ROIs. -1 represents complete left lateralization and +1 represents complete right lateralization. Between-group differences were assessed using two sample *t*-tests. Values are reported as mean and standard deviation - *M* (*SD*).

	AUT	**TYP**	***p***
Higher spectral complexity			
STG			
LI Voxel Count M (SD)	0.069 (0.155)	0.023 (0.25)	0.834
LI Voxel Value M (SD)	0.081 (0.216)	0.035 (0.291)	0.878
IFG			
LI Voxel Count M (SD)	0.034 (0.404)	0.013 (0.351)	0.801
LI Voxel Value M (SD)	0.038 (0.431)	0.012 (0.378)	0.841
Increasing temporal complexity			
STG			
LI Voxel Count M (SD)	-0.048 (0.226)	-0.033 (0.084)	0.96
LI Voxel Value M (SD)	-0.047 (0.287)	-0.026 (0.082)	0.0957
IFG			
LI Voxel Count M (SD)	-0.132 (0.344)	-0.203 (0.367)	0.582
LI Voxel Value M (SD)	-0.153 (0.369)	-0.215 (0.4)	0.552

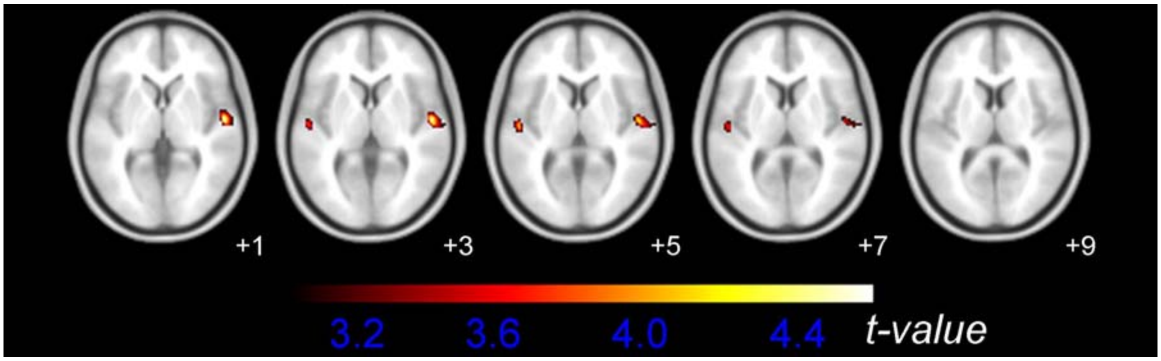

Figure S1. Common areas of activity related to spectral complexity. BOLD-contrast activity conjunction maps showing increasing spectral complexity effects across both groups. *T*-statistical map, using an uncorrected critical threshold of p <.001, is superimposed on the SPM5 T1 template. Axial images are shown using the neurological convention with MNI z-coordinate labels.

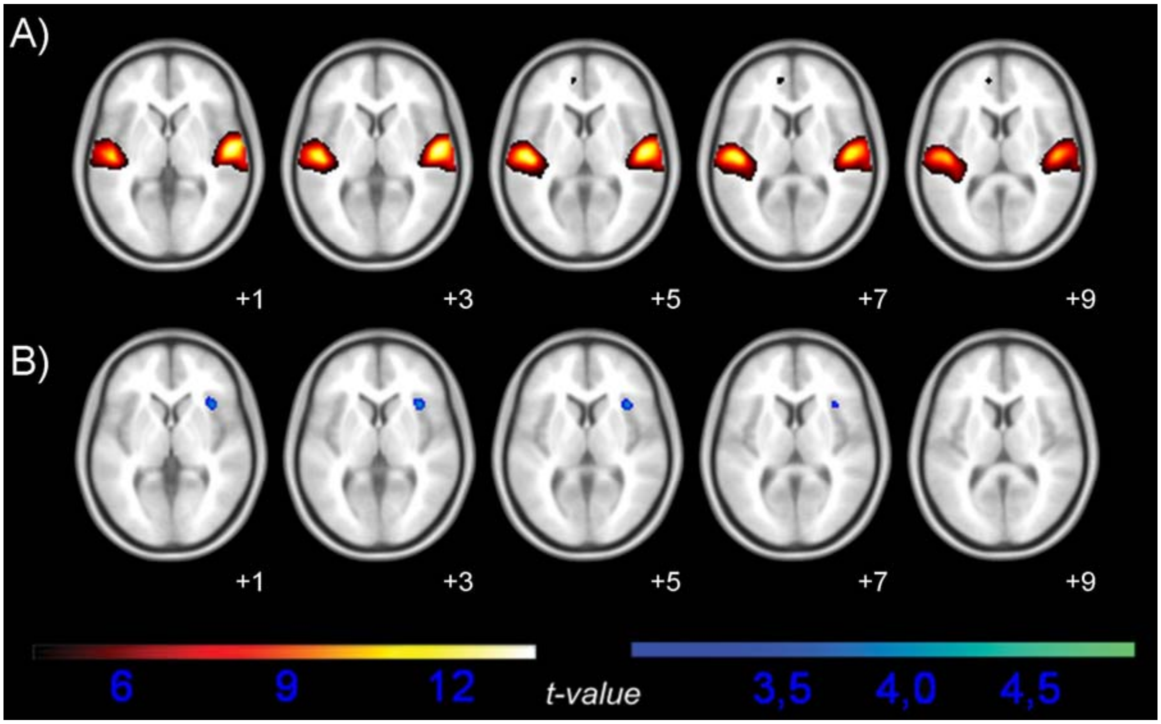

Figure S2. Common areas of activity related to temporal complexity. (A) BOLD-contrast activity increases conjunction associated with increasing temporal complexity across both groups. (B) BOLD-contrast activity decreases conjunction associated with increasing temporal complexity across both groups. A *t*-statistic map, using an uncorrected critical threshold of *p* <.001, is superimposed on the SPM5 T1 template. Axial images are shown using the neurological convention with MNI z-coordinate labels.

Chapitre 5. Discussion

5.1 Résumé des objectifs et des résultats

Cette thèse avait pour but de vérifier la possible extension des prédictions de l'hypothèse spécifique à la complexité à la modalité auditive dans l'autisme. Suite à l'observation d'une dissociation de performance lors du traitement de l'information visuelle de *bas niveau*, Bertone et ses collaborateurs (2005) ont formulé l'hypothèse suggérant que les autistes obtiendraient des performances supérieures ou inférieures par rapport à celles des non autistes pour traiter les stimuli requérant l'implication d'une seule ou de plusieurs régions corticales fonctionnelles, respectivement. Dans l'autisme, un traitement perceptif atypique est observé tant pour le traitement de l'information visuelle qu'auditive (Mottron et al., 2006). Il est donc possible qu'une hypothèse d'abord formulée pour expliquer certaines particularités du traitement de l'information visuelle puisse aussi s'appliquer à la modalité auditive.

Ce travail visait donc, d'abord, à vérifier si un parallèle pouvait être tracé entre les particularités du traitement de l'information visuelle et auditive dans l'autisme. Pour ce faire, une revue de la littérature a permis d'explorer les particularités du traitement auditif dans cette population. Ensuite, la généralisation de l'hypothèse spécifique à la complexité à la modalité auditive nécessitait l'identification de stimuli auditifs qui, tout comme les stimuli visuels de premier et deuxième ordre, pouvaient être dissociés selon l'étendue du réseau cortical requis pour les traiter. Une méthode de méta-analyse quantitative a donc été utilisée afin d'étudier comment la complexité acoustique est représentée au niveau cortical. Enfin, une étude empirique a permis de directement vérifier la généralisation des prédictions de l'hypothèse spécifique à la complexité à la modalité auditive. Ainsi, la réponse corticale associée au traitement de stimuli auditifs simples et complexes a été mesurée et comparée chez des participants autistes et non autistes.

5.1.1 Niveau de performance et complexité auditive dans l'autisme

La première partie de cette thèse visait à examiner les particularités du traitement de l'information auditive dans l'autisme via une revue exhaustive des études disponibles en 2006. L'hypothèse spécifique à la complexité a été formulée suite à l'observation d'une dissociation de performance associée au traitement de stimuli visuels dans l'autisme. Pour pouvoir généraliser les prédictions de cette hypothèse à la modalité auditive, il était nécessaire de mettre en évidence l'existence d'une dissociation de performance lors du traitement auditif, possiblement analogue à celle observée en vision. Ainsi, la présente étude allait servir à identifier les conditions auditives pour lesquelles les autistes obtiennent des performances supérieures ou inférieures à celles des non autistes.

Dans le but de dépeindre le profil de performance associé au traitement de l'information auditive dans l'autisme, les différentes études de la littérature ont été revues et classifiées. Idéalement, afin de vérifier la présence d'une dissociation de performance similaire à celle observée en vision, soit selon la complexité du matériel présenté, il aurait fallu pouvoir limiter la revue aux études à travers lesquelles seulement la complexité des stimuli variait. Cependant, la revue a plutôt été faite à travers les différentes études du traitement de l'information auditive dans l'autisme et la classification selon la complexité des stimuli ainsi que de la tâche à effectuer. Donc, il est important de préciser que la présente revue démontre un lien inverse entre complexité des stimuli ainsi que de la tâche et le niveau de performance. Il est donc possible de conclure que la complexité semble un élément pertinent pour révéler une dissociation de performance dans l'autisme. Cette dissociation pourrait se retrouver tant au niveau de la complexité du matériel que de celle de la tâche.

De manière générale, on constate une correspondance inverse entre le niveau de performance et la complexité du matériel auditif à traiter. En effet, les autistes obtiennent de manière consistante des performances supérieures à celles des non autistes pour traiter les stimuli auditifs simples, c'est-à-dire les sons purs. Cette supériorité est principalement remarquée pour des tâches de discrimination, de catégorisation et de mémorisation de sons purs (Bonnel, et al., 2010; Bonnel, et al., 2003; Heaton, 2003; Jones, et al., 2009; O'Riordan & Passetti, 2006). De manière similaire, les études d'électrophysiologie ont montré une augmentation de la réponse corticale aux stimuli simples, à la fois plus rapide (Gomot, et al., 2002) et plus ample (Ferri et al., 2003; Lepisto et al., 2008; Lepisto, et al., 2005; Lepisto, Nieminen-von Wendt, von Wendt, Naatanen, & Kujala, 2007). Inversement, les études rapportant un niveau de performance inférieur chez les autistes en comparaison aux non autistes impliquent plutôt le traitement de matériel auditif plus complexe; par exemple, pour le traitement des sons vocaux présentés sur un fond bruité (Alcantara, Weisblatt, Moore, & Bolton, 2004; Groen et al., 2009) ou pour percevoir les indices prosodiques (Kujala, Lepisto, Nieminen-von Wendt, Naatanen, & Naatanen, 2005; Peppe, McCann, Gibbon, O'Hare, & Rutherford, 2007). On observe aussi une diminution de l'activité cérébrale associée au traitement de sons complexes langagiers (Ceponiene et al., 2003; Gervais, et al., 2004; Lepisto, et al., 2005; Russo, Zecker, Trommer, Chen, & Kraus, 2009; Whitehouse & Bishop, 2008) ainsi que pour des sons complexes non-vocaux (Boddaert et al., 2003; Boddaert, Chabane, Belin, et al., 2004) chez les autistes par rapport aux non autistes.

La synthèse des études de la littérature révèle donc la présence d'une relation inverse entre complexité et performance lors du traitement de l'information auditive dans l'autisme. Ceci permet donc de considérer la généralisation des prédictions de l'hypothèse spécifique à la complexité à la modalité auditive. En effet, il est possible que, tel que proposé en vision, certaines difficultés à traiter l'information auditive complexe puissent être comprises comme des conséquences d'un traitement cortical auditif atypique dans l'autisme. Les études disponibles en 2006 ont permis de mettre en évidence une supériorité pour traiter les stimuli simples de *bas niveau* (sons purs) ainsi que certains déficits associés au traitement auditif de niveau *intermédiaire* et de *haut niveau* (sons complexes non-vocaux et langagiers). Aucune étude portant sur des stimuli complexes de *bas niveau* n'était disponible. Or, selon l'hypothèse spécifique à la complexité, les autistes devraient aussi démontrer des performances inférieures à celles des non autistes lors du traitement de stimuli auditifs complexes de bas niveau. Une première investigation de cette hypothèse au niveau comportemental n'a cependant pas démontré le déficit prédit (Bonnel et al., 2010). En effet, dans cette étude, les autistes ont démontré des seuils de discrimination similaires à ceux des non autistes pour des sons spectralement (sons harmoniques) et temporellement complexes (sons modulés par la fréquence ou l'amplitude).

Ce résultat peut suggérer que les stimuli utilisés dans l'étude ne correspondent pas aux stimuli pour lesquels la présence d'un traitement cortical atypique entraînerait une baisse de la capacité de traitement, comme les stimuli complexes musicaux pour lesquels les autistes ne montrent pas de déficit (Heaton, 2003; Heaton, Hermelin, & Pring, 1999; Mottron, et al., 2000). Il est aussi possible de considérer que l'hypothèse spécifique à la complexité ne peut être généralisée à la modalité auditive considérant l'absence de déficit pour traiter des stimuli auditifs de bas niveau complexes dans l'autisme. Alternativement, en supposant qu'un traitement cortical atypique caractérise effectivement l'analyse de l'information auditive dans l'autisme, les performances intactes observées par Bonnel et ses collaborateurs (2010) suggèrent qu'un traitement cortical atypique pourrait plutôt avoir des conséquences au-delà des processus de bas niveau dans la modalité auditive. Au niveau cortical, il est possible que le traitement cortical atypique prédit par l'hypothèse de la complexité se reflète par des différences qualitatives d'activité cérébrale des régions auditives sous-tendant les processus de bas niveau sans nécessairement avoir de conséquence directe au niveau des capacités de traitement perceptif à ce niveau. L'hypothèse spécifique à la complexité pourrait donc se retrouver au sens plus large en audition, avec des conséquences comportementales retrouvées au niveau intermédiaire et pour les processus perceptifs de haut niveau.

En bref, cette première partie de la thèse a permis de mettre en lumière la présence d'une relation entre les capacités de traitement des informations auditives simples et complexes dans l'autisme, ce qui permet de considérer étendre les prédictions de l'hypothèse de la complexité à la modalité auditive.

5.1.2 Représentation corticale de la complexité auditive chez les non autistes

La deuxième partie de la thèse allait servir à identifier des stimuli auditifs pouvant être considérés comme analogues des stimuli visuels de premier et deuxième ordre, c'est-à-dire des stimuli pouvant être dissociés selon l'étendue du réseau de régions corticales impliquées dans leur traitement. Pour ce faire, il était d'abord nécessaire de valider qu'une organisation fonctionnelle hiérarchique caractérise le traitement de l'information au niveau du cortex auditif. Il s'agissait donc d'examiner comment la complexité acoustique est représentée au niveau cortical dans une population non autiste. Ceci allait ensuite permettre d'identifier les stimuli auditifs pouvant être décrits comme simples et complexes en regard de la complexité du réseau cortical requis pour les traiter.

Une méthode de méta-analyse quantitative a été utilisée pour recenser et synthétiser les résultats de 59 études de neuroimagerie rapportant la localisation des activités cérébrales associées à la présentation de matériel de complexité acoustique variable chez des non autistes. Cette méthode permet de visualiser les régions étant le plus systématiquement activées à travers les différentes études en réponse à un type de tâche ou de matériel particulier (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009).

D'abord, en classifiant le matériel utilisé dans chacune des études selon les catégories de sons classiquement retrouvées dans la littérature (sons purs, bruits, musique et sons vocaux), l'organisation fonctionnelle hiérarchique du cortex auditif a été validée. En effet, l'activité associée au traitement des sons simples (sons purs) est limitée au niveau des aires auditives primaires (gyrus de Heschl) tandis que le traitement des catégories de sons complexes (bruit, musique, voix) implique à la fois les aires auditives primaires et non primaires (gyrus temporal supérieur postérieur, latéral et antérieur). Ce patron d'activité correspond donc à une organisation hiérarchique du traitement cortical; soit une augmentation de la sensibilité de la réponse associée aux propriétés complexes des stimuli des aires sensorielles primaires vers les régions non primaires.

Ensuite, considérant que les prédictions de l'hypothèse de la complexité concernent plus spécifiquement les mécanismes cérébraux sous-tendant les processus perceptifs de *bas niveau*, il devenait nécessaire d'identifier des stimuli auditifs traités de manière hiérarchique au sein de ce niveau de traitement. En psychoacoustique, l'augmentation de la complexité passe par des variations de la composition fréquentielle d'un stimulus (complexité spectrale) ou encore des changements au niveau de son décours temporel (complexité temporelle). Ces variations sont d'ailleurs aussi à la base de la composition du matériel auditif de plus haut niveau, comme les sons vocaux ou musicaux. Dans la méta-analyse présentée ici, un système alternatif de classification des stimuli reposant sur la composition acoustique des stimuli est proposé. Cette classification permet l'identification de stimuli de bas niveau incluant soit une composition spectrale ou une composition temporelle complexe (voir haut de la Figure 1). Ainsi, afin d'évaluer la relation entre complexité et traitement cortical de l'information auditive de bas niveau, les régions d'activation systématiquement rapportées à travers les différentes études de neuroimagerie en lien avec l'écoute des sons simples (rouge), spectralement (vert) et temporellement (bleu) complexes ont été superposées (voir bas de la Figure 1).

En accord avec la présence d'un traitement hiérarchique, la superposition permet de visualiser que les régions auditives primaires (gyrus de Heschl) sont activées à la fois par les sons simples et spectralement complexes (les régions en jaune représentant l'intersection des activités présentées en rouge et en vert) ainsi que par les sons simples et temporellement complexes (les régions en violet représentant l'intersection des activités présentées en rouge et en bleu). De plus, l'activité associée à l'écoute de sons complexes s'étend aux régions non primaires situées au niveau du gyrus temporal supérieur antérieur et latéral. Les activations liées au traitement des sons complexes impliquent donc à la fois les aires primaires et non primaires. Le patron d'activité observé suggère que l'analyse des sons spectralement et temporellement complexes nécessite l'implication d'un réseau d'aires corticales fonctionnelles incluant les aires auditives primaires et non primaires.

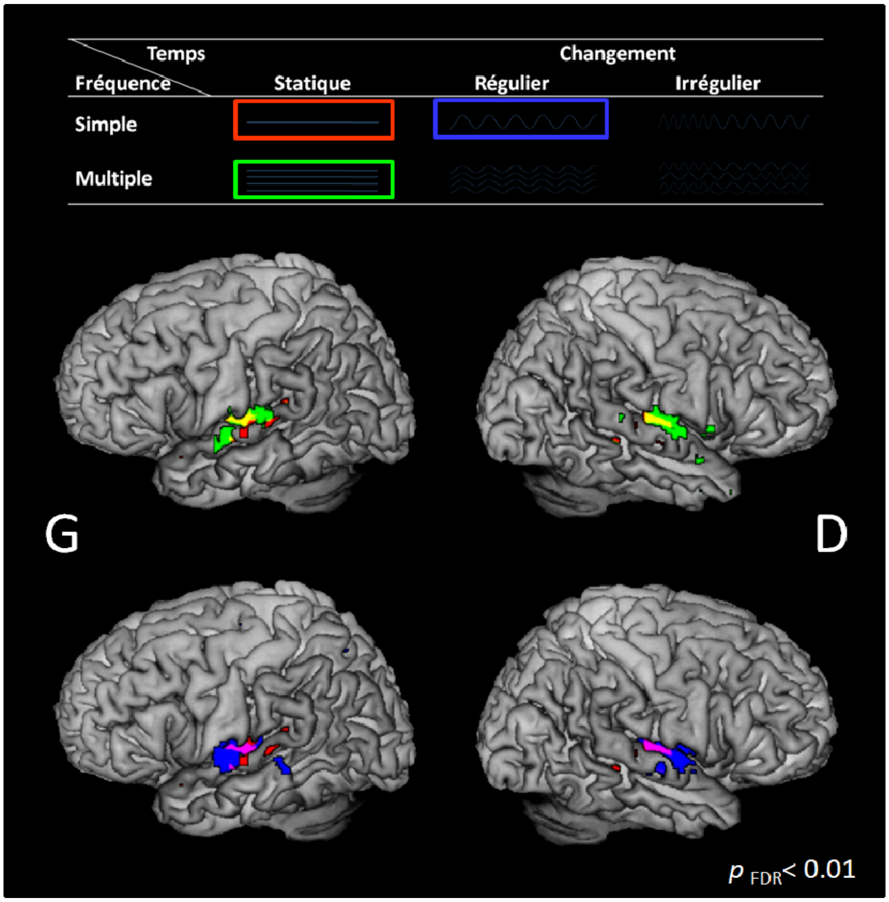

Figure 1. Superposition des régions d'activation systématiquement rapportées dans la littérature à l'écoute des sons simples (rouge), spectralement (vert) et temporellement (bleu) complexes.

Ce résultat permet donc de poursuivre l'analogie entre audition et vision. La représentation corticale hiérarchique des sons purs et complexes (spectralement et temporellement) permet de définir ces stimuli comme simples et complexes en regard de l'étendue du réseau cortical impliqué dans leur traitement. Ces stimuli représentent donc des analogues aux stimuli visuels de premier et de deuxième ordre. Ainsi, la complexité définie au niveau cortical semble être un concept permettant de tracer un parallèle entre les modalités visuelle et auditive.

5.1.3 Vérifier les prédictions de l’hypothèse spécifique à la complexité en audition dans l’autisme

Les deux premières parties de cette thèse ont permis de valider les postulats à la base de la généralisation des prédictions de l’hypothèse de la complexité de la modalité visuelle à la modalité auditive dans l’autisme. D’une part, l’existence d’une relation entre complexité et performance en audition a été démontrée dans la population autistique. D’autre part, des stimuli auditifs analogues aux stimuli visuels de bas niveau simples et complexes ont pu être identifiés.

Conséquemment, la troisième partie de la thèse visait à tester l’hypothèse suggérant qu’un traitement atypique de l’information au niveau cortical puisse sous-tendre certaines difficultés des personnes autistes à traiter des stimuli complexes, c’est-à-dire ceux dont le traitement nécessite l’implication de plusieurs régions fonctionnelles. Inversement, le traitement des stimuli simples, c’est-à-dire ceux dont l’analyse n’implique qu’une région cérébrale fonctionnelle, serait supérieur chez les autistes. Spécifiquement, cette partie de la thèse avait pour objectif de vérifier si les stimuli identifiés comme simples et complexes étaient représentés différemment au niveau du cortex auditif dans l’autisme. Il s’agit d’une première étape pour pouvoir éventuellement lier traitement perceptif et comportement atypique dans la modalité auditive.

Selon l’hypothèse spécifique à la complexité, les autistes devraient démontrer une baisse de l’activité auditive non primaire à l’écoute de sons complexes en comparaison aux non autistes. Pour vérifier cette prédiction, les variations d’activité cérébrale liées à l’écoute de sons analogues aux stimuli visuels de premier et de deuxième ordre ont été mesurées à l’aide de l’IRMf chez un groupe d’individus autistes et un groupe de non autistes. D’abord, en mettant en lumière une extension de l’activité cérébrale aux aires auditives non primaires lors du traitement de l’information auditive complexe versus simple, la présente étude a mis en évidence l’organisation fonctionnelle hiérarchique du traitement de l’information auditive de bas niveau dans les deux groupes.

Ensuite, tel qu’attendu, les analyses de comparaison entre les groupes ont permis de démontrer que les régions corticales non primaires, recrutées pour l’analyse de stimuli auditif complexes, sont sollicitées de manière moins importante chez les autistes, spécifiquement lors du traitement de sons temporellement complexes. Aucune différence significative d’activité cérébrale n’est observée entre les groupes en réponse à la complexité spectrale. En définissant la complexité selon l’extension du réseau cortical requis pour traiter les stimuli, la variation spectrale utilisée ici semble moins complexe que la modulation temporelle. En effet, l’extension de l’activité aux régions auditives non primaires apparaît plus importante pour les stimuli temporellement complexes que pour les stimuli spectralement complexes (voir Chapitre 4). Bien que le modèle de Bertone et al (2005) ne permette pas de faire des prédictions à priori quant aux différences corticales associées à la complexité spectrale versus temporelle en audition, il permet de proposer que les différences entre autistes et non autistes devraient être plus marquées pour les stimuli dont le traitement cortical est plus complexe, plus étendu et requiert une intégration de l’information à travers un plus grand réseau neuronal. Les résultats obtenus ici semblent donc confirmer une telle prédiction.

En plus, le design utilisé ici a permis d’investiguer les variations d’activité cérébrale associées à l’augmentation de la complexité, par exemple pour des stimuli dont la complexité variait simultanément au niveau des composantes spectrales et temporelles. Cette analyse démontre une réduction de l’activité auditive non primaire dans l’autisme plus marquée pour ces stimuli spectro-temporellement complexes que pour des stimuli n’incluant que des variations au niveau temporel. Chez le sujet typique, on rapporte que le traitement de sons spectro-temporellement complexes implique une plus grande extension aux régions auditives non primaires que le traitement des sons variant selon un seul axe de complexité (Hall et al., 2002; Hart, Palmer, & Hall, 2003). Ce résultat supporte donc l’hypothèse de la complexité suggérant que les différences entre autistes et non autistes devraient être maximisées pour des stimuli dont le traitement nécessite l’implication d’un réseau étendu d’aires cérébrales.

En bref, la présente étude a permis de valider que la complexité était représentée de manière atypique au niveau cortical chez les personnes autistes en comparaison aux non autistes. Ce résultat supporte la généralisation des prédictions de l’hypothèse spécifique à la complexité à la modalité auditive.

5.2 Discussion générale

L’ensemble des études présentées seront maintenant discutées, d’abord au niveau de la concordance entre les résultats de la méta-analyse quantitative et ceux de l’étude du traitement cortical de l’information auditive. Ensuite, les différences d’activité corticale associées au traitement de stimuli complexes seront mises en relation avec la capacité de traitement de l’information auditive et langagière dans l’autisme. Elles seront aussi discutées en lien avec les particularités neuroanatomiques et du traitement auditif sous-cortical décrites dans l’autisme. De plus, l’extension des résultats à travers les troubles du spectre autistique, spécifiquement le syndrome d’Asperger, sera examinée. Enfin, les implications cliniques ainsi que les possibles futures avenues de recherche seront abordées.

5.2.1 Représentation corticale de l’information auditive : validation des stimuli

Afin de valider que les stimuli utilisés permettaient effectivement d’étudier le traitement cortical hiérarchique de l’information auditive de bas niveau, il était d’abord nécessaire de vérifier la concordance entre les activations cérébrales associées au traitement de l’information auditive complexe à travers la littérature (Chapitre 3) et dans l’étude empirique (Chapitre 4). D’abord dans la méta-analyse, afin de mettre en évidence les régions spécifiquement sensibles à l’augmentation de la complexité auditive, les régions d’activation systématiquement rapportées à travers la littérature en réponse à des sons simples, spectralement et temporellement complexes (respectivement en rouge, vert et bleu à la figure 1) ont été comparées. La figure 2 présente les résultats de ces comparaisons, représentant les régions dont l’activité est associée au traitement de la complexité spectrale (spectralement complexe > simple) et de la complexité temporelle (temporellement complexe > simple). Les effets associés à l'analyse de sons spectralement complexes impliquent les portions latérale et antérieure du gyrus temporal supérieur ainsi que les régions postérieures du cortex auditif, principalement à gauche. Pour la complexité temporelle, on observe une activité auditive bilatérale au niveau de la portion latérale du gyrus de Heschl et s'étendant principalement vers les régions antérieures du gyrus temporal supérieur.

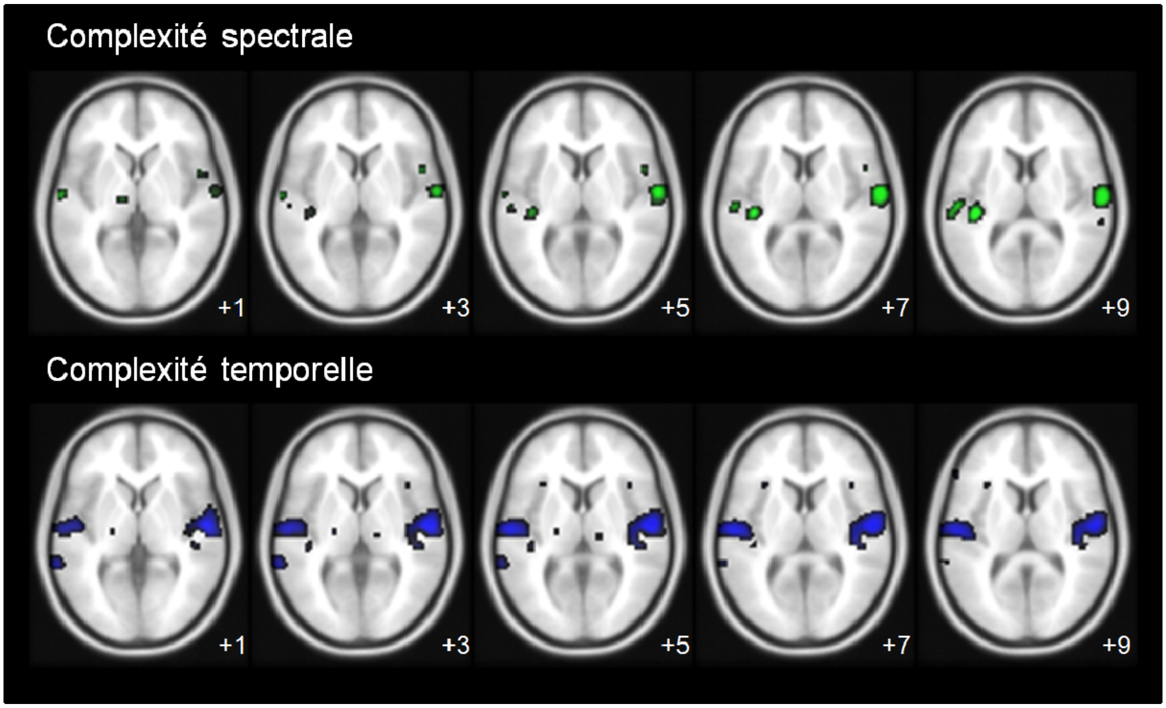

Figure 2. Comparaisons des régions d'activation systématiquement rapportées dans la littérature à l'écoute des sons spectralement complexes versus simples (haut) et temporellement complexes versus simples (bas).

De manière similaire dans l'étude empirique (voir Chapitre 4), les conditions de sons spectralement et temporellement complexes ont été comparées aux conditions de sons simples afin de mettre en évidence les régions spécifiquement recrutées lors de l'écoute des sons complexes. Ces analyses démontrent une extension de l'activité au delà des régions auditives primaires consistante avec les résultats de la méta-analyse, tant pour la complexité spectrale que temporelle, dans chacun des groupes de participants.

D'abord, tant chez les participants non autistes que les participants autistes, la comparaison entre les stimuli harmoniques versus non harmoniques a permis d'isoler l'activité cérébrale associée au traitement de la complexité spectrale et révèle une activité auditive primaire bilatérale s'étendant anterolatéralement au long du gyrus de Heschl et atteignant le gyrus temporal supérieur. Ces résultats correspondent donc assez bien avec ceux de la méta-analyse exposant les régions systématiquement rapportées à travers la littérature comme étant sensibles à l'augmentation de la complexité spectrale. Par contre, l'amplitude et l'étendue de l'activité observée dans l'étude 3 (Chapitre 4) semble réduite par rapport à certains travaux de la littérature, spécifiquement ceux utilisant plus d'un niveau de complexité spectrale permettant de révéler les régions sensibles à l'augmentation progressive du nombre de composantes fréquentielles (Jamison, Watkins, Bishop, & Matthews, 2006; Schonwiesner, Rubsamen, & von Cramon, 2005; Zatorre & Belin, 2001). Ceci suggère que le cortex auditif soit plus sensible à l'augmentation paramétrique de la complexité spectrale, plutôt qu'à la comparaison catégorielle entre un son spectralement complexe et un son simple tel que présenté ici. Ensuite, l'analyse de l'activité associée à l'augmentation de la complexité temporelle dans l'étude 3 (Chapitre 4) révèle des effets bilatéraux au niveau du gyrus de Heschl et des portions antérieure, latérale et postérieure du gyrus temporal supérieur dans les deux groupes de participants, un pattern correspondant aux résultats de la comparaison entre sons temporellement complexes et sons simples dans la méta-analyse quantitative.

La concordance soulignée ici entre les résultats de la littérature (reflétés par la méta-analyse, Chapitre 3) et les résultats expérimentaux (Chapitre 4) confirme que les stimuli spectralement et temporellement complexes peuvent être définis comme étant complexes en regard de la réponse corticale y étant associée. L'investigation systématique du traitement cortical de sons simples, spectralement et temporellement complexes a donc permis de valider l'organisation hiérarchique du traitement de l'information auditive, et ce tant dans notre groupe de participants non autistes qu'autistes. De plus, ceci confirme que l'étude empirique peut effectivement servir à tester la généralisation de l'hypothèse spécifique à la complexité en audition.

Donc, la présente étude confirme que l'architecture fonctionnelle du cortex auditif est similaire dans l'autisme et dans le développement typique. Ainsi, il semble que l'association décrite entre certaines tâches fonctionnelles et régions corticales chez le sujet non autiste s'applique aussi dans l'autisme. Une telle similitude a aussi été retrouvée pour le traitement cortical de l'information visuelle de bas niveau (Hadjikhani et al., 2004). Ceci suggère que c'est le niveau d'implication de chacune des régions fonctionnelles qui pourrait s'avérer différent dans l'autisme (Samson, et al., sous presse).

5.2.2 Traitement cortical auditif atypique dans l'autisme

5.2.2.1 Confirmation des hypothèses

En plus de démontrer une organisation fonctionnelle similaire chez les autistes et les non autistes lors du traitement auditif de bas niveau, le présent travail a permis de mettre en lumière des différences d'activité cérébrale entre les deux groupes. En effet, les participants autistes ont montré une réduction de l'activité auditive non primaire en réponse aux stimuli auditifs temporellement complexes. Les résultats supportent les prédictions de l'hypothèse de la complexité selon laquelle l'information définie comme complexe en regard du nombre de régions fonctionnelles requises serait traitée différemment chez les autistes.

La présente étude a aussi permis de vérifier la prédiction du modèle EPF suggérant un biais vers les étapes plus précoces de traitement de l'information dans l'autisme. Selon cette hypothèse, l'activité associée au traitement des sons complexes devrait plutôt être restreinte au niveau des aires primaires chez les autistes. En support à ce modèle, on observe un niveau plus élevé de la réponse auditive au niveau du cortex primaire en réponse aux stimuli complexes dans le groupe autiste comparativement au groupe non autiste. La présence d'un biais général vers les processus perceptifs dans la cognition autistique a récemment été démontrée pour la modalité visuelle (Samson, et al., sous presse). En lien avec les prédictions du modèle EPF, le pattern d'activité atypique associé au traitement de stimuli auditifs complexes suggère d'abord une possible extension de ce biais à la modalité auditive et, ensuite, que ce biais pourrait se retrouver à travers les niveaux de traitement de l'information de même qu'au sein de processus définis comme plus strictement perceptifs.

En bref, certains aspects du traitement cortical auditif de bas niveau peuvent être définis comme atypiques dans l'autisme. Les particularités observées sont en accord avec les propositions de l'hypothèse de la complexité ainsi que celles du modèles EPF. Les sections suivantes visent à interpréter le présent ensemble de résultats en regard des capacités de traitement de l'information auditive et langagière dans l'autisme.

5.2.2.2 Relation avec capacité de traitement auditif

Le présent ensemble de résultats démontre des différences au niveau de l'activité corticale associée au traitement de l'information auditive complexe non langagière entre des individus autistes et des individus non autistes. Ces différences peuvent servir de piste d'interprétation pour expliquer certaines particularités du traitement auditif dans cette population.

D'abord, selon l'hypothèse de Bertone et ses collaborateurs (2005), une réduction de l'intégration entre régions corticales fonctionnelles entraînant une baisse de l'activité des régions non primaires lors du traitement de stimuli complexes pourrait sous-tendre les difficultés rencontrées par les autistes pour traiter ce type d'information. Dans le présent travail, une réduction de l'activité non primaire a été spécifiquement observée pour la complexité temporelle; les comparaisons des variations d'activité corticale associées au traitement de la complexité spectrale ne révélant pas de différences entre les groupes. De plus, on observe chez les autistes une augmentation de l'activité auditive primaire à l'écoute de sons complexes. Au niveau empirique, on rapporte un pattern de performance consistant avec ces résultats.

La présente étude suggère un traitement cortical intact des sons spectralement complexes dans l'autisme. Il possible de considérer que ce résultat soit en lien avec le design de l'expérience, n'incluant que deux niveaux de complexité spectrale comparativement à quatre pour la complexité temporelle. Si le cortex auditif non primaire présente effectivement une sensibilité accrue à l'augmentation paramétrique de la complexité spectrale (voir section 5.2.1), il est possible que le paradigme utilisé ici ne représente pas la manière optimale de révéler la présence de différences du traitement de la complexité spectrale dans l'autisme. De prochaines études devraient donc tenter de vérifier si le présent profil d'activation est observé pour un paradigme incluant une augmentation paramétrique de la complexité spectrale.

De la même façon, la tâche comportementale utilisée ici pourrait avoir eu un impact sur les différences d'activité corticale observées. En effet, en demandant aux participants de détecter la présence ou l'absence de la modulation, leur attention était nécessairement dirigée vers les aspects temporaux des stimuli plutôt que vers leur composition spectrale. Ceci pourrait possiblement expliquer que les différences entre les groupes aient été spécifiquement observées pour le traitement de sons temporellement complexes. Tel que précédemment mentionné (voir section 1.2), certaines des demandes associées à la tâche, comme les modulations attentionnelles, peuvent influencer l'activité des régions en amont. De tels effets sont rapportés, entre autres, au niveau des régions auditives primaires (Fritz, et al., 2005; Fritz, et al., 2003) et non primaires (Polley et al., 2006; Woods, et al., 2010). Il est possible que l'attention dirigée des participants vers la composition temporelle des stimuli ait pu avoir un impact sur l'activation des régions auditives associées au traitement de ces stimuli. Les différences entre les groupes observées pourraient donc aussi refléter des différences de l'effet d'une modulation attentionnelle sur l'activité sensorielle dans l'autisme. Ceci est en lien avec de récents résultats d'études d'IRMf rapportant une hausse de l'activité des régions associées à l'attention sélective chez les autistes en comparaison aux non autistes lorsque leur attention était dirigée vers une cible auditive (Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008), mais une baisse de cette activité chez les autistes par rapport aux contrôles lors de l'écoute passive d'un même paradigme de détection auditive (Gomot et al., 2006). Il semble donc que les mécanismes attentionnels dans l'autisme puissent fonctionner de manière atypique, particulièrement lors du traitement de l'information auditive, et que l'activité des régions auditives pourrait être modulée différemment par l'attention dans cette population. Il serait donc intéressant que de prochaines études se penchent sur l'effet des modulations attentionnelles sur l'activité des régions sensorielles dans l'autisme et, spécifiquement en lien avec le présent projet, de vérifier si certaines différences peuvent être mises en évidence lorsque les participants doivent diriger leur attention sur la composition spectrale plutôt que temporelle des stimuli.

Cependant, il est probable que ce résultat témoigne plutôt de la capacité intacte des personnes autistes à traiter ce type de stimuli. En effet, les études ayant investigué le traitement de stimuli spectralement complexes dans l'autisme rapportent, de manière générale, des niveaux de performance équivalents à ceux des non autistes. Au niveau comportemental, une investigation systématique des capacités de discrimination de stimuli auditifs simples et complexes ne rapporte aucune différence significative entre autistes et non autistes pour discriminer des sons avec plusieurs composantes fréquentielles (sons harmoniques ou spectralement complexes) (Bonnel et al., 2010). D'autres études rapportent des indices électrophysiologiques suggérant un traitement cortical similaire des sons spectralement complexes chez des individus autistes et non autistes (Ceponiene et al., 2003; Whitehouse & Bishop, 2008).

L'association entre baisse d'activité auditive non primaire et niveau de performance inférieur prédite par l'hypothèse de la complexité serait-elle donc limitée à la complexité temporelle en audition ? Une telle proposition semble consistante avec les résultats d'études comportementales démontrant une altération spécifique liée au traitement de la complexité temporelle, et non spectrale, pour une tâche de détection de mots présentés dans du bruit (Alcantara et al., 2004; Groen et al., 2009). Spécifiquement, cette tâche mesure les seuils de détection de mots selon différents types de bruits requérant soit une intégration de l'information temporelle ou de l'information spectrale. Dans les deux études, les participants autistes ont démontré une capacité réduite à utiliser les variations temporelles du bruit de fond pour extraire le signal en comparaison à des individus non autistes, tandis qu'aucune différence n'a été retrouvée pour l'information spectrale. Il semble donc que l'activité réduite des régions auditives non primaires lors du traitement de sons temporellement complexes puisse être associée à une difficulté à analyser ce type d'information dans l'autisme. Cependant, une récente étude a rapporté des niveaux de performance équivalents entre autistes et non autistes pour une tâche de discrimination de sons temporellement complexes (Bonnel et al., 2010), suggérant que les différences corticales sous-tendraient plutôt une difficulté à intégrer l'information temporelle lors de la réalisation de tâches plus complexes, comme la détection de sons présentés dans du bruit, ou encore lors du traitement de stimuli plus complexes. Par exemple, des études d'imagerie cérébrale ont rapporté une réduction de l'activité du cortex auditif chez les autistes en réponse à des stimuli non langagiers mais possédant toute la complexité de sons vocaux (Boddaert et al., 2003; Boddaert et al., 2004). En bref, le présent travail a permis de valider, du moins en partie, les prédictions de l'hypothèse de la complexité. En effet, la réduction de l'activité des régions auditives non primaires en réponse à l'augmentation de la complexité temporelle dans l'autisme semble pouvoir être associée à un traitement atypique de ce type d'information auditive dans cette population.

L'augmentation de l'activité auditive primaire associée à l'écoute de sons complexes dans l'autisme pourrait aussi sous-tendre certaines particularités du traitement auditif dans l'autisme. En effet, les autistes, en utilisant les mécanismes opérant au niveau de l'aire auditive primaire pour traiter l'information complexe, pourraient plus facilement percevoir et analyser les différentes composantes des sons. Ceci pourrait possiblement sous-tendre la capacité supérieure des autistes à identifier les sons composants un accord (Heaton, 2003), à repérer un changement local dans une séquence de sons (Foxton et al., 2003; Mottron et al., 2000) ou encore à détecter plus rapidement un changement de hauteur dans une séquence de sons harmoniques (Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008). Le cortex auditif primaire, de par son organisation tonotopique (Formisano et al., 2003), est, entre autres, spécialisé pour le traitement des composantes fréquentielles. Une réponse auditive primaire plus importante dans l'autisme pourrait être en lien avec une meilleure décomposition et analyse des fréquences composant le matériel auditif complexe, entraînant ainsi des performances supérieures pour des tâches pouvant bénéficier d'une telle décomposition. L'hyperactivité du cortex auditif primaire rapporté ici peut aussi être mise en lien avec le phénomène d'hyperacoustie fréquemment rapporté dans l'autisme (Gomes, et al., 2004). L'hypothèse d'une origine centrale de cette particularité sensorielle est supportée par des travaux montrant un traitement auditif périphérique typique chez les autistes (Gravel, Dunn, Lee, & Ellis, 2006). De plus, en électrophysiologie, lors de la détection d'un changement dans une séquence de sons purs, les autistes montrent une réponse corticale précoce consistante avec l'hypothèse d'une hyper-réactivité auditive dans cette population (Gomot, et al., 2002). Il est donc possible de considérer l'hyper-discrimination et l'hyper-réactivité auditive dans l'autisme comme deux manifestations comportementales d'un traitement accru au niveau des régions auditives primaires.

5.2.2.3 Relation avec le traitement langagier

Les différences d'activité cérébrale observées ici en réponse au traitement de stimuli auditifs complexes peuvent aussi être interprétées à la lumière des particularités de traitement de l'information langagière chez les autistes. Considérant que la présente expérience a été menée avec une population d'autistes possédant un quotient intellectuel verbal comparable à celui des individus non autistes, il est possible d'interpréter les résultats d'une manière plus spécifique. En effet, des différences d'activité cérébrale entre un groupe d'individus à développement typique et un groupe d'autistes n'ayant pas développé la parole pourraient être en lien soit avec l'autisme ou soit avec le déficit au niveau du langage. Dans un tel cas, les deux interprétations ne pourraient être dissociées, ce qui rend ce type de résultat assez peu informatif. L'inclusion d'individus autistes aux capacités verbales comparables à celles des individus non autistes dans la présente étude permet donc des interprétations spécifiques au diagnostic d'autisme.

L’observation d’une réduction de l’activité des régions auditives non primaires limitée au traitement de l’information temporellement complexe suggère une relation avec un traitement atypique de l’information langagière dans l’autisme. En effet, la reconnaissance et la compréhension des sons vocaux et langagiers reposent essentiellement sur l’analyse des variations temporelles qu’ils contiennent (Shannon, Zeng, Kamath, Wygonski, & Ekelid, 1995; Tallal, Miller, & Fitch, 1993). Il est donc possible qu’un traitement cortical atypique de sons temporellement complexes puisse sous-tendre aussi le traitement atypique des stimuli à caractère langagier. Chez les autistes, certaines études rapportent des réponses électrophysiologiques d’amplitude réduite (Ceponiene et al., 2003; Jansson-Verkasalo et al., 2003; Kuhl, Coffey-Corina, Padden, & Dawson, 2005; Lepisto et al., 2005; Lepisto et al., 2006; Russo et al., 2009; Whitehouse & Bishop, 2008) ou encore de latence plus tardive (Oram Cardy, Flagg, Roberts, & Roberts, 2005) en réponse à des voyelles ou des syllabes. De manière similaire, une étude d’IRMf a rapporté une absence d’activité du sulcus temporal supérieur, région spécifiquement recrutée lors du traitement de la voix, en réponse à des stimuli vocaux chez un groupe d’autistes en comparaison à un groupe d’individus à développement typique (Gervais et al., 2004). Au sein du cortex auditif, le traitement de l’information se fait de manière hiérarchique. Ainsi, les stimuli vocaux et langagiers sont d’abord décomposés et analysés au niveau des aires auditives primaires et non primaires avant de rejoindre des régions corticales plus spécialisée (Binder et al., 2000; Scott & Johnsrude, 2003; Uppenkamp, Johnsrude, Norris, Marslen-Wilson, & Patterson, 2006). Il est donc possible que des différences au niveau du traitement auditif plus élémentaire, comme l’extraction des indices de variations temporelles, puissent avoir des conséquences sur le traitement de plus haut niveau. De plus, bien que les stimuli temporellement complexes utilisés dans le présent travail soit non-vocaux, le taux de modulation utilisé ici (5 Hz) correspond au niveau de modulation temporelle étant considéré comme essentiel à la reconnaissance des sons langagiers (Hall et al., 2002; Houtgast & Steeneken, 1985). Ceci suggère donc que la réduction de l’activité auditive non primaire en réponse aux stimuli temporellement complexes pourrait sous-tendre certaines des difficultés rapportées dans l'autisme.

Un autre aspect du traitement cortical atypique des stimuli auditifs complexes peut être interprété en lien avec certaines particularités du traitement langagier dans l'autisme. En effet, l'observation d'une plus grande activité auditive primaire en réponse aux stimuli complexes dans l'autisme pourrait refléter un traitement plus perceptif des stimuli langagiers dans cette population. En effet, certaines études rapportent une capacité supérieure pour traiter des stimuli langagiers en extrayant leur composition fréquentielle dans l'autisme. Par exemple, une étude de cas a permis de démontrer une supériorité lors de l'identification du « pitch » de stimuli syllabiques chez un individu autiste par rapport à un groupe d'individus non autistes (Heaton, Davis, & Happe, 2008). Aussi, en utilisant une tâche de discrimination de paires de mots monosyllabiques de fréquences variables, Heaton et al. (2008) ont démontré un niveau de performance supérieur chez les autistes pour discriminer les paires différentes par rapport aux non autistes. Enfin, des tâches de traitement de stimuli langagiers pouvant être réalisées en utilisant l'information soit perceptive ou sémantique ont révélé un traitement supérieur des composantes perceptives de la parole dans l'autisme et un biais vers le niveau sémantique dans le développement typique (Jarvinen-Pasley & Heaton, 2007; Jarvinen-Pasley et al., 2008). En bref, il est possible que le patron d'activité cérébrale atypique observé ici en réponse aux stimuli temporellement complexes puisse sous-tendre certaines particularités du traitement des voix et du langage dans l'autisme.

5.2.2.4 Relation avec les particularités anatomiques et de connectivité

Les présents résultats s'inscrivent à la suite d'études démontrant des anomalies anatomiques au niveau des régions abritant le cortex auditif dans l'autisme. De manière générale, plusieurs études rapportent des différences morphométriques au niveau du lobe temporal dans cette population. Par exemple, on trouve une réduction (Waiter et al., 2004) ou une augmentation (Jou, Minshew, Keshavan, Vitale, & Hardan, 2010) du volume du gyrus temporal supérieur chez des autistes avec un niveau de langage équivalent à celui du groupe contrôle. Une baisse de la densité de matière blanche et de la matière grise a aussi été observée au niveau du lobe temporal chez des autistes possédant des capacités langagières inférieures à celles du groupe non-autistes (Abell et al., 1999; Boddaert, Chabane, Gervais, et al., 2004). Bien que les résultats obtenus à ce jour ne permettent pas de dégager un profil consistant de hausse ou de baisse générale de volume au niveau temporal, il semble que cette région cérébrale soit systématiquement identifiée comme présentant des atypies morphométriques dans l'autisme. Il a d'ailleurs été proposé qu'une meilleure caractérisation des anomalies anatomiques au niveau du lobe temporal chez des individus avec un autisme primaire (sans autre maladie associée) puissent représenter une avenue de recherche prometteuse au niveau de l'étiologie de ce trouble (Boddaert et al., 2009).

En lien avec les différences observées ici, certaines études rapportent une diminution de volume des régions auditives non primaires, spécifiquement au niveau du planum temporale, chez des adultes (Rojas, Bawn, Benkers, Reite, & Rogers, 2002) et les enfants/adolescent (Rojas, Camou, Reite, & Rogers, 2005) autistes comparativement aux non autistes. Parallèlement, une augmentation de l'épaisseur corticale du gyrus de Heschl dans l'autisme a récemment été rapportée (Hyde, Samson, Evans, & Mottron, 2009). Notons que la majorité des participants de cette étude anatomique ont aussi été inclus dans l'étude d'imagerie fonctionnelle présentée ici. Il semble donc qu'un parallèle puisse être tracé entre les particularités fonctionnelles et anatomiques retrouvées au sein des régions auditives dans l'autisme. L'observation d'un traitement cortical atypique, soit d'une augmentation de l'activité au niveau des aires auditives primaires et d'une baisse de l'activité non primaire lors du traitement de stimuli auditifs temporellement complexes, semble consistante avec les particularités morphométriques de ces régions. Spécifiquement, cette concordance anatomo-fonctionnelle suggère une relation positive entre le volume et le niveau d'activité des régions corticales auditives dans l'autisme.

Au moment de la formulation de leur hypothèse, Bertone et al., (2005) ont proposé que la présence d'une anomalie anatomique, soit une connectivité atypique entre les différentes régions corticales dans l'autisme, puisse sous-tendre les différences comportementales observées ainsi que les différences d'activité corticale prédites. Spécifiquement, les auteurs ont suggéré qu'une connectivité diminuée entre les régions corticales (V1 et V2/V3) chez les autistes pourrait expliquer les difficultés rencontrées pour discriminer les stimuli de deuxième-ordre, pour lesquels une intégration entre les différents niveaux de traitement est requise. Ceci est basé sur la théorie proposant une baisse de la connectivité entre les régions cérébrales fonctionnelles dans l'autisme (« underconnectivity hypothesis »). Cette hypothèse a principalement été basée sur des résultats d'analyses de connectivité fonctionnelle en imagerie qui permettent de mesurer le niveau de synchronie de la réponse neuronale entre différentes régions corticales. Chez les autistes, plusieurs études ont proposé une diminution de la connectivité fonctionnelle, principalement entre les régions frontales et les régions corticales postérieures pour une variété de tâches cognitives et même lorsque l'activité cérébrale est mesurée au repos (pour une revue voir Schipul, Keller, & Just, 2011). Notons par contre qu'on rapporte aussi des hausses de connectivité fonctionnelle chez les autistes par rapport aux non autistes, spécifiquement entre les régions associées à la perception visuelle et les autres régions corticales (Leveille et al., 2010).

Dans le présent projet, il aurait été intéressant de faire des analyses de connectivité fonctionnelles afin de vérifier si le niveau de synchronie entre les différentes régions auditives est diminué chez les autistes par rapport aux non-autistes. Une telle démonstration aurait permis de proposer que les différences d'activité observées puissent être liées à une baisse de la transmission de l'information entre les régions auditives primaires et non primaires dans l'autisme. Ceci pourrait être interprété en regard des études d'imagerie en tenseur de diffusion (« Diffusion Tensor Imaging », DTI) démontrant une microstructure corticale (fibres de matière blanche transmettant l'influx nerveux) atypique dans cette population. En effet, ces études ont rapporté des anomalies au niveau des propriétés de diffusion de la matière blanche du lobe temporal chez les autistes (Lee, et al., 2007). Plus spécifiquement en lien avec le présent travail, de récents travaux suggèrent une connectivité locale (« courte-distance ») atypique au sein des régions temporales dans l'autisme (Shukla, Keehn, Smylie, & Muller, 2011) consistante avec une baisse de la coordination locale de l'activité auditive dans cette population (Wilson, et al., 2007). Ces résultats suggèrent que certaines anomalies de la microstructure corticale au niveau auditif dans l'autisme pourraient avoir une influence sur la transmission nerveuse et, donc, sur l'intégration de l'information entre les régions corticales dans cette population. Ces particularités pourraient possiblement sous-tendre les différences d'activité corticale observées dans le présent travail.

5.2.2.5 Relation avec les mécanismes auditifs sous-corticaux

La fenêtre d'observation du traitement de l'information auditive a été limitée aux aspects corticaux dans le présent travail. Ceci s'explique par le fait que l'hypothèse proposée par Bertone et al. (2005) concerne spécifiquement les mécanismes de traitement de l'information au niveau cortical. Cependant, les résultats obtenus peuvent aussi être discutés en regard du traitement de l'information auditive au niveau sous-cortical. En effet, les régions sous-corticales dont le noyau cochléaire, le complexe de l'olive supérieur, le collicule inférieur et le corps genouillé médian jouent diverses fonctions de décodage, transmission et intégration de l'information auditive simple et complexe (voir section 1.2). Un traitement atypique de l'information à ce niveau dans l'autisme pourrait entraîner une modification des signaux afférents et sous-tendre certaines particularités observées au niveau cortical.

D'abord, au niveau anatomique, on rapporte une baisse du volume du tronc cérébral, région abritant le noyau cochléaire, l'olive supérieure et le collicule inférieur, chez les autistes par rapport aux non-autistes (Hashimoto, Tayama, Miyazaki, Murakawa, & Kuroda, 1993; Hashimoto, et al., 1995; Jou, et al., 2009). Aussi, de récentes études post-mortem ont observé des changements morphologiques des neurones (taille réduite et forme arrondie caractéristiques des cellules immatures) des noyaux de l'olive supérieure ainsi qu'un baisse de la densité cellulaire à ce niveau (Kulesza, Lukose, & Stevens, 2011; Kulesza & Mangunay, 2008). Ces auteurs proposent que de tels changements puissent être associés à une réponse électrophysiologique atypique du tronc cérébral dans l'autisme. En effet, un délai et une amplitude réduite des potentiels auditifs du tronc cérébral (« Auditory Brainstem Response ») ont été observés chez les individus avec un trouble du spectre autistique (Kallstrand, Olsson, Nehlstedt, Skold, & Nielzen, 2010; Kwon, et al., 2007; Tas, et al., 2007).

Plus spécifiquement en lien avec les résultats obtenus dans la présente étude, il a été suggéré que les potentiels auditifs du tronc cérébral représentent une mesure de la capacité d'intégration des indices temporaux, particulièrement lors du traitement de stimuli langagiers, au niveau sous-cortical (Johnson, Nicol, Zecker, & Kraus, 2007). Dans l'autisme, on observe des réponses sous-corticales moins amples et plus lentes lors du traitement de stimuli vocaux, mais une activité similaire à celles des non-autistes pour les stimuli non-langagiers (Russo, et al., 2009). Ces résultats suggèrent donc une intégration atypique des indices liés à la compréhension de la parole au niveau des noyaux sous-corticaux dans l'autisme. Considérant que le traitement des stimuli langagiers repose principalement sur la résolution adéquate des indices temporels (Shannon et al., 1995), il est possible que les différences corticales observées dans notre étude en réponse aux stimuli temporellement complexes soit associée à un traitement atypique de ces informations au niveau sous-cortical. D'autres études ont d'ailleurs proposé qu'un traitement atypique au niveau sous-cortical puisse sous-tendre certaines particularités de la réponse corticale auditive observées chez les autistes (Redcay & Courchesne, 2008; Roberts, et al., 2010). Il serait donc intéressant de complémenter la présente étude par une investigation des particularités de traitement de stimuli temporellement complexes au niveau sous-cortical.

5.2.3 Traitement auditif atypique et phénotype

Au sein des troubles du spectre autistique, on distingue l'autisme du syndrome d'Asperger principalement sur la base de la présence ou de l'absence d'un retard d'acquisition de la parole. Malgré une absence de retard du développement du langage oral, les individus avec syndrome d'Asperger démontrent certaines particularités lors du traitement d'informations auditives en comparaison à des individus à développement typique. En effet, les études rapportent la présence d'une hypersensibilité auditive (Myles et al., 2004), d'une réduction de l'orientation spontanée aux sons vocaux (Lepisto et al., 2007; Lepisto et al., 2006), ainsi que des difficultés à traiter la prosodie (Korpilahti et al., 2007; Kujala et al., 2005). Donc, il est possible qu'un traitement cortical atypique de l'information auditive puisse aussi être mis en lumière chez les individus avec syndrome d'Asperger. Considérant que le syndrome d'Asperger est caractérisé à la fois par une absence de retard d'acquisition de la parole et par des difficultés à interagir socialement, il est possible de suggérer que ces individus démontrent un niveau d'activité cérébrale intermédiaire entre ceux des groupes autistes et non autistes. Afin de vérifier cette hypothèse, une série d'analyses supplémentaires incluant un groupe de 16 individus avec syndrome d'Asperger est présentée en annexe (Annexe 2).

En bref, cette série d'analyse révèle, tout comme dans les groupes autistes et non autistes, la présence d'un traitement fonctionnel hiérarchique de l'information auditive de bas niveau dans le groupe d'individus avec syndrome d'Asperger. En termes de différences entre les groupes, les comparaisons ont permis de mettre en évidence les régions où le niveau d'activité varie linéairement à travers les trois groupes lors du traitement de stimuli simples et complexes. Une plus grande activité dans les aires auditives non primaires en réponse aux stimuli temporellement complexes est observée chez les individus non autistes par rapport aux groupes cliniques (Non autistes > Asperger > Autistes). Ce résultat suggère donc que, comme dans l'autisme, les prédictions de l'hypothèse de la complexité pourraient aussi possiblement sous-tendre les difficultés présentées par les individus avec syndrome d'Asperger pour traiter certains aspects des stimuli auditifs complexes (Jansson-Verkasalo et al., 2003; Kujala et al., 2005; Lepisto et al., 2007; Lepisto et al., 2006).

Cette série d'analyses a aussi permis de démontrer que la hausse d'activité primaire associée au traitement de stimuli complexes caractérise spécifiquement les individus autistes; les groupes d’individus non autistes et avec syndrome d’Asperger démontrent tous deux un niveau d’activité inférieur par rapport aux autistes. Ceci suggère que la prédiction du modèle EPF de l’existence d’un biais vers les étapes de traitement en amont ne s’appliquerait qu’aux individus avec un diagnostic d’autisme et non pas à ceux avec syndrome d’Asperger. Une telle distinction semble concorder avec certaines particularités du traitement auditif. En effet, au niveau comportemental, il a récemment été soulevé que la supériorité pour traiter les sons purs pourrait être retrouvée seulement chez les individus avec un trouble du spectre autistique présentant un retard de développement de la parole (autistes) et non chez ceux ne présentant pas un tel délai (syndrome d’Asperger) (Bonnel et al., 2010; Jones et al., 2009). En démontrant une hausse de l’activité auditive primaire en réponse à des sons complexes uniquement dans le groupe d’individus autistes et non dans le groupe d’individus avec syndrome d’Asperger, le présent travail suggère qu’un surfonctionnement primaire pourrait effectivement sous-tendre la capacité supérieure à traiter les sons purs dans l’autisme. Il est aussi intéressant de souligner qu’une récente étude menée au sein de la même population (10 sujets autistes communs) a permis de démontrer une augmentation de l’épaisseur corticale du gyrus de Heschl, région abritant le cortex auditif primaire, dans un groupe de participants autistes (présentant un retard d’acquisition de la parole) en comparaison à un groupe non autiste (Hyde, Samson, Mottron, & Evans, 2009), suggérant qu’un épaississement au niveau auditif primaire pourrait possiblement sous-tendre les supériorités du traitement auditif de bas niveau dans l’autisme. Une telle distinction n’est pas retrouvée entre les individus non autistes et ceux avec un syndrome d’Asperger (Hyde, Samson, Evans, & Mottron, 2010).

Il semble donc que la complexité représente une variable pertinente pour explorer les différences aussi bien entre les individus à développement typique et ceux présentant un trouble du spectre autistique qu’à l’intérieur même de ce spectre.

5.2.4 Implications

Le présent travail représente une avancée au niveau de la caractérisation des mécanismes sous-tendant le traitement perceptif atypique rapporté de manière consistante dans l'autisme (Behrmann et al., 2006; Dakin & Frith, 2005; Mottron et al., 2006). Les implications de ce type d'étude se retrouvent tant au niveau fondamental que clinique.

D'abord, une meilleure compréhension des atypies perceptives dans l'autisme et, conséquemment, des systèmes sous-jacents pourrait contribuer à mieux comprendre les processus influençant le développement cérébral dans cette population. En effet, lorsqu'un cerveau en développement est confronté à certaines contraintes, il y aurait une adaptation des connections, des réseaux et systèmes neuronaux qui entraînerait une organisation cérébrale atypique (Johnson, Halit, Grice, & Karmiloff-Smith, 2002). Dans l'autisme, il a été proposé que certaines contraintes au sein des processus perceptifs de bas niveau puissent entraver le développement des systèmes sous-tendant les processus cognitifs de plus haut niveau (Belmonte, Cook et al., 2004). Ceci pourrait expliquer, par exemple, la tendance qu'ont les autistes à concentrer leur attention et leur perception sur des composantes de plus bas niveau. L'étude du fonctionnement des processus de bas niveau devient donc primordial à la compréhension de l'autisme, les symptômes autistiques pouvant possiblement être compris comme conséquences de la réaction d'un cerveau dont les circuits de base sont construits de manière atypique (Belmonte, Cook et al., 2004).

Au niveau clinique, une meilleure compréhension des atypies perceptives dans l'autisme pourrait éventuellement mener à l'identification de marqueurs diagnostiques. Par exemple, en vision, une étude longitudinale menée avec la fratrie d'enfants portant un diagnostic d'autisme rapporte qu'une évaluation des comportements atypiques (temps plus long de fixation des objets) des enfants à l'âge d'un an permet de discriminer ceux qui seront ultérieurement diagnostiqués autistes par rapport à ceux qui ne le seront pas (Zwaigenbaum et al., 2005). Aussi, Osterling et ses collaborateurs (2002) rapportent que les enfants présentant des comportements stéréotypés à l'âge d'un an (visionnement à posteriori d'enregistrements vidéo) sont ceux qui obtiendront éventuellement un diagnostic d'autisme. De manière similaire au niveau auditif, une étude rapporte des « réactions atypiques aux stimuli auditifs » chez tous les enfants autistes et chez aucun des enfants non autistes de leur échantillon (Dahlgren & Gillberg, 1989), suggérant le caractère spécifique de telles particularités sensorielles. L'accumulation de données supportant des particularités perceptives dans l'autisme pourrait mener à la modification et au raffinement des outils utilisés pour le diagnostic. En effet, un des outils standardisés utilisés pour le diagnostic - l'ADI-R (Lord et al., 1994)- ne comporte qu'une question portant spécifiquement sur les comportements sensoriels atypiques (i.e. unusual sensory interest). Une meilleure description des critères spécifiques à la perception aurait comme conséquence une possible augmentation de la spécificité et de la sensibilité des outils diagnostiques.

Au niveau des méthodes de réadaptation, une meilleure compréhension des particularités perceptives chez les autistes pourrait aider à adapter l'environnement ainsi que la façon de leur présenter l'information afin de maximiser leur apprentissage. En effet, une étude récente portant sur la relation entre le traitement sensoriel atypique et la réussite scolaire chez des enfants autistes d'intelligence normale rapporte que l'hypersensibilité aux bruits ainsi que la difficulté à filtrer l'information auditive en classe expliquerait, en majeure partie, les difficultés académiques de ces enfants (Ashburner, Ziviani, & Rodger, 2008). Une adaptation de l'environnement scolaire pourrait donc permettre de potentialiser l'assimilation de l'information et le développement cognitif des autistes. De plus, une adaptation de l'environnement pourrait possiblement permettre aux enfants autistes de se familiariser à leur façon avec différents matériels et, ainsi, de développer certaines capacités (Dawson et al., 2008). Par exemple, on rapporte un apprentissage de la lecture chez des enfants autistes ayant un accès libre à du matériel écrit ou encore le développement d'une capacité spéciale (e.g. savant musicien) lorsque l'enfant est exposé librement à un type de matériel spécifique (e.g. musique, piano) (Mottron, Peretz, Belleville, & Rouleau, 1999).

5.2.5 Avenues de recherche

À partir de la démonstration d'une généralisation des prédictions de l'hypothèse de la complexité à la modalité auditive, il est possible de suggérer des pistes de recherche futures.

D'abord, afin de compléter la caractérisation multi-modale des particularités du traitement perceptif visuel et auditif dans l'autisme en lien avec l'hypothèse de la complexité, une investigation IRMf du traitement des stimuli visuels simples et complexes dans l'autisme permettrait de vérifier la présence d'une association entre la difficulté des personnes autistes à discriminer les stimuli visuels de deuxième ordre et la complexité du réseau cortical requis pour les traiter.

Ensuite, considérant que les difficultés de traitement de l'information auditive semblent plutôt concerner les composantes temporellement complexes associées au traitement des stimuli langagiers dans l'autisme, il serait intéressant d'investiguer les bases cérébrales du traitement de sons complexes à valeur écologique, comme les sons vocaux. Cette étude devrait inclure un groupe de participants avec syndrome d'Asperger pour vérifier si le moment d'acquisition de la parole pourrait être associé à des différences spécifiques au niveau des systèmes corticaux sous-tendant le traitement des voix et du langage au sein des troubles du spectre autistique.

Aussi, le présent travail n'ayant pas permis d'investiguer les bases cérébrales du traitement cortical des sons purs, il serait intéressant de construire un paradigme permettant de vérifier si, tel que prédit par le modèle EPF, un surfonctionnement des aires auditives primaires pourrait sous-tendre la capacité supérieure à discriminer les sons purs rapportée de manière consistante dans l'autisme.

De plus, les différents mécanismes proposés pour expliquer les comportements à la base de la formulation de l'hypothèse de la complexité pourraient être investigués. Par exemple, une inhibition latérale excessive au niveau de l'aire auditive primaire pourrait possiblement être mise en lumière en tant que processus sous-tendant les différences d’activité cérébrale observées ici. Au niveau comportemental, des paradigmes portant sur le phénomène de « continuité auditive » permettent de faire des inférences sur les processus d’inhibition latérale en audition (Houtgast, 1972). Une telle étude contribuerait certainement à la compréhension du traitement de l’information dans l’autisme. Des études récentes ont d’ailleurs démontré des résultats supportant cette hypothèse en vision (Keita, et al., 2010; Vandenbroucke et al., 2008). Tel que précédemment mentionné, l’organisation corticale du cortex auditif primaire étant similaire à celle du cortex visuel, il est possible de penser retrouver de telles différences chez les autistes par rapport aux non autistes en audition.

Enfin, comme la présente étude a été menée auprès d’une population majoritairement adulte, il n’est pas possible de préciser si les différences observées ici représentent des caractéristiques fondamentales de l’organisation du cerveau autiste ou encore les conséquences de phénomènes de compensation. De prochaines études, idéalement longitudinales, devront se pencher sur l’origine du traitement atypique de l’information dans l’autisme. En ce sens, l’étude du développement des réponses corticales atypiques dans l’autisme via des mécanismes de plasticité cérébrale différents représente une ligne de recherche à poursuivre.

Conclusion

Cette thèse avait pour objectif de vérifier si l'hypothèse spécifique à la complexité formulée pour tenter d'expliquer certaines particularités du traitement de l'information visuelle dans l'autisme pouvait être généralisée à la modalité auditive.

D'abord, les évidences comportementales et neurofonctionnelles permettant de considérer le caractère multimodal de l'hypothèse ont été mises en lumière. Ceci a ensuite permis de tester directement les prédictions de cette hypothèse en audition dans l'autisme. En démontrant un traitement cortical atypique associé à l'écoute de sons temporellement complexes chez les autistes, il a été possible de valider les prédictions de l'hypothèse de la complexité en audition. Ces différences d'activité corticale ont été interprétées en regard des capacités de traitement de l'information auditive et langagière dans cette population. En bref, cette thèse supporte la généralisation de l'hypothèse spécifique à la complexité à la modalité auditive.

Le présent ensemble de résultats suggère qu'il existe dans l'autisme des différences fondamentales au niveau des mécanismes d'acquisition et de traitement de l'information perceptive dans l'autisme. Il devient primordial de mieux comprendre le fonctionnement de ces processus de bas niveau considérant que les symptômes autistiques pourraient possiblement être compris comme des conséquences de la réaction développementale d'un cerveau dont les circuits de base sont construits de manière atypique (Belmonte et al., 2004).

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Annexe I. Enhanced visual functioning in autism: an ALE meta-analysis

Samson, F., Mottron, L., Soulières, I. & Zeffiro, T.A. (sous presse) Enhanced visual functioning in autism: an ALE meta-analysis. *Human Brain Mapping*

Enhanced visual functioning in autism: an ALE meta-analysis

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ABSTRACT

Autistics often exhibit enhanced perceptual abilities when engaged in visual search, visual discrimination, and embedded figure detection. In a similar fashion, while performing a range of perceptual or cognitive tasks, autistics display stronger physiological engagement of the visual system than do non-autistics. To account for these findings, the Enhanced Perceptual Functioning model proposes that enhanced autistic performance in basic perceptual tasks results from stronger engagement of sensory processing mechanisms, a situation that may facilitate an atypically prominent role for perceptual mechanisms in supporting cognition. Using quantitative meta-analysis of published functional imaging studies from which Activation Likelihood Estimation maps were computed, we asked whether autism is associated with enhanced task-related activity for a broad range of visual tasks. To determine whether atypical engagement of visual processing is a general or domain-specific phenomenon, we examined three different visual processing domains: faces, objects, and words. Overall, we observed more activity in autistics compared to non-autistics in temporal, occipital, and parietal regions. In contrast, autistics exhibited less activity in frontal cortex. The spatial distribution of the observed between-group differential patterns varied across processing domains. Autism appears to be characterized by atypical, and generally superior regional functional resource allocation across a broad expanse of brain regions associated with visual processing and expertise. Atypical organizational patterns may reflect developmental neural plasticity resulting in a number of characteristics of the autistic phenotype, including enhanced visual skills, atypical face processing and hyperlexia.

INTRODUCTION

Atypical perceptual processing, often manifested as enhanced perceptual performance (Dakin and Frith 2005), is now included as an associated feature of the autistic phenotype (Belmonte, et al. 2004). Autistic visual strengths are consistently reported for the Block Design subtest of the Wechsler Intelligence Scales (Caron, et al. 2006; Shah and Frith 1993), the Embedded Figures Task (Jolliffe and Baron-Cohen 1997), visual search tasks (Joseph, et al. 2009; Kemner, et al. 2008; O'Riordan 2004; O'Riordan, et al. 2001), and visual discrimination tasks (Bertone, et al. 2005; Plaisted, et al. 1998). In addition, an increasing number of studies have demonstrated autistic early sensory processing advantages or atypicalities in stimulus dimension extraction, with examples including crowding {Baldassi, 2009 #1029; Keita, 2010 #2}, contour and texture processing (Pei, et al. 2009; Vandenbroucke, et al. 2008) and spatial frequency processing (Jemel, et al. 2010; Milne, et al. 2009). These behavioral characteristics, along with other aspects of the autistic perceptual phenotype, have been summarized in the Enhanced Perceptual Functioning Model (EPF) (Mottron, et al. 2006). Assuming generally stronger physiological engagement of the visual system in autism, this model predicts generally superior perceptual performance and a wider role for perceptual processes in autistic cognition. It also incorporates the observation that autistics3 display better access to information typically masked by top-down influences (Wang, et al. 2007), as well as superior autonomy of perceptual processes from top-down influences (Caron, et al. 2006; Soulières, et al. 2009).

Several neuroimaging studies have revealed stronger task-related activity in visual cortex in autism, evidenced as either higher levels of activity associated with visual information processing, or as serendipitous findings in studies employing memory or language tasks. In association with the Embedded Figures Test, autistic brain activity is higher in right occipital cortex, left posterior parietal cortex, bilateral occipital cortex, and bilateral cerebellar cortex, and lower in frontal cortex (Lee, et al. 2007; Manjaly, et al.

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[3] Throughout the report we respectfully use the term autistics, following Sinclair, J. (1999). Why I dislike "person first" language. http://www.jimsinclair.org/person_first.htm

2007; Ring, et al. 1999). Higher occipital cortex activity in autistics is seen in relation to faster and more accurate visual search (Keehn, et al. 2008). These results suggest that the autistics' behavioral advantages might arise from stronger and more pervasive engagement of visual processing mechanisms. Stronger occipital activity has also been reported in association with reduced frontal activity in autism for tasks incorporating a broad range of cognitive and perceptual components, including embedded figure detection (Ring, et al. 1999), attention shifting (Belmonte and Yurgelun-Todd 2003), word learning (Hazlett, et al. 2004), saccades to visual targets (Luna, et al. 2002), working memory (Koshino, et al. 2005), visuomotor learning (Muller, et al. 2003), face processing (Hubl, et al. 2003), and social attribution (Castelli, et al. 2002). The wide variety of tasks associated with higher activity in autistics' visual cortical areas suggests that the atypical physiological processing mechanisms may be related to task performance in a less straightforward way than initially posited by the EPF model.

Quantitative meta-analysis of functional neuroimaging studies is one means to characterize the role of perceptual processes in autism. Neuroimaging meta-analysis combines results from independent experiments to achieve a quantitative summary of the state of research in a specific domain (Turkeltaub, et al. 2002). It assesses the replicability of results across imaging techniques, tasks, and laboratories by revealing consistently modulated voxel activity in a collection of studies. In addition, meta-analysis can establish the specificity of the relationship between a region or network of regions and a particular task type (Wager, et al. 2009). Voxel-wise meta-analysis of neuroimaging studies, called Activation Likelihood Estimation (ALE; Turkeltaub, et al. 2002) has recently been used in autism to document between-group differences in activity related to social compared to non-social tasks (Di Martino, et al. 2009).

We used ALE meta-analysis to summarize patterns of activity related to visual processing by merging activity maxima reported in experiments including both autistic and non-autistic groups, a process that resulted in group maps assessing the regions of common task-related modulation across studies. Maps revealing regions differently engaged between groups were then generated by contrasting the within-group ALE maps (Laird, et al. 2005).

We included the coordinates of activity increases for each group instead of using the reported coordinates of differential activity between autistics and non-autistics, an approach used in a recent autism meta-analysis (Di Martino, et al. 2009). Our method allowed identification of processing activity without any a priori bias that might result from including only studies reporting higher or lower activity in autistics compared to non-autistics. For instance, some reports do not include tables listing coordinates related to higher activity in autistics, even when such findings are described in the body of the paper. To minimize regional selection bias, we also limited our meta-analysis to studies that reported coordinates resulting from whole-brain analysis, as contrasted with region-of-interest (ROI) analysis. Because the resource allocation proposition, stated as Principle 4 of the EPF model (Mottron, et al. 2006), was primarily based on a review of neuroimaging studies of visual perception in autistics, and because there are only a limited number of neuroimaging studies of auditory processing, we limited the analysis to studies employing visual stimuli.

In this meta-analysis our aim was to quantitatively summarize the neuroimaging findings concerning visual processing in autism in order to test the prediction that autistics will exhibit generally stronger engagement of the visual system. Additionally, we explored the relative domain specificity of atypical visual processes in autism, by examining whether any differences between autistics and non-autistics showed specificity for face, object, or word stimulus classes.

MATERIALS AND METHODS

Literature review and contrast selection

We performed a PubMed literature search (www.pubmed.org) to identify functional neuroimaging studies published from 1995 to July 2009 in which visual stimuli were presented to both autistic and non-autistic groups. For this analysis, what we call the autistic group included participants with diagnostic assignments falling within what are generally referred to as autism spectrum conditions. We used the following search terms: «(Autism OR Asperger OR PDD) AND (fMRI OR PET OR Neuroimaging)» and retrieved

787 articles. Among those, 692 were excluded through an initial review of the abstracts. Studies excluded were 217 reviews, 207 reports without an autistic group, 255 reports not using PET or fMRI, and 19 reports including no visual stimuli. Of the remaining 89 studies, 22 were rejected because of small sample size (n<10), 21 because of partial brain coverage or analysis, 11 because results were not reported in a standard anatomical space, and 9 because only between-group contrasts were presented. The remaining 26 peer-reviewed fMRI articles reporting within-group results using whole brain acquisition techniques in a standardized stereotaxic space were included in the meta-analysis. Coordinates reported in MNI space were converted to Talairach anatomical space using the "Convert Foci" tool of the GingerALE 1.1 program (Laird, et al. 2005). This tool uses the icbm2tal Lancaster transform (Lancaster, et al. 2007). The total number of participants included 370 typical controls and 357 individuals with an autism spectrum condition determination. Most studies were conducted on adults and all included participants with Full Scale IQ in the normal range. Seven out of the 26 studies included only autistics, while the others included autistics, individuals with Asperger syndrome and Pervasive Developmental Disorder Not Otherwise Specified (Table 1).

A total of 48 contrasts (504 foci) for the non-autistic and 44 (415 foci) for the autistic group were identified in the 26 included studies. These contrasts were categorized according to domain specificity into face, object, and word categories. The contrasts for one study (Silani, et al. 2008) could not be classified, as the stimuli contained both faces and animal pictures. These contrasts were eliminated from the domain specific analysis. The face processing domain included face viewing, discrimination, matching, recognition, imitation, and identification tasks as well as one task involving facial emotional state inference and one task involving gaze direction identification. Fourteen contrasts (134 foci) for the autistic group and 14 contrasts (175 foci) for the non-autistic group were included in this domain. For the object processing domain, stimuli included pictures of houses, arrows, geometric shapes, complex figures, letters, patterns, in addition to more complex stimuli, including problems from the Tower of London task and Raven's Progressive Matrices. The tasks required matching, response inhibition, interference, identification, mental state attribution to shapes, and simple viewing. A total of 14 contrasts (123 foci) were assigned to the object processing domain for the autistic group and 15 contrasts (166 foci) for the non-autistic group. Finally, the word processing domain included visually presented words or sentences, with participants identifying word category, making a semantic judgment, answering reading comprehension questions, counting words, or generating words in a given category (verbal fluency). The word processing domain included 14 contrasts (137 foci) for the autistic group and 17 contrasts (136 foci) for the non-autistic group. In addition, we investigated the effect of contrasting high to low level baselines across all tasks, by computing separate ALE maps using either low level baselines, such as fixation or rest, or high level baselines such as complex figure matching. Both types of maps yielded superimposable patterns for both the autistic and non-autistic groups. Therefore, in an effort to increase statistical power, contrasts with both high and low level baselines were pooled for all subsequent analyses.

ALE meta-analysis

ALE maps were computed using GingerALE (version 1.1 www.brainmap.org/ale) software (Laird, et al. 2005), based on methods introduced by Turkeltaub et al. {, 2002 #984}. The ALE technique models the uncertainty in location of task-related activity foci as Gaussian probability distributions, yielding statistical maps in which each voxel value represents an estimate of the likelihood that activity occurred in the studies included in the meta-analysis. The critical threshold for the ALE map is set using a Monte Carlo permutation analysis of sets of randomly distributed foci. A FWHM of 8 mm was selected for the Gaussian probability distributions to reflect the average smoothness of the fMRI data from which the foci were derived. The critical threshold was set using a 5,000 permutations test, corrected for multiple comparisons (False Discovery Rate (FDR); Laird, et al. 2005). The model is of the fixed-effects class and permits inferences over the studies included in the meta-analysis.

Maps reflecting regions of convergence across all reported coordinates both within- and between-groups were first computed, using maxima drawn from all three processing domains. As there was an imbalance between the total number of foci included for the non-autistic (48 experiments, 504 foci) and autistic (44 experiments, 415 foci) samples, it was necessary to randomly remove experiments from the non-autistic group to equalize the number of foci between groups (44 experiments, 438 foci), increasing the possibility that the difference maps would reflect activity differences between groups rather than an imbalance in coordinate numbers between categories (Laird, et al. 2005). Second, domain specific (face, object, and word) within-group ALE maps were computed. For each domain, the number of experiments and foci were similar enough for direct comparison. To compare activity patterns between autistics and non-autistics, the within-group ALE maps were subtracted from one another and randomization testing with 5000 permutations was performed. This procedure tests for the presence of differences between the groups under the null hypothesis that both sets of foci are uniformly distributed (Laird, et al. 2005). The critical threshold was set at $pFDR < 0.05$ ($k = 250$ voxels). In order to present results in the anatomical space most commonly used in the current literature, the ALE coordinate results were transformed into the MNI anatomical space using the Lancaster transform (Lancaster, et al. 2007).

RESULTS

Behavior

Table 2 summarizes the behavioral findings for all studies included in the meta-analysis. In the majority of studies, autistics and non-autistics exhibited similar accuracies or response times. There were no significant between-group differences in performance in 69% of the studies (18/26), whereas autistics showed better performance in 7.6% of the studies (2/26) and poorer performance in 23% of the studies (6/26). Across domains, no between-group behavioral differences were observed in 64% of the face tasks (9/14 contrasts), 93% of the object tasks (14/15) and 71% of the word tasks (12/17 contrasts).

Five studies included information about eye movement characteristics, reporting the number or duration of fixations or saccades or the eye movement related fluctuations in the orbital BOLD-contrast signal. None of these studies found any significant between-group differences in eye movement measures acquired either during the scanning sessions

(Greimel, et al. 2009; Soulières, et al. 2009) or in separate experimental sessions (Bird, et al. 2006; Dapretto, et al. 2006; Kleinhans, et al. 2008b).

Combined face, object and word processing

Within-group maps. We first analyzed the task-related activity across all processing domains within each group. ALE maxima values for the autistic and non-autistic groups are presented in Table 3. Figures 1 show a broadly overlapping pattern of activity in the two groups, with large clusters in bilateral striate and extrastriate areas (BA 17, 18, 19); fusiform gyrus (BA 37); precuneus (BA 7); inferior (BA 44, 45, 47), middle (BA 46), and superior (BA 8, 9) frontal gyri; precentral (BA 6) gyrus; and the insula (BA 13).

Between-group maps. Direct comparisons between autistic and non-autistic group maps revealed differing ALE values in occipito-temporal and frontal regions (Table 4; Figures 1). Overall higher ALE values in striate (BA 17) and extrastriate (BA 18, 19) cortex were found in autistics. Small bilateral clusters in posterior extrastriate cortex (BA 18) exhibits lower ALE values in autistics. While both groups showed strong activity in BA 37, lower ALE values were found in autistics bilaterally in the anterior fusiform gyrus and in the medial part of the left fusiform gyrus. Additionally, autistics had lower ALE values in left middle temporal gyrus (BA 21) and higher ALE values in the left precuneus and intraparietal sulcus (BA 7).

In the frontal cortex, lower ALE values were observed in autistics in bilateral precentral (BA 4, 6), superior frontal (BA 6, 8, 9) and inferior frontal (BA 45, 47) gyri. Higher ALE values in autistics were limited to small regions in the posterior part of the left inferior frontal gyrus (BA 47) and in right medial frontal gyrus (BA 8). Clusters of lower activity in the autistics were also observed in bilateral insula (BA 13) and in cingulate cortex (BA 24).

To better visualize the spatial pattern of the differential visual activity in both groups, we computed the number of voxels for which ALE values differed between autistics and non-autistics in the left and right hemispheres for the frontal, parietal, occipital, temporal and subcortical regions (Table 5). Combining counts across all tasks, 6368 voxels had higher ALE values, and 2016 voxels had lower ALE values in the temporal, occipital and parietal lobes of the autistics compared to the non-autistics. In contrast, the frontal lobes of the autistics exhibited a reversed pattern, with higher ALE values in 1360 voxels and lower ALE values in 4808 voxels (Figure 4). The associated analysis of variance revealed a significant effect of Region, F (4, 10) = 6.4, p = .008 and a Region x Group interaction F (4, 10) = 6.2, p = .009. These patterns reveal a spatial redistribution of visual processing in autism, seen as a posterior to anterior gradient of group activity differences, with the autistics exhibiting generally higher ALE values in posterior regions and lower ALE values in frontal regions.

Face processing

Within-group maps. We then restricted the analysis to the face processing domain (Table 6). Figures 1 shows partially overlapping clusters of group activity. While both groups had high ALE values bilaterally along the fusiform gyrus (BA 19, 37), the largest overlap was observed in the anterior and middle fusiform gyrus, involving more posterior and lateral regions on the left than on the right. Additionally, both groups had high ALE values in right superior temporal gyrus (BA 22) and medial parietal cortex (BA 7). Moreover, both groups displayed activity in the posterior cingulate, the globus pallidus and at the temporo-occipital junction (BA 21, 39). Significant ALE values in frontal cortex were more numerous in non-autistics (BA 4, 6, 9, 10, 44, 45, 46) and overlap between the groups was limited to ALE values in precentral gyrus (BA 6) and insula (BA 13).

Between-group maps. Between-group comparisons of face processing revealed areas of differential activity in occipital, temporal and frontal cortex (Table 7; Figures 1 and 3). First, higher ALE values in autistics were found in the fusiform gyrus (BA 37) bilaterally, while regions immediately posterior showed lower ALE values. Autistics also had higher ALE values in the middle portion of the left fusiform gyrus, the right lingual gyrus (BA 18, 19) and primary visual cortex (BA 17), with below threshold clusters at -20, -95, +3; vx = 48 and -14, -99, +1; vx = 32. Maxima were also seen in left middle temporal gyrus (BA 21), with greater ALE values for autistics in the extreme anterior portion and lower values in autistics in the posterior part of the gyrus. The autistics had lower ALE values in left superior temporal gyrus (BA 39), while the corresponding region on the right had higher ALE values. The between-group differences in frontal cortex all involved lower ALE values in the autism group. For instance, differences were observed in right dorsolateral cortex (BA 9, 46), right anterior prefrontal cortex (BA 10), bilateral inferior frontal cortex (BA 44), bilateral premotor cortex (BA 6) and left primary motor cortex (BA 4). The autistics also exhibited lower ALE values in right anterior insula (BA 13).

Voxel count in the fusiform gyrus for faces. To visualize the differential activity related to visual processing, we computed the number of voxels in the fusiform gyrus for which ALE values differed between autistics and non-autistics for the different processing domains in both hemispheres (Table 8). The associated analysis of variance revealed higher ALE values for the autistics with a significant main effect of Group, F (1 ,6) = 9.12, p = .023 and a Task x Group trend suggesting more activity in the autistics related to face processing, F (2, 6) = 4.64, p = .008 (Figure 5).

Object processing

Within-group maps. The within-group analysis for contrasts involving object processing revealed a roughly overlapping pattern of activity in both groups (Table 9; Figures 2), including bilateral clusters in the anterior fusiform gyrus (BA 37) and posterior extrastriate cortex (BA 18, 19). In contrast, most of the activity in the occipital gyri did not exhibit overlap between groups. In the parietal cortex, overlapping ALE values were seen in medial parietal cortex (BA 7), while activity was observed in slightly different portions of the inferior parietal lobule (BA 40) in each group. Overlapping activity was also seen bilaterally in anterior insula (BA 13), and precentral and middle frontal (BA 6) gyri.

Between-group maps. Widespread between-group differences in visual object processing were seen in occipital, temporal, parietal and frontal cortex (Table 10; Figures 2 and 3). In occipital regions, the autistic group had greater ALE values bilaterally in the posterior fusiform gyrus (BA 19) and the middle occipital gyrus (BA 19). Conversely, autistics had lower ALE values in left lingual gyrus (BA 18) and the right anterior fusiform gyrus (BA 37). Additionally, autistics had lower values in the left mid-fusiform gyrus (BA

19; +29, -68, -14), in an area anterior and medial to the area in which autistics had higher values. Both groups had ALE value maxima in the medial (precuneus) and lateral parietal cortex. Higher ALE values in autistics were more medial than those of non-autistics in right inferior parietal cortex (BA 40) and anterior to those of controls in right lateral and medial superior parietal cortex (BA 7). As for frontal cortex, lower ALE values were observed in superior frontal gyrus (BA 6) in the autistics. Additionally, the autistic group exhibited lower ALE values in the right anterior insular cortex (BA 13) and higher ALE values in the cingulate gyrus (BA 24).

Word processing

Within-group maps. ALE maps were computed for contrasts involving word processing (Table 11; Figure 2). In both groups, activity was observed in striate (BA 17) and extrastriate cortex (BA 18), overlapping mostly in the right hemisphere, while left hemisphere activity was slightly more anterior in autistics. In parietal cortex, both groups showed overlapping activity in the medial parietal cortex (BA 7), while activity in left middle temporal gyrus (BA 21) was observed in a more posterior location in autistics. In frontal cortex, both groups had significant ALE values in inferior (left BA 45, 47), middle (BA 6, 46), and superior frontal (BA 6, 8, 9) gyri, with overlapping activity in the left inferior and superior frontal gyri. We observed group overlap in subcortical activity in the thalami, right cingulate gyrus (BA 31), and left parahippocampal gyrus (BA 36).

Between-group maps. Between-group ALE maps revealed differences in word processing activity (Table 12; Figures 2 and 3). First, ALE values differed between groups in occipitotemporal areas, with lower activity in bilateral striate cortex in autistics, just under the critical threshold on the right (+16, -95, -7), and higher activity in autistics in extrastriate cortex (BA 18; -14, -87, -5 and +25, -98, -9). Autistics also had higher activity in both the right fusiform gyrus (BA 19, 37) and, more ventrally, in the left ventral fusiform gyrus (BA 19). In parietal cortex, the autistics had higher ALE values in bilateral medial parietal cortex (BA 7), although the values were subthreshold on the left (-28, -68, +38; vx = 144). Between-group differences were also seen in the middle temporal gyrus, with higher ALE values found posteriorly in autistics and anteriorly in non-autistics on the left.

A more complex pattern of effects was observed in frontal and subcortical regions. For example, while autistics generally had more areas exhibiting lower ALE values in frontal cortex compared to non-autistics, the lower ALE values were seen primarily in left inferior, superior frontal, and precentral gyri (BA 4, 8, 47) and higher ALE values were found bilaterally in left posterior inferior frontal gyrus (BA 47), left superior frontal gyrus (BA 6), as well as left and right middle frontal gyri (BA 8, 9, 46). At the subcortical level, the right caudate nucleus, and bilateral thalami (sub-threshold cluster on the right; +29, -26, -2; vx = 120) exhibited lower ALE values in autistics, while the left putamen had higher ALE values in autistics.

DISCUSSION

Summary of findings

On the basis of the behavioral, cognitive and physiological characteristics previously summarized in the enhanced perception function model, we predicted that autistics would exhibit stronger engagement of the visual system across a range of tasks. In addition, we were interested in whether any observed atypical visual activity patterns in autism were specific to particular processing domains. We compared the magnitude and spatial distribution of brain activity associated with visual processing in autistics and non-autistics using ALE meta-analysis, including data drawn from 26 neuroimaging studies using visual stimuli. The analysis provided information about between-group differences with respect to location and amplitude of task-related activity. Combining all visual tasks, we observed widespread effects in both groups in regions spanning temporal, occipital, parietal, and frontal cortex. However, compared to non-autistics, autistics displayed generally higher task-related activity in posterior regions, and lower task-related activity in frontal cortex. In addition, for each processing domain, we observed spatial overlap in activity in autistics and non-autistics, accompanied by an atypical functional spatial distribution of domain-specific responses in autism.

Domain-independent similarities and differences

As visual stimuli were used in all studies, large clusters of activity were found in both groups in the cortical areas involved in the first visual processing stages, namely striate (BA 17) and extrastriate (BA 18, 19) cortex. Both groups had responses in inferotemporal cortex, a region involved in recognition and identification of visually presented animate or inanimate objects (Op de Beeck, et al. 2008). Both groups also displayed posterior parietal cortex activity mainly in the medial parietal cortex (BA 7), an associative region involved in visuospatial information processing (Cavanna and Trimble 2006). In addition, both groups exhibited activity in the dorsal (BA 6, 8, 9, 46) and ventral (BA 44-47) prefrontal cortex, regions involved in multiple aspects of sensorimotor and cognitive control (D'Esposito, et al. 2000; Duncan and Owen 2000; Petrides 1996; Petrides 2005). The high ALE values seen in both groups across a broad network comprising temporal, occipital, parietal, and frontal regions were consistent with the wide range of visual processing tasks included in the study.

Between-group comparisons using the combined face, object, and word processing tasks revealed an atypical pattern of resource allocation in autistics, with relatively higher activity in posterior visual processing regions and lower activity in frontal regions, as demonstrated by voxel count lobar distributions (Figure 4). In inferotemporal, occipital, and inferior parietal regions, more voxels showed higher ALE values in autistics than in non-autistics in areas subserving integration of local visual features, manipulation of visual features, object recognition and object identification (Wandell, et al. 2007). Moreover, autistics displayed higher activity bilaterally in the precuneus (BA 7), a region subserving visual imagery (Suchan, et al. 2002), visual search and detection (Brown, et al. 2006; Hufner, et al. 2008; Patel and Sathian 2000), and the maintenance of visual information in working memory (Owen 2004; Suchan, et al. 2006; Yeh, et al. 2007).

Conversely, ALE values in more anterior frontal regions (BA 4, 6, 8, 9, 45, and 47) were mostly lower in autistics. These areas include a range of regions with specialization for movement execution, movement planning, and cognitive control. The most posterior frontal region (BA 4) in the precentral gyrus is involved in fine motor control and sensorimotor transformations (He, et al. 1993; Rizzolatti and Luppino 2001). The posterior part of the dorsolateral prefrontal cortex (DLPFC; BA 6, 8) is responsible for response selection, attention shifting between alternative stimuli or responses in visuomotor tasks

(Petrides 1994; Petrides 2005). The mid-DLPFC (BA 9) is involved in planning and monitoring of behavior in accordance with internal goals (Petrides 1991; Petrides 2000). The adjacent mid-ventrolateral prefrontal cortex (VLPFC; BA 45, 47) plays an important role in decision making (Petrides 2002), response comparison, selection and inhibition based on stored stimulus representations (Badre and Wagner 2007; Petrides 2005). Finally, BA 6 and 9 are believed to be involved in cognitive control, mainly through the activation of task representations to adjust behavior to changing contexts (Brass, et al. 2005).

Our principal finding resulting from the examination of results from the pooled face, object and word domains is that, in performing predominantly visual tasks, autistics exhibit a consistent pattern of stronger engagement of posterior cortical regions known to support visual processes of varying complexity. In addition, autistics exhibit lower activity in frontal regions subserving motor and cognitive control functions across a wide range of stimulus and task types.

Domain-specific similarities and differences

Although our results are largely consistent across the visual processing categories, examining the domain-specific patterns of differential activity informs the understanding of specific atypical functional resource allocation patterns in autism. The decision to classify the included tasks broadly by stimulus type rather than by specific cognitive operation was dictated by the difficulty in identifying sufficient numbers of studies utilizing tasks employing comparable cognitive operations. As the number of papers using functional neuroimaging to explore the neural mechanisms of perception and cognition in autism is expanding rapidly, it may soon be possible to attempt meta-analysis of particular cognitive processes in autism.

Face processing. Much effort has been directed towards identifying the nature of face processing in autism. Our meta-analysis of face processing tasks revealed strong, and partially overlapping, occipital and temporal activity in both groups. Face processing involves occipital and temporal cortical areas that show selectivity for face versus non-face stimuli in typical groups (Haxby, et al. 2000; Kanwisher, et al. 1997). Consistent identification of preferential activity for face stimuli have been observed in the middle and lateral fusiform gyri, sometimes referred to as the Fusiform Face Area (FFA). This region generally shows stronger responses to faces compared to objects. Activity in the FFA correlates with successful face detection (Andrews and Schluppeck 2004; Grill-Spector, et al. 2004). A region in the lateral inferior occipital gyrus, referred to as the occipital face area (OFA), also shows selectivity for faces (Gauthier, et al. 2000). While the OFA is mostly sensitive to the individual physical features of faces, the FFA shows strong responses to both face parts and configurations (Liu, et al. 2009; Rotshtein, et al. 2005). The third face-selective region is found in the posterior superior temporal sulcus and is called fSTS, showing stronger responses to more complex aspects of face processing, such as eye-gaze direction (Hoffman and Haxby 2000) and emotional expression (Haxby, et al. 2000).

With regards to face processing, spatial overlap in activity for autistics and non-autistics was observed in the FFA (Kanwisher, et al. 1997; Lehmann, et al. 2004; Rhodes, et al. 2009; Scherf, et al. 2010). Activity was also seen in the OFA (Rhodes, et al. 2009; Rotshtein, et al. 2005). In addition, activity in fSTS was seen in both groups on the right, but only in non-autistics on the left. Therefore, the results of our meta-analysis do not support the notion that autism is characterized by an overall hypoactivation in face-selective areas. We believe that the reported reduction of FFA activity in autism in response to face images (Dalton, et al. 2005; Pierce, et al. 2001; Schultz, et al. 2000) could be dependent on specific task properties, rather than related to a generalized dysfunction of fusiform gyrus mechanisms or stemming from a lack of face expertise (Hadjikhani, et al. 2004; Hadjikhani, et al. 2007; Pierce, et al. 2004).

However, our results do suggest that face stimuli are processed in an atypical fashion in autism, such that stronger, but less category-specific, occipital and temporal activity may underlie face processing in this population. Specifically, compared to non-autistics, autistics showed bilateral clusters of higher ALE values in the anterior fusiform gyrus, extending into the posterior part of the parahippocampal gyrus (Figure 3). In typical individuals, these areas are thought to be important for face recognition (Hudson and Grace 2000), perceptual expertise (Gauthier, et al. 1999), and object processing (Grill-Spector

2003). Moreover, previous studies have identified functional response selectivity for places and spatial layout in the posterior parahippocampal cortex (Epstein and Kanwisher 1998). In our results, autistics showed greater activity bilaterally in extrastriate (BA 18, 19) and striate (BA 17) cortex compared to non-autistics. Therefore, face processing in autistics seems to rely on a large network of occipital and temporal areas specifically responsive to other visual categories in non-autistics. Interestingly, the more anterior inferotemporal areas were more responsive to non-face objects in non-autistics. A recent fMRI study looking at response specificity to faces, objects, and places in autism reported a similar atypical distribution of activity, in the form of bilateral displacement of the face-specific response to the postero-ventral fusiform gyrus in autistics, while non-autistics showed greater object-related responses in the same region (Scherf, et al. 2010). These findings are consistent with the results of our meta-analysis, indicating a general pattern of atypical facial response selectivity in autism, with a corresponding atypical spatial distribution of place- and object-specific responses.

The differential activity we observed in autistics could reflect an atypical processing strategy for facial stimuli. Langdell (1978) first reported superior performance in judging face identity based on the presentation of elementary facial features such as the eye or mouth in autistic children compared to non-autistics. More recent studies confirmed that autistics rely to a greater extent on individual features to process faces (Deruelle, et al. 2004; Lahaie, et al. 2006; Pelphrey, et al. 2002). However, these atypical processing strategies are not behaviorally detrimental, as both autistics and non-autistics exhibited similar performance in 9 out of 14 contrasts included in the meta-analysis.

We observed generally lower activity in prefrontal cortex in autistics during face processing, consistent with previous reports (Di Martino, et al. 2009; Scherf, et al. 2010). It is known that frontal top-down mechanisms may modulate extrastriate and inferotemporal activity during "deep" processing of faces, facilitating facial feature recognition (Haxby, et al. 2000; Johnson, et al. 2007; Li, et al. 2009; Mechelli, et al. 2004) and visual category determination (Jiang, et al. 2007; Jiang, et al. 2006). Our findings suggest that, although frontal processes are consistently engaged for face processing in non-autistics, the perceptual mechanisms in temporal, occipital, and parietal regions may be sufficient to allow for successful face processing in autistics. Although it is possible that the lack of task-related frontal activity in autistics could result from localized dysfunction of the frontal cortex, suggested by some current models (e.g. Courchesne and Pierce 2005), an alternative account is that utilization of frontal processing mechanisms may not be mandatory under some circumstances in autistics due to the existence of more efficient perceptual processing resources available in posterior cortical structures (Soulières, et al. 2009). Finally, the reduced engagement of frontal regions may reflect atypical connectivity between anterior and posterior regions, resulting in reduced coupling during visual processing. As our results are consistent with all of these hypothetical mechanisms, further studies are warranted to better delineate the physiological basis of the generalized frontal cortical hypoactivity commonly seen in autism.

Object processing. Autistics often exhibit unexpectedly strong and atypical abilities in visual tasks involving object detection or manipulation. For object processing, we observed activity in both groups in occipital (BA 17, 18, 19), temporal (BA 37), medial and lateral superior parietal (BA 7), inferior parietal (BA 40), and dorsal and ventral lateral prefrontal cortex (BA 6, 9 46, 47). Object processing is typically associated with activity in occipital and temporal cortex, with previous studies identifying responses in lateral occipital cortex to pictures of common objects (Malach, et al. 1995), line drawings of objects (Kanwisher, et al. 1996) and shapes (Hayworth and Biederman 2006). We observed activity in both groups that was located more medially than previously reported, possibly due to the heterogeneity of stimuli and tasks combined in the current analysis. While the lateral occipital region plays a specific role in object recognition (Grill-Spector, et al. 2001), object recognition as such was not a prominent component of all the tasks included in the meta-analysis. Activity common to both groups was also observed in the anterior fusiform gyrus, another area involved in object processing (Grill-Spector 2003) and spatial relations (Epstein and Kanwisher 1998). Overall, both groups showed occipital and temporal activity in brain regions typically recruited by material-independent visual information processing, such as integration of local visual features and manipulation of visual properties (Wandell, et al. 2007).

Both groups also showed responses in prefrontal cortical regions, consistent with cognitive control requirements of the object processing tasks. For instance, lateral prefrontal cortex activity has been reported in relation to set shifting (Rogers, et al. 2000), inhibitory control (Konishi, et al. 1999), and category discrimination (Jiang, et al. 2007; Jiang, et al. 2006), processes common in object processing tasks (Dichter and Belger 2007; Schmitz, et al. 2006; Schmitz, et al. 2008; Solomon, et al. 2009). The observed prefrontal activity could also be related to planning and categorization (Petrides 2005), processes critical to tasks such as the Embedded Figure Test (Lee, et al. 2007; Manjaly, et al. 2007), the Tower of London task (Just, et al. 2007), spatial reasoning, and pattern matching (Soulières, et al. 2009).

Both groups showed activity in superior parietal cortical areas involved in visuospatial attention (Corbetta, et al. 1993; Nobre, et al. 1997) and manipulation of information in working memory (Cabeza 2008; Cabeza, et al. 2008). Despite the variability of the tasks and stimuli combined within the object category, we observed a pattern concordant with the previous literature.

Regarding between-group differences in activity related to object processing, autistics had higher ALE values in occipital (BA 19) and parietal (BA 7, 40) areas and lower values in the fusiform gyri (BA 37). The clusters of between-group differential activity were smaller for the object than the face domains, which may be explained by greater task and stimulus variability for the object vs. face domain. Greater task variability within each domain might be expected to lead to a greater degree of spatial variability and consequently weaker constructive interference among the local maxima. As with face processing, autistics performed similarly to non-autistics while displaying lower ALE values in the superior frontal gyrus (BA 6). Enhanced autistic performance has been reported in a broad range of visual perceptual tasks based on pattern detection, matching, and manipulation of objects, aspects encompassed here in the very general object processing domain. Therefore, we tentatively relate the atypical functional allocation of activity in visual perceptive regions in autism to enhanced performance in object processing.

Word processing. Some autistics acquire reading skills at an unexpectedly early age, a phenomenon known as hyperlexia. It is possible that these atypical reading skills result from differential organization in the visual areas responsible for processing letters or words. In our meta-analysis results, group activity distributions related to word processing corresponded well to the known functional neuroanatomy of reading systems. A first level of word analysis in the occipito-temporal junction supports word identification; a second level at the parieto-temporal junction supports phonological processing; and a third level in the inferior frontal cortex supports semantics, phonology and articulation (Shaywitz and Shaywitz 2008). Both groups displayed bilateral posterior fusiform and lingual activity, presumably associated with word form analysis (Fiez and Petersen 1998; Price 2000). Also consistent with this finding are the previous studies that have reported occipitotemporal and lateral occipital sensitivity to letter strings (Puce, et al. 1996) and written words (Baker, et al. 2007). In addition, both groups displayed activity in regions typically associated with semantic processing (Howard, et al. 1992; Martin and Chao 2001; Petersen, et al. 1988; Poldrack, et al. 1999), verbal fluency (Abrahams, et al. 2003; Gaillard, et al. 2000), and sentence comprehension (Just, et al. 1996; Roder, et al. 2002), including the left middle temporal gyrus, the left superior temporal gyrus, the left inferior frontal gyrus and multiple lateral prefrontal regions. The word processing tasks included semantic decision (Gaffrey, et al. 2007; Harris, et al. 2006), sentence judgment and comprehension (Just, et al. 2004; Kennedy and Courchesne 2008; Mason, et al. 2008), word counting (Kennedy, et al. 2006), and verbal fluency (Kleinhans, et al. 2008a), for which we observed the expected activity in a number of left hemisphere language regions.

We observed group differences for the word processing tasks, with higher task-related ALE values in autistics in the fusiform gyrus (mostly on the right; BA 19, 37), medial parietal cortex (BA 7), middle posterior temporal gyrus (BA 21), left inferior frontal gyrus (BA 44), and bilateral lateral prefrontal cortex (BA 6, 8, 9, 46). Many of these areas are also part of the reading network seen in non-autistics. However, predominant left-lateralization, expected based on previous studies of language in typical samples, was not seen here in autism, in line with reports of reduced leftward hemispheric response lateralization for speech processing in autism (Boddaert, et al. 2003; Boddaert, et al. 2004; Lepisto, et al. 2005). Higher activity for words in the fusiform gyrus and medial parietal cortex supports the hypothesis that autistics more strongly engage mental imagery and visualization to process written sentences (Just, et al. 2004) and words (Gaffrey, et al. 2007; Toichi and Kamio 2001). In addition, we observed lower activity in the autistic group in many reading regions, including occipital (BA 17, 18), left parieto-temporal (BA 21, 39) and left inferior frontal (BA 47) cortex. In summary, the regional functional allocation of word related activity is clearly atypical in autism, as we observed more right-lateralized activity in autistics related to reading as well as stronger involvement of regions typically involved in broader aspects of perceptual expertise (BA 19, 37).

This atypical activity pattern could explain the emergence of hyperlexic abilities in some autistics. Hyperlexia is defined as reading skills exceeding those predicted by an individual's general intelligence or language comprehension capacities (Grigorenko, et al. 2003). Hyperlexia occurs in about 5-10% of autistic children (Burd, et al. 1985). While it has been suggested that enhanced visual pattern recognition may underlie hyperlexia (Cobrinik 1982), heightened phonological and orthographic abilities may also contribute to precocious reading skills (Goldberg and Rothermel 1984). Although hyperlexic children could engage typical reading strategies to attain superior word recognition abilities, word recognition mechanisms could operate more autonomously from more abstract word comprehension mechanisms in this group (Newman, et al. 2007). The atypical pattern of occipital and temporal word processing activity seen in our meta-analysis might underlie this autonomy, a phenomenon that we called functional independence in a different cognitive context (Soulières, et al. 2009).

Interpretations of the observed between-group differences

Could atypical saccades cause the observed atypical occipital and parietal activity?

Differences in brain activity apparently associated with visual processing might trivially result from differences in eye movements used to explore the stimuli, rather than from differences in perceptual processing per se. We argue that this is not the case for the following reasons. First, all studies included in the meta-analysis that reported eye movement data found no differences between the autistic and non-autistic groups (Bird, et al. 2006; Dapretto, et al. 2006; Greimel, et al. 2009; Kleinhans, et al. 2008b; Soulières, et al. 2009), in line with other studies reporting no differences in visual saccade or fixation properties between autistics and non-autistics (Dalton, et al. 2005; Kemner, et al. 2004; Luna, et al. 2007; Luna, et al. 2002; Takarae, et al. 2004; Takarae, et al. 2007). Second, the spatial pattern of activity across tasks for the between-group differences reported here does not overlap with the network thought to control visual search and saccades. For instance, both groups exhibited activity in lateral prefrontal cortex in the frontal eye fields (FEF; Amiez and Petrides 2009; Grosbras, et al. 2005). This area is consistently involved in controlling saccade and pursuit eye movements (Astafiev, et al. 2003; Ettinger, et al. 2008; Grosbras, et al. 2005). It is also active in tasks requiring changes in visuospatial attention, even in the absence of saccades (Armstrong, et al. 2009). Nevertheless, no significant between-group differences were observed in this region. Similarly, regions previously reported as less active in autism in association with visually-guided saccades (Takarae, et al. 2007) do not correspond to the areas of lower activity reported here in autistics across all visual tasks. Lower ALE values in non-autistics were observed in the dorsal part of the medial frontal gyrus, anterior to the supplementary eye fields (Grosbras, et al. 1999). However, this region is known to be less active in autism well beyond the context of saccade generation, specifically during executive and working memory tasks (Gilbert, et al. 2008; Silk, et al. 2006). Therefore, the pattern of between-group differences reported here is unlikely to be related to oculomotor effects.

Are the observed activity patterns explained by differences in task complexity?

Another interpretation of the differential engagement of cortical regions in autistics across a range of visual tasks could be that these differences are driven mainly by tasks incorporating more substantial perceptual complexity. However, the autistic pattern of relative posterior hyperactivity was consistently found for a range of tasks involving visual information ranging from simple to complex, and cognitive complexity ranging from low to high. For instance, our meta-analysis included stimuli varying from simple shapes (i.e. letters in Keehn, et al. 2008) to more complex visual patterns (i.e. facial stimuli in Hall, et al. 2003; Raven's Progressive Matrices in Soulières, et al. 2009). Tasks of varying complexity were included as well, ranging from passive viewing of faces (e.g. Bird, et al. 2006) and stimulus matching (e.g. Bookheimer, et al. 2008; Lee, et al. 2007) to sentence comprehension (e.g. Mason, et al. 2008), mental state inference (e.g. Kana, et al. 2009) and abstract reasoning (Soulières, et al. 2009). In sum, more strongly engaged perceptual processing regions engaged across a disparate collection of tasks indicates a greater role for perceptual processes in autism for tasks not necessarily incorporating complex perceptual or cognitive components.

Does differential between-group performance explain the observed activity patterns?

It is possible that performance differences could be responsible for atypical neural activity patterns in autistics. However, autistics and non-autistics exhibited similar performance levels in 18 of the 26 included studies, compared to 2 studies with enhanced and 6 studies with diminished performance in autistics. While enhanced autistic performance was reported in the form of faster responses for sentence comprehension tasks (Just, et al. 2004; Knaus, et al. 2008), diminished performance was mainly observed in the form of reduced accuracy. Even in studies where accuracy was significantly reduced, the autistics still performed fairly well. While one study reported 93% correct responses in autistics compared to 100% in non-autistics (Bookheimer, et al. 2008), another observed reduced but significantly greater than chance (81.9% and 73.8%) accuracy for a semantic decision task in autistics (Gaffrey, et al. 2007). Kleinhans et al. (2008a) reported that autistics generated fewer words than non-autistics in a verbal fluency task, while no group differences in error number were seen. One study (Hubl, et al. 2003) reported longer response times for autistics detecting the sex of real and scrambled faces, but the task instructions did not explicitly require participants to respond as quickly as possible. Other studies reported more errors when autistics were asked to judge emotional states from weak facial expressions (Greimel, et al. 2009) or when they had to overcome an automatic response tendency (Solomon, et al. 2009). Given that atypical visual processing is observed in association with mostly typical performance levels in autism, we suggest that autistics make more use of perceptual processes than do non-autistics in executing cognitive tasks involving complex operations.

Is hemispheric asymmetry for visual processing atypical in autism?

Face processing was associated with generally similar hemispherical effects in autistics and non-autistics. Both groups showed bilateral activity in the FFA and the OFA. However, while activity increases was seen in posterior fSTS in both groups on the right, it was observed only in non-autistics on the left. For face processing in autistics, some have hypothesized atypical regional allocation of activity, not necessarily reflecting reduced lateralization of the face-specific activity compared to non autistics (Pierce, et al. 2001). In addition, recent studies have demonstrated displacement of the face-specific response in autism to regions typically responsive to non-face visual stimuli in non-autistics in both hemispheres (Humphreys, et al. 2008; Scherf, et al. 2010). One other meta-analysis of functional neuroimaging studies looking at social vs. non social tasks did not report activity lateralization differences between autistics and non-autistics (Di Martino, et al. 2009). With regards to the object processing domain, cortical activity was similarly distributed between hemispheres in both groups. The laterality of word processing is atypical in autism, as we observed more symmetric activity in autistics related to reading. Predominantly left lateralization, expected based on previous studies of language in typical samples, was not seen here in autism. With respect to language tasks in general, some studies have suggested that atypical hemispheric specialization might be related to the communication difficulties observed in autistics. Atypical leftward lateralization in autism has been most consistently observed at the structural level in frontal language areas (Herbert, et al. 2005) and in temporal regions such as planum temporale, middle and inferior temporal gyri (Herbert, et al. 2005; Rojas, et al. 2002). Some functional imaging studies have reported reduced left frontal activity associated with language tasks (Gaffrey, et al. 2007; Just, et al. 2004; Kana, et al. 2006) and others have reported reduced leftward temporal response lateralization for auditory language tasks in autism (Boddaert, et al. 2003; Boddaert, et al. 2004; Lepisto, et al. 2005). It is possible that the lateralization effects related to language might be task-dependent, as the hemispheric differences between autistics and non-autistics were not the same for two language tasks examined in a study in which autistics showed reduced leftward asymmetry for one task (fluency) and typical lateralization for the other (categorization) (Kleinhans, et al. 2008a).

In summary, while we observed a trend for decreased hemispheric asymmetry in autism for word processing, the left/right differences in associated ALE values were more subtle than the more consistent finding of higher ALE values across all three task domains in posterior cortical regions.

Are the results consistent with the predictions of the EPF model?

Our ALE meta-analysis results both confirm and extend the original EPF model, demonstrating that: 1) perceptual processing in autistic individuals plays an enhanced role across a wide range of visual tasks and 2) that the neural organization of perceptual processing is atypically organized, extending to areas involved in the development of perceptual expertise. The first major finding of this study consists of evidence for generally stronger engagement of visual processing regions in autism across a range of tasks, consistent with our previous non-quantitative review of brain imaging results (Mottron, et al. 2006). In addition, the observed stronger engagement of visual areas emerges despite multiple sources of noise introduced by variations in matching strategies, participant age and general intelligence, and whether group assignment was defined using a specific diagnosis of autism versus the broader classification of autism spectrum condition. Our findings are consistent with the hypothesis that autistics rely more heavily on visual processing mechanisms regardless of the stimulus domain, particularly for language functions (Gaffrey, et al. 2007; Just, et al. 2004; Lambert, et al. 2004). Enhanced activity in brain regions related to visual processing may therefore represent a core atypicality in autistic neural organization.

However, while behavioral evidence for visuospatial strengths in autism is now strong, it is not possible to simply associate higher levels of neural activity with superior behavioral performance, a relationship that has been clearly demonstrated in only a limited number of studies. For instance, we recently reported increased extrastriate (BA 18) combined with reduced prefrontal (BA 9) and parietal (BA 7) activity during performance of a matrix reasoning task in a group of autistics who had been matched with a non-autistic group on both accuracy and response time (Soulières, et al. 2009). In this study, an autistic behavioral advantage, as evidenced by faster performance, and enhanced occipital activity both increased as task complexity increased. The relative independence of the observed occipital findings with respect to task performance in the present study indicates that higher levels of neural activity may only be associated with more efficient task performance in some circumstances.

The second main finding of this meta-analysis is that atypical regional functional resource allocation, involving both primary and associative visual cortices across a range of visual processing tasks, engages mechanisms responsible for the development of perceptual expertise in areas such as the fusiform gyrus. This important finding allows an extension of the original EPF model that suggests that the overall process of perceptual expertise development, as well as the specific nature of related category-specific responses, may be atypical in autism. Material-independent variations in the acquisition of autistic perceptual expertise, their reciprocal interactions with low-level perceptual processes, and their involvement in a broad range of both social and non-social atypical behaviors characteristic of autism, may all represent promising fields for future investigation.

Lastly, considering that atypical spatial allocation of brain resources may be an indication of functional plasticity, our results could indicate that enhanced cortical plasticity is beneficial to visual perception in autism, in the light of preliminary findings of superior cortical plasticity, including enhanced long-term potentiation of the strength of synapses in animal model of autism (Rinaldi, et al. 2008), and more lasting changes in cortical excitability following in vivo theta burst stimulation, in a few autistics (Oberman et al, 2010).

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TABLES

TABLE 1. Participant characteristics for the studies included in the meta-analysis.

Reference	N	Age M (SD)	N	Age M (SD)	AUT	AS	PDD
Bird et al., 2006	16	33.3 (11.5)	16	35.3 (12.1)	1	15	
Bookheimer et al., 2008	12	11.9 (2.4)	12	11.3 (4.0)	unspecified		
Dapretto et al., 2006	10	12.38 (2.2)	10	12.05 (2.5)	unspecified		
Ditcher & Belger, 2007	15	23.2 (5.7)	14	22.9 (5.2)	11	3	
Gaffey et al., 2007	10	25.3 (9.8)	10	26.1 (10.5)	8	2	
Greimel et al., 2010	15	15 (1.4)	15	14.9 (1.6)	3	12	
Harris et al., 2006	22	31 (9)	14	36 (12)	7	5	2
Hubl et al., 2003	10	25.3 (6.9)	10	27.7 (7.8)	10		
Just et al., 2004	17	N/A	17	N/A	17		
Just et al., 2007	18	24.5 (9.9)	18	27.1 (11.9)	18		
Kana et al., 2009	12	24.4 (3.7)	12	24.6 (6.9)	12		
Kennedy et al., 2006	14	26.07 (7.95)	12	25.49 (9.61)	8	3	1
Kennedy et al., 2008	12	27.5 (10.9)	13	26.9 (12.3)	6	6	1
Kleinhans et al., 2008a	14	22.41 (8.67)	14	23.79 (9.58)	8	3	3
Kleinhans et al., 2008b	21	25.1 (7.6)	19	23.5 (7.8)	8	9	2
Knaus et al., 2008	12	14.94 (2.71)	12	15.45 (2.48)	unspecified		
Koshino et al., 2007	11	28.7 (10.9)	11	24.5 (10.2)	11		
Lee et al., 2007	14	10.85 (1.47)	17	10.37 (1.85)	8	9	
Manjaly et al., 2007	12	14.3 (2.7)	12	14.4 (2.8)	3	9	
Mason et al., 2008	18	27.4 (NA)	18	26.5 (NA)	18		
Schmitz et al., 2006	12	39 (6)	10	38 (9)	2	8	
Schmitz et al., 2008	10	20-50	10	20-50	3	7	
Silani et al., 2008	15	33.7 (10.3)	15	36.6 (11.7)	unspecified		
Solomon et al., 2009	23	15.9 (2.1)	22	15.2 (1.7)	10	12	
Soulières et al., 2009	13	20.15 (3.02)	12	22.08 (4.91)	12		
Uddin et al., 2008	12	12.23 (2.10)	12	13.19 (2.61)	unspecified		

TABLE 2. A listing of: 1) studies included in the meta-analysis, 2) tasks, 3) stimuli, 4) observed performance, 5) task contrasts, 6) processing domain, and 7) number of maxima for the autistic (AUT) and non-autistic (nAUT) groups.

						Maxima	
Reference	**Task**	**Stimuli**	**Performance**	**Contrast**	**Domain**	**nAUT**	**AUT**
Bird et al., 2006	Look at a fixation cross in the center of each face or house picture	Photographs of houses and faces	No task	Faces vs. Houses	Faces	5	5
				Houses vs. Faces	Objects	7	7
	Indicate if two faces or two houses were the same or different (four pictures presented at same time, with attention directed to the houses or faces)		No between-group differences in RT or ACC	Attended faces vs. Unattended faces	Faces	3	2
				Attended houses vs. Unattended houses	Objects	2	0
Bookheimer et al., 2008	Select one of two choices to match a target face / target shape	Oval forms and pictures of faces (upright or inverted)	Less accurate responses in autistics for upright faces but no between-group differences in RT	Matching upright face to target vs. Form matching	Faces	10	6
				Matching inverted face to target vs. Form matching	Faces	9	8
Dapretto et al., 2006	Observe or imitate faces	Pictures of emotional faces	No between-group differences in RT or ACC	Imitation of emotional faces vs. Fixation	Faces	36	16
				Observation of emotional faces vs. Fixation	Faces	14	10
Ditcher & Belger, 2007	Reaction time flanker task: Indicate by button press whether a central stimulus (flanked by same or different direction stimuli) point to the left of to the right	Arrow flanked by arrows	No between-group differences in RT or ACC	Incongruent arrow vs. Congruent arrow	Objects	8	10
		Gaze pictures flanked by gaze pictures		Incongruent gaze vs. Congruent gaze	Faces	8	2
Gaffrey et al., 2007	Semantic: Indicate category (Tool, Color, Feeling) membership of words Perceptual: Indicate if a target letter is present in an consonant string	Words or letters	No between-group differences in RT, but the control group was more accurate for Colors and Feeling categories	Semantic vs. perceptual	Words	14	13
Greimel et al., 2010	Empathize with the person whose face is presented and infer the emotional state (Other) or judge their own response (Self) Baseline: Judge the width of neutral faces	Happy, sad, neutral faces	No between-group differences in RT, but autistics made more errors when judging emotional state from weak expressions.	Other vs. Face width judgment	Faces	19	23
				Self vs. Face width judgment	Faces	19	14
Harris et al., 2006	Indicate if a word is positive/negative (semantic)or in upper/lower case (perceptual)	Words	No between-group differences in RT or ACC	Concrete vs. Abstract	Words	8	4
				Semantic vs. Perceptual	Words	7	3
Hubl et al., 2003	Button press to happy face or face of a woman (for the real faces blocks) No task for the scrambled faces blocks	Emotional and scrambled face pictures	No between-group differences in ACC, however RT were longer in autistics	Real vs. Scrambled	Faces	12	12
Just et al., 2004	Read a passive or active sentence and respond to a probe	Sentences and probe	No between-group differences in ACC, but autistics responded faster than controls	Sentence comprehension vs. Fixation	Words	8	10
Just et al., 2007	Tower of London task : rearrange the position of 3 balls until they match a goal configuration	Initial and goal configuration	No between-group differences in RT or ACC	Tower of London (number of steps to goal) vs. Fixation	Objects	13	19
Kana et al., 2009	Theory of mind: attributing mental state to the movement of geometrical figures	Geometrical figures	No between-group differences in RT or ACC	Theory of Mind vs. Random animations	Objects	12	5
Kennedy et al., 2006	Count the number of presented words (emotional, neutral or number words) and select response (3, 4, 5 words).	Words	No between-group differences in RT or ACC	Count number of words vs. Fixation	Objects	8	8
				Count emotional vs. neutral words	Objects	3	0
Kennedy et al., 2008	Statement: Make true/false judgments for statements about themselves (self) or a close other person (other) describing psychological personality traits (internal) or observable characteristics (external) Equation: Indicate if a math equation was true or false	Statements or math equations	No between-group differences in RT or ACC	All statements vs. Equation	Words	11	8
				Internal vs.External	Words	4	0
				External vs. Internal	Words	7	12
				Other vs. Self	Words	6	4
Kleinhans et al., 2008a	Verbal fluency: Generate as many words as possible beginning with a given letter or items in given category	Letters or categories	Autistics generated less words than control group for both conditions, but no between group differences in number of errors (word repetition, non-target item, neologism)	Generate words starting with a given letter vs. repeat "nothing"	Words	1	1
				Generate words in a given category vs. repeat "nothing"	Words	3	3
				Generate words in a category vs. starting with a given letter	Words	5	0
Kleinhans et al., 2008b	Press a button whenever identical stimuli appear in succession (1-back)	Pictures of neutral faces and houses	No between-group differences in RT or ACC	Faces vs. Houses	Faces	1	3
				Houses vs. Faces	Objects	2	2

Knaus et al., 2008	Reading: select a word that best match a three-word phrase description Letter judgment: Indicate whether letter strings were in upper or lower case	Sentences or letter strings	Autistics have better and faster responses than controls.	Reading and responding vs. Letter judgment	Words	7	8
Koshino et al., 2007	Face recognition (0-back, 1-back, 2-back): Identify a remembered target face	Grayscale pictures of faces	No between-group differences in RT or ACC	Face recognition vs. Fixation	Faces	15	9
Lee et al., 2007	Embedded Figure Task: Select one of two probe figure that contained the target shape Matching Task: Select one of two probe figure that is identical to the target shape	Pairs of complex figures and target shapes	No between-group differences in RT or ACC	Embedded Figure Task vs. Matching Task	Objects	11	3
Manjaly et al., 2007	Embedded Figure Task: Decide if a target figure matched a subpart of a complex figure Matching Task: Indicate if a highlighted part of a complex figure matched a target shape	Complex and target figure	No between-group differences in RT or ACC	Embedded Figure Task vs. Matching task	Objects	2	4
Mason et al., 2008	Read three-sentence stories and respond to a simple yes/no comprehension question based on a physical (direct consequence), intentional (character's goal) or emotional (character's emotion) inference	Sentence and question	N/A	Intentional inference vs. Fixation	Words	12	20
				Emotional inference vs. Fixation	Words	15	17
				Physical inference vs. Fixation	Words	17	26
Schmitz et al., 2006	Motor response inhibited or executed depending on GO /no Go signal	Arrow pointing left or right	No between-group differences in RT or ACC	Go vs. No Go	Objects	11	6
	Stoop: Press a button if an arrow indicating left (or right) is displayed on left (or right)	Arrow on left or right side	No between-group differences in RT or ACC	Correct stroop inhibition vs. Congruent	Objects	5	9
	Shift attention and switch response to new association patterns	Red dot and four squares	No between-group differences in RT or ACC	Switch vs. Repeat set trials	Objects	9	9
Schmitz et al., 2008	Press a button to two target letters, one of which was linked to monetary reward	Letter	No between-group differences in RT or ACC	Successful reward vs. Successful unrewarded	Objects	5	4
Silani et al., 2008	Rate (visual analogue scale) the emotional value or the ratio of black/white pixels in pleasant, unpleasant or neutral pictures	Affective pictures	No between-group differences in RT or ACC	Emotion vs. Color rating	*	24	8
				Unpleasant vs. Neutral	*	3	13
Solomon et al., 2009	Preparing to overcome prepotency (POP) task (response inhibition): Press key on same or different side as target	Squares and arrows	No differences in RT, but autistics made more errors on trials requiring response inhibition	Inhibition vs. No Inhibition	Objects	16	4
Soulières et al., 2009	Pattern matching: Select one of 8 response that best match a pattern	Target pattern or RSPM plus 8 response choices	No between-group differences in RT or ACC	Pattern matching vs. Fixation	Objects	33	23
	Raven's standard progressive matrices (RSPM): Select one of 8 response to matrices from which the final entry is missing			Raven vs. Fixation	Objects	30	18
Uddin et al., 2008	Press a button if the face presented looks like self and another button if it looks like another or scrambled face	Pictures of participant and another person	No between-group differences in RT or ACC	Own face vs. Fixation	Faces	12	18
				Other face vs. Fixation	Faces	12	6

TABLE 3. ALE maxima of regions showing within-group effects for combined «FACES, OBJECTS and WORDS» processing domains ($p_{FDR}< 0.05$, k= 250vx).

	Left					Right			
Region	BA	x	y	z	ALE (x10^{-3})	x	y	z	ALE (x10^{-3})
Non-autistic									
Occipital									
Inferior occipital gyrus	18	-18	-95	-4	39.10	14	-95	-7	30.83
Fusiform gyrus	19	-31	-87	-9	36.88	42	-74	-9	33.00
	19	-42	-81	-12	34.62				
Lingual gyrus	17	-18	-94	7	22.00				
	18	-18	-78	-10	27.02				
Temporal									
Fusiform gyrus	37	-42	-54	-19	53.51	41	-59	-13	28.54
						42	-47	-21	40.38
Middle temporal gyrus	21	-53	-35	-7	30.23	59	-37	-2	29.67
	21	-55	-32	2	21.62				
	21	-61	-47	-4	20.19				
Parietal									
Precuneus	7	-1	-59	35	30.21	32	-65	42	32.15
Superior parietal lobule	7					26	-62	50	26.13
Angular gyrus	39	-30	-58	44	26.23				
Frontal									
Precentral gyrus	6	-46	1	34	37.45	47	7	28	63.17
Middle frontal gyrus	46					42	33	12	40.01
	9	-46	15	30	31.66	42	26	21	24.04
	9	-1	57	17	29.53				
	9	-46	23	25	20.22				
Superior frontal gyrus	6	0	15	52	39.52				
	6	-5	9	57	38.34				
	8	-11	55	37	29.90				
	8	-3	29	42	28.23				
	9	-25	51	27	27.14				
Inferior frontal gyrus	47	-47	27	-4	35.11				
	45	-53	22	10	27.29				
	44	-55	14	-1	25.92	53	9	9	21.71
Insula	13	-31	23	0	24.50	31	26	-1	52.71
	13					44	14	9	24.94
Subcortical									
Cingulate gyrus	31	-1	-47	31	43.46				
Parahippocampal gyrus	37	-27	-46	-11	27.81	29	-46	-12	37.16
	27	-25	-31	-8	29.53				
Thalamus						27	-26	-3	34.68
Caudate						21	-24	18	34.23
Putamen		-23	0	3	25.61				
Autistic									
Occipital									
Fusiform gyrus	19	-48	-72	-5	24.78	38	-74	-9	46.87
	19	-40	-66	-18	48.79	29	-83	-15	23.81
	19	-20	-81	-10	24.48				
Middle occipital gyrus	18	-31	-85	-7	42.92	34	-87	10	27.23
	18	-22	-93	18	26.71	23	-98	-9	25.31
	19					32	-80	23	21.51

Cuneus	17	-12	-99	3	32.31				
Lingual gyrus	19					23	-71	-2	28.53
	18					8	-77	3	22.37
Temporal									
Fusiform gyrus	37	-44	-51	-17	34.13	31	-47	-16	51.51
	37	-33	-63	-7	29.81	46	-49	-16	36.56
	37	-33	-48	-22	26.59				
Superior temporal gyrus	39					60	-60	25	27.09
	22	-50	-55	20	23.97				
Parietal									
Precuneus	7	-26	-67	41	39.29	4	-55	37	27.34
	7					30	-65	42	27.23
Superior parietal lobule	7	-22	-64	51	15.04				
Frontal									
Inferior frontal gyrus	47	-49	22	-10	44.14				
Middle frontal gyrus	9	-48	19	26	30.82	56	23	35	32.84
	9					47	6	39	16.45
Superior frontal gyrus	6	-7	10	60	39.76				
	6	-3	15	43	19.38				
	9					3	59	18	23.42
Precentral gyrus	6					51	7	27	35.58
	6					40	11	32	26.44
Insula	13	-31	24	5	36.79	36	24	1	45.55
Subcortical									
Putamen		-25	6	4	32.22				
Globus pallidus		-25	-10	-10	29.41				
Cingulate gyrus	31					2	-51	32	27.35
	24					3	43	0	26.35
Parahippocampal gyrus	28	-25	-27	-8	25.76				
	19					27	-54	-6	23.02
	37	-27	-46	-11	21.69				
Thalamus		-12	-19	9	24.20	27	-30	0	25.57
						25	-24	-5	22.32

TABLE 4. ALE maxima of regions showing between-group differences for combined «FACES, OBJECTS and WORDS» processing domains ($p_{FDR}< 0.05$, k= 250vx).TABLE 5. Autistics show a generalized rightward shift of temporal and parietal lobe visual activity when compared to non-autistics. The differential between-group voxel counts for the left and right hemisphere lobes are shown for the combined « FACES, OBJECTS and WORDS » domains ($p_{FDR}< 0.05$).

	Left					Right			
Region	BA	x	y	z	ALE (x10^{-3})	x	y	z	ALE (x10^{-3})
Non-autistic > Autistic									
Occipital									
Fusiform gyrus	19					29	-66	-17	27.25
Inferior occipital gyrus	18	-18	-95	-4	31.23				
Temporal									
Fusiform gyrus	37	-40	-56	-19	34.50				
	37	-44	-63	-25	18.35				
Middle temporal gyrus	21	-51	-35	-7	29.58				
	21	-55	-33	2	21.12				
Frontal									
Precentral gyrus	4	-44	1	34	25.73	47	7	30	38.91
Superior frontal gyrus	6					4	13	52	35.91
	9	-25	51	27	27.14				
	8	-3	29	42	27.51				
Inferior frontal gyrus	45					44	31	12	33.29
	47	-44	29	-5	26.21				
Insula	13					31	25	-3	37.00
Subcortical									
Cerebellum						18	-74	-35	31.99
Autistic > Non-autistic									
Occipital									
Fusiform gyrus	19	-29	-86	-2	25.97	38	-74	-9	35.29
						38	-68	-12	31.87
Middle occipital gyrus	18	-22	-93	18	26.27	34	-85	10	22.62
	19					32	-82	19	19.26
	19					32	-80	23	19.14
Parietal									
Precuneus	7	-28	-67	41	32.61				
Temporal									
Fusiform gyrus	37	-38	-67	-18	43.26	32	-49	-14	30.20
	37	-33	-63	-5	27.91	36	-49	-14	37.16
	37	-34	-48	-22	24.89				
Frontal									
Inferior frontal gyrus	47	-49	22	-10	37.33				
Middle frontal gyrus	8					55	23	35	29.17

TABLE 5. Autistics show a generalized rightward shift of temporal and parietal lobe visual activity when compared to non-autistics. The differential between-group voxel counts for the left and right hemisphere lobes are shown for the combined « FACES, OBJECTS and WORDS » domains ($p_{FDR} < 0.05$).

Region	Autistics > Non-autistics		Non-autistics > Autistics	
	LEFT	RIGHT	LEFT	RIGHT
Temporal lobe	1384	2960	1216	200
Occipital lobe	968	904	384	96
Parietal lobe	96	296	552	80
Frontal lobe	872	488	2104	2704
Subcortical	448	392	264	617

TABLE 6. ALE maxima of regions showing within-group effects for the «FACES» processing domain ($p_{FDR} < 0.05$, k= 250vx).

	Left					Right			
Region	BA	x	y	z	ALE ($x10^{-3}$)	x	y	z	ALE ($x10^{-3}$)
Non-autistic									
Occipital									
Fusiform gyrus	19	-42	-81	-12	26.88	42	-74	-9	32.95
	19	-29	-86	-16	22.67	29	-64	-17	22.24
	19					31	-59	-15	20.76
Middle occipital gyrus	18	-31	-84	4	16.47				
	18	-33	-87	-7	14.62				
Lingual gyrus	18	-18	-79	-10	22.79				
	18	-12	-76	-1	13.52				
Temporal									
Fusiform gyrus	37	-42	-56	-19	38.18	42	-47	-21	30.45
						42	-59	-13	28.37
Superior temporal gyrus	22	-61	-45	30	22.40	53	-45	19	17.40
Middle temporal gyrus	21	-62	-42	-4	19.84	59	-39	-2	20.53
						57	-44	8	14.18
Parietal									
Precuneus	19					34	-65	42	18.74
Frontal									
Middle frontal gyrus	46					42	33	12	35.95
	10					40	48	10	22.27
Precentral gyrus	6	-44	-2	34	13.81	47	5	28	33.36
	4	-44	-7	42	17.49				
Inferior frontal gyrus	44	-55	14	-1	25.53	53	9	9	21.70
	45					55	30	-2	23.20
Insula	13					44	14	9	24.89
	13					33	28	5	24.36
Subcortical									
Cingulate gyrus	31	-1	-47	31	31.16				
Globus Pallidus		-18	-10	-10	24.02				
Autistic									
Occipital									
Fusiform gyrus	19	-31	-85	-9	25.30	40	-74	-9	32.96
	19	-36	-61	-9	25.12	29	-83	-15	23.02
	19	-38	-62	-16	23.30				
	19	-42	-79	-14	19.35				
Lingual gyrus	18	-25	-74	-6	14.38	23	-71	-2	28.33
	17					8	-77	3	18.32
Middle occipital gyrus	19	-51	-76	-3	19.38				
Temporal									
Fusiform gyrus	37	-44	-51	-17	29.61	36	-49	-14	47.93
		-34	-48	-22	24.63				
Superior temporal gyrus	39					62	-60	23	21.50
	22	-48	-54	20	20.01	59	-39	-2	21.21
Middle temporal gyrus	21	-36	0	-42	21.04				
	38					35	2	-26	22.85
Parietal									
Precuneus	19	-28	-67	43	22.15				
Frontal									

Precentral gyrus	6					42	10	34	17.78
Insula	13					36	24	1	20.12
Subcortical									
Cerebellum		-5	-67	2	15.25	3	-67	-3	13.23
Cingulate gyrus	31	2	-51	32	22.74	12	-51	32	12.66
	31	-9	-49	30	12.77				
Globus Pallidus		-25	-10	-10	16.25				

TABLE 7. ALE maxima of regions showing between-group differences for the «FACES» processing domain (p_{FDR}< 0.05, k= 250vx).

	Left					Right			
Region	BA	x	y	z	ALE (x10^{-3})	x	y	z	ALE (x10^{-3})
Non-autistic > Autistic									
Occipital									
Fusiform gyrus	19					38	-69	-3	13.75
	19					34	-69	-5	13.50
	19					29	-64	-17	21.13
Temporal									
Fusiform gyrus	37	-40	-54	-19	25.06				
	37	-42	-63	-25	19.96				
	37	-42	-55	-7	13.25				
Superior temporal gyrus	39	-61	-45	30	22.40				
Middle temporal gyrus	21	-62	-42	-4	19.85				
Frontal									
Middle frontal gyrus	46					42	33	9	29.05
	10					40	48	10	22.22
	9					51	13	29	13.10
Inferior frontal gyrus	44	-55	14	-1	25.50	53	9	9	21.63
Precentral gyrus	6	-44	-2	34	13.80	47	5	28	24.78
	4	-44	-7	42	17.45				
Insula	13					44	14	9	24.70
	13					31	28	5	20.41
Autistic > Non-autistic									
Occipital									
Lingual gyrus	19					23	-71	-2	27.89
Fusiform gyrus	19	-33	-61	-7	22.15				
		-36	-66	-15	13.21				
Temporal									
Fusiform gyrus	37	-34	-47	-23	23.30	33	-46	-14	41.65
Middle temporal gyrus	21	--36	0	-42	21.04				
Superior temporal gyrus	39					62	-60	22	21.41

TABLE 8. Autistics exhibited relatively stronger engagement of the right fusiform gyrus for face processing. The differential between-group voxel counts for the « FACES », « OBJECTS » and « WORDS » processing domains are shown for the left and right hemispheres ($p_{FDR} < 0.05$).

Domain	**Autistics > Non-autistics**		**Non-autistics > autistics**	
	LEFT FG	**RIGHT FG**	**LEFT FG**	**RIGHT FG**
Faces	1440	2688	592	168
Objects	1136	1616	1232	952
Words	624	520	496	8

TABLE 9 ALE maxima of regions showing within-group effects for the «OBJECTS» processing domain ($p_{FDR}< 0.05$, k= 250vx).

	Left					Right			
Region	BA	x	y	z	ALE (x10^{-3})	x	y	z	ALE (x10^{-3})
Non-autistic									
Occipital									
Inferior occipital gyrus	18	-16	-93	-2	27.07				
Cuneus	17	-18	-94	9	21.79				
Middle occipital gyrus	18	-29	-92	3	13.08				
Fusiform gyrus	19	-27	-68	-13	20.46				
	19	-29	-87	-9	12.49				
Parietal									
Precuneus	7	-18	-66	52	24.86	28	-63	39	26.33
	7	-24	-61	44	15.97				
	7	-13	-72	57	13.05				
Precuneus	31	-26	-75	30	22.48				
Superior parietal lobule	7					26	-62	50	26.09
Inferior parietal lobule	40	-35	-41	47	21.36				
	40	-50	-48	44	14.12				
	40	-44	-54	46	13.67				
Frontal									
Precentral gyrus	6					47	7	30	30.85
						60	9	23	14.31
Superior frontal gyrus	6	2	13	52	30.01	4	19	45	13.63
	6	-24	-2	54	26.45	28	0	53	21.70
Middle frontal gyrus	9					42	23	24	19.53
Insula	13	-31	25	0	20.93	31	25	-3	36.33
Subcortical									
Parahippocampal gyrus	36	-27	-46	-11	26.33	29	-44	-12	35.78
Putamen		-25	-1	-2	17.34				
Brainstem						3	-36	-41	23.45
Autistic									
Occipital									
Fusiform gyrus	19	-36	-81	-9	19.43	36	-76	-9	21.79
Middle occipital gyrus	19					32	-84	17	18.92
	19					38	-81	9	13.38
	18	-22	-93	16	24.11	32	-87	10	16.55
	18	-27	-88	-2	15.57	34	-88	1	15.91
	18	-27	-90	2	15.55				
	18	-31	-87	11	13.23				
Inferior occipital gyrus	18					38	-84	-4	15.21
	18					24	-93	-3	14.87
Cuneus	17					25	-97	0	14.31
Lingual gyrus	17	-11	-97	1	20.34				
Parietal									
Superior parietal lobule	7	-22	-64	51	14.52	32	-51	49	23.13
Inferior parietal lobule	40	-44	-26	-48	18.64	36	-39	43	19.40
	40					36	-33	56	13.64
	40					56	-26	46	14.65
Precuneus	7	-24	-63	42	15.51	23	-59	55	22.32
	7	-15	-66	51	13.99				
	31					30	-75	25	12.65

Frontal									
Precentral gyrus	6	-48	9	31	13.64	53	7	30	25.69
	6	-46	3	34	14.25				
	6	-55	2	31	13.00				
Middle frontal gyrus	6	-24	-2	54	19.13				
Insula	13	-31	23	3	22.89	38	24	1	16.74
Subcortical									
Cingulate gyrus	24	-3	-6	30	23.85				
	24	-3	5	31	13.34				
	32					8	25	40	15.49
Parahippocampal gyrus	36	-27	-46	-11	20.42				
Thalamus		-14	-19	9	19.83				

TABLE 10. ALE maxima of regions showing between-group differences for the «OBJECTS» processing domain ($p_{FDR} < 0.05$, k= 250vx).

	Left					Right			
Region	BA	x	y	z	ALE ($x10^{-3}$)	x	y	z	ALE ($x10^{-3}$)
Non-autistic > Autistic									
Occipital									
Lingual gyrus	18	-18	-93	-4	25.07				
	18	-18	-94	7	17.91				
Temporal									
Fusiform gyrus	37					29	-44	-10	24.82
Parietal									
Precuneus	7					28	-61	39	26.12
Superior parietal lobule	7					28	-62	48	20.65
Inferior parietal lobule	40	-35	-41	47	20.89				
	40	-50	-48	-43	14.10				
	40	-43	-54	46	13.67				
Frontal									
Superior frontal gyrus	6	2	13	52	30.02				
Insula	13					31	25	-3	33.33
Subcortical									
Putamen		-25	0	0	16.75				
Autistic > Non-autistic									
Occipital									
Middle occipital gyrus	19	-24	-91	16	22.78				
Fusiform gyrus	19	-36	-79	-10	19.16	36	-76	-9	21.24
Parietal									
Superior parietal lobule	7					32	-51	49	22.99
Inferior parietal lobule	40					34	-39	43	17.32
	40					36	-32	47	14.72
Subcortical									
Cingulate gyrus	24	-3	-6	30	23.39				

TABLE 11. ALE maxima of regions showing within-group effects for the «WORDS» processing domain ($p_{FDR}< 0.05$, k= 250vx).

	Left					Right			
Region	BA	x	y	z	ALE ($x10^{-3}$)	x	y	z	ALE ($x10^{-3}$)
Non-autistic									
Occipital									
Inferior occipital gyrus	17	-18	-97	-4	20.85	14	-96	-7	30.74
Lingual gyrus	18	-10	-96	-11	19.55				
Temporal									
Middle temporal gyrus	21	-51	-35	-5	24.30				
	21	-55	-33	2	21.16				
	39					56	-66	26	17.94
Parietal									
Precuneus	7	2	-59	37	18.08				
Frontal									
Superior frontal gyrus	8	-18	28	47	25.57				
	8	-12	55	37	21.17				
	8	-7	47	45	16.68				
	8	-13	33	53	13.59				
	9	-1	60	19	20.53				
	8	-1	34	44	18.88				
	6	-5	9	57	26.20				
Inferior frontal gyrus	45	-49	24	12	20.48				
	47	-47	27	-6	23.50				
	47	-40	29	-5	19.21				
	47	-32	33	-12	13.18				
Middle frontal gyrus	46	-46	21	23	13.18				
	6	-44	8	49	13.95				
Precentral gyrus	4	-55	-3	46	24.87				
	6	-50	6	45	14.62				
	6	-44	0	50	13.59				
Subcortical									
Parahippocampal gyrus	27	-25	-31	-8	29.49				
	36	-21	-42	-9	13.71				
Caudate						21	-24	18	33.27
Thalamus		-18	-47	5	21.50	27	-27	7	31.97
Cingulate	29	-5	-51	10	17.58				
	30	-3	-62	8	13.10				
Autistic									
Occipital									
Fusiform gyrus	19	-40	-69	-17	37.16	38	-68	-12	25.65
Inferior occipital gyrus	17					23	-98	-9	23.84
Lingual gyrus	18	-14	-87	-7	16.75				
Temporal									
Middle temporal gyrus	21	-57	-42	-2	17.79				
	21	-61	-47	8	13.87				
Fusiform gyrus	37					46	-49	-14	23.50
Parietal									
Precuneus	7	-5	-59	37	13.96	4	-57	37	20.54
	7	-9	-54	41	13.62	30	-65	42	22.02
Frontal									

Inferior frontal gyrus	47	-49	22	-10	42.79				
	45	-49	24	5	13.28				
Superior frontal gyrus	6	-7	10	60	36.64				
	8	-9	50	38	20.25	12	45	49	17.32
	9	1	58	26	18.25				
Middle frontal gyrus	46	-44	21	21	26.65				
	9					56	23	35	20.67
	8					28	28	44	19.59
Subcortical									
Putamen		-25	6	4	32.21				
		-25	-8	-8	13.34				
Thalamus		-5	-12	12	15.07	27	-30	0	25.37
		-7	-16	13	14.99				
Parahippocampal gyrus	35	-25	-27	-10	24.76	12	-51	5	13.20
Insula	13	-31	24	5	13.82				
	13	-40	23	3	13.81				
	13	-31	27	0	13.05				
Amygdala		-23	-10	-12	14.30				
		-29	-8	-14	13.41				
Cingulate	30					4	-53	7	15.25

TABLE 12. ALE maxima of regions showing between-group differences for the «WORDS» processing domain ($p_{FDR} < 0.05$, k= 250vx).

	Left					Right			
Region	BA	x	y	z	ALE ($\text{x}10^{-3}$)	x	y	z	ALE ($\text{x}10^{-3}$)
Non-autistic > Autistic									
Occipital									
Inferior occipital gyrus	17	-18	-97	-4	20.28				
Lingual gyrus	18	-10	-96	-11	19.32				
Temporal									
Middle temporal gyrus	21	-51	-36	-7	23.83				
	21	-55	-33	2	20.66				
	39					56	-66	26	17.94
Frontal									
Precentral gyrus	4	-55	-3	46	24.85				
Superior frontal gyrus	8	-18	26	47	22.24				
	8	-1	34	44	18.88				
Inferior frontal gyrus	47	-40	31	-5	18.21				
Subcortical									
Caudate						21	-24	18	24.97
Thalamus		-27	-33	-5	19.14				
Parahippocampal gyrus	36	-21	-42	-9	13.67				
	36	-18	-36	-14	13.61				
Autistic > Non-autistic									
Occipital									
Fusiform	19	-40	-69	-17	36.82				
Temporal									
Middle temporal gyrus	21	-59	-44	-2	17.03				
Fusiform gyrus	37					46	-49	-14	23.50
Parietal									
Precuneus	7					30	-65	42	22.02
Frontal									
Inferior frontal gyrus	44	-49	22	-10	36.82				
Superior frontal gyrus	6	-7	81	55	23.15				
Middle frontal gyrus	46	-42	29	18	13.09				
	8					56	23	35	20.66
	9	-51	17	26	19.91				
	9	-42	21	21	17.23				
Subcortical									
Putamen		-25	6	4	30.20				

FIGURE 1. Within- and between-group distribution of task-related activity in inferior occipital and inferotemporal cortex. (A) Regions showing increases in autistics (RED), non-autistics (GREEN), and their overlap (YELLOW) for «FACES, OBJECTS and WORDS» tasks combined. (B) Regions showing more task-related activity in autistics (RED-YELLOW) and less task-related activity in autistics (BLUE-GREEN) for the combined «FACES, OBJECTS and WORDS» tasks. (C) Regions showing increases in autistics (RED), non-autistics (GREEN), and their overlap (YELLOW) for the «FACES» tasks. (D) Regions showing more task-related activity in autistics (RED-YELLOW) and less task-related activity in autistics (BLUE-GREEN) for the «FACES» tasks. ALE maps ($p_{FDR} < 0.05$) are superimposed on axial slices from a gray matter template in MNI space. Anatomical left is image left.

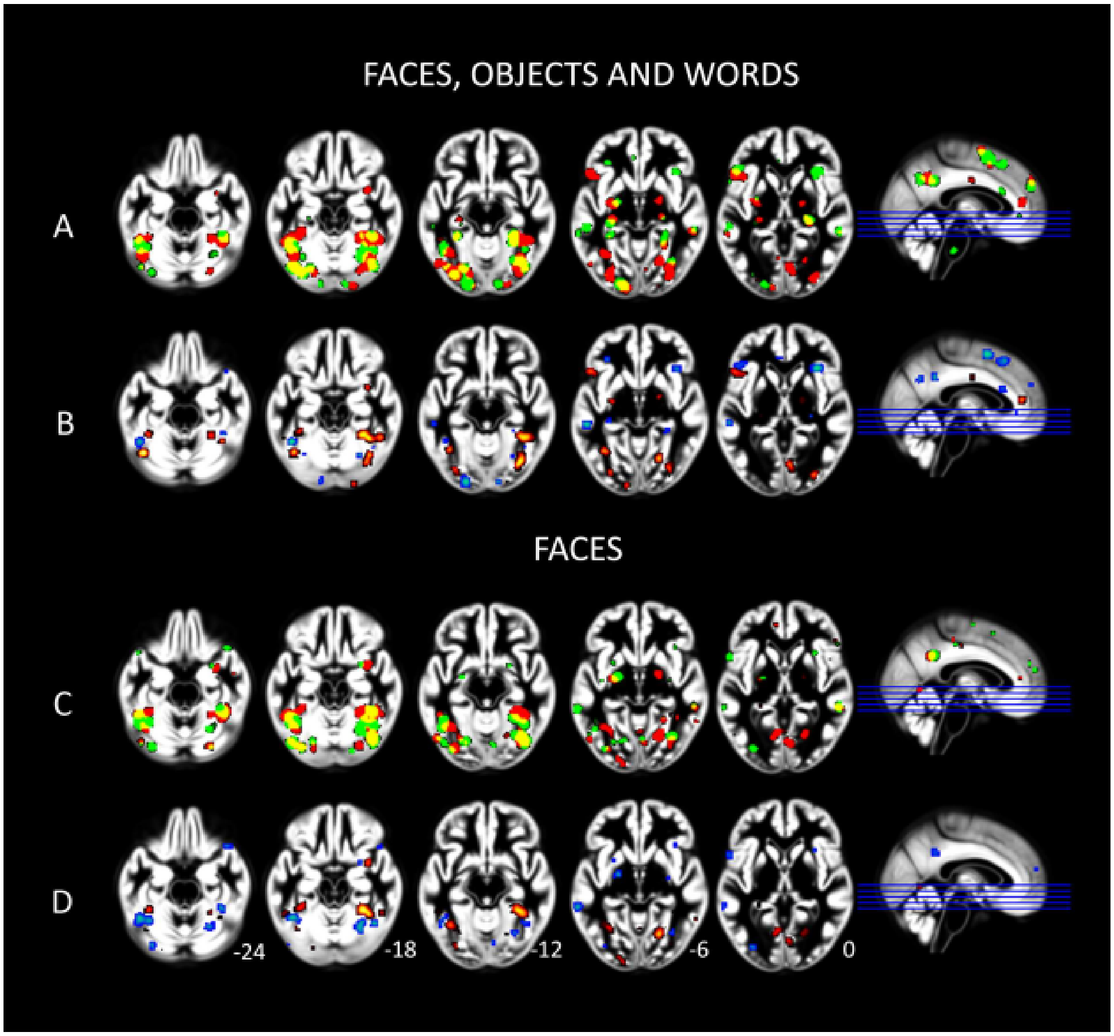


FIGURE 2. Within- and between-group distribution of task-related activity in inferior occipital and inferotemporal cortex. (A) Regions showing increases in autistics (RED), non-autistics (GREEN), and their overlap (YELLOW) for the «OBJECTS» tasks. (B) Regions showing more task-related activity in autistics (RED-YELLOW) and less task-related activity in autistics (BLUE-GREEN) for the «OBJECTS» tasks. (C) Regions showing increases in autistics (RED), non-autistics (GREEN), and their spatial overlap (YELLOW) for the «WORDS» tasks. (D) Regions showing more task-related activity in autistics (RED-YELLOW) and less task-related activity in autistics (BLUE-GREEN) for the «WORDS» tasks. ALE maps ($p_{FDR} < 0.05$) are superimposed on axial slices from a gray matter template in MNI space. Anatomical left is image left.

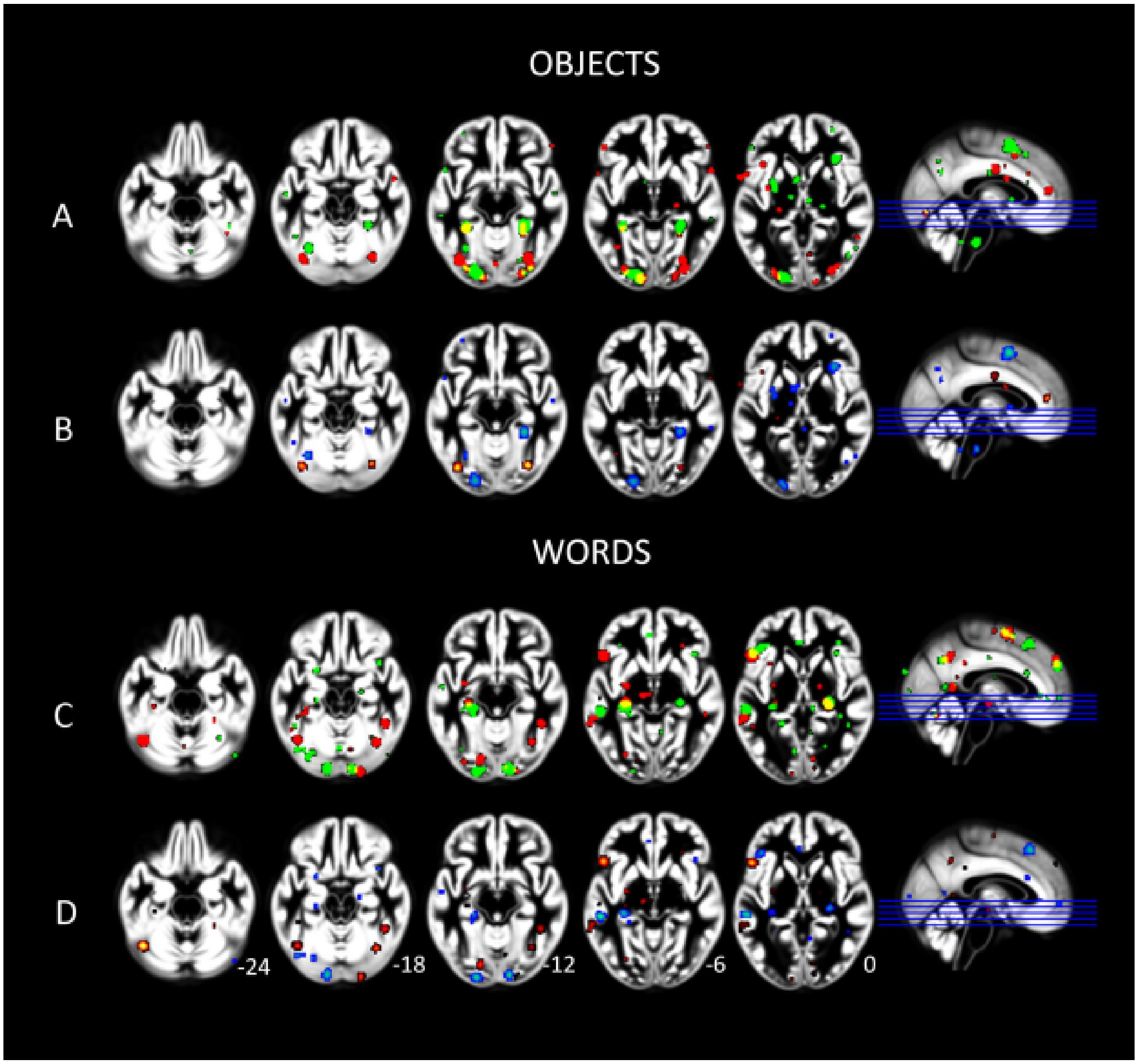


FIGURE 3. Spatial distribution of regions showing more task-related activity in autistics than non-autistics for the 3 processing domains: «FACES» in RED, «OBJECTS» in GREEN, and «WORDS» in BLUE. ALE maps ($p_{FDR} < 0.05$) are superimposed on slices from a gray matter template in MNI space. LEFT –a right hemisphere sagittal slice at x = +3; RIGHT –. an axial slice at z = -18.

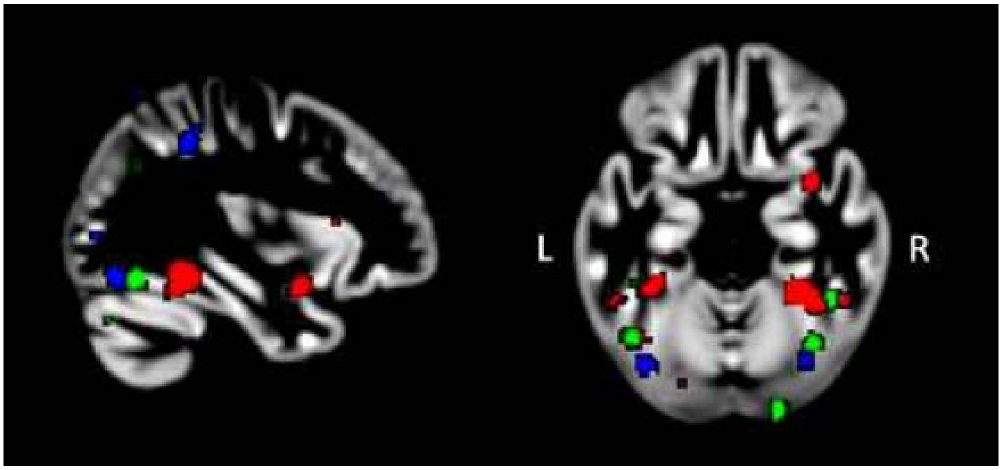


FIGURE 4. In both hemispheres, autistics exhibit more activity in temporal and occipital cortex. Between-group differences in task-related effects related to the combined «FACES, OBJECTS and WORDS» processing domains are shown with individual bars representing the number of voxels showing higher ALE values (BLACK) and lower ALE values (WHITE) in autistics vs. non-autistics ($p_{FDR} < 0.05$). Voxel counts are presented separately for the left and right temporal, occipital, parietal and frontal lobes.

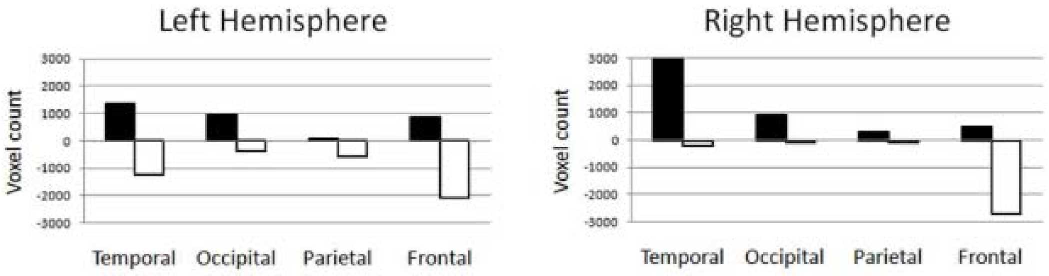
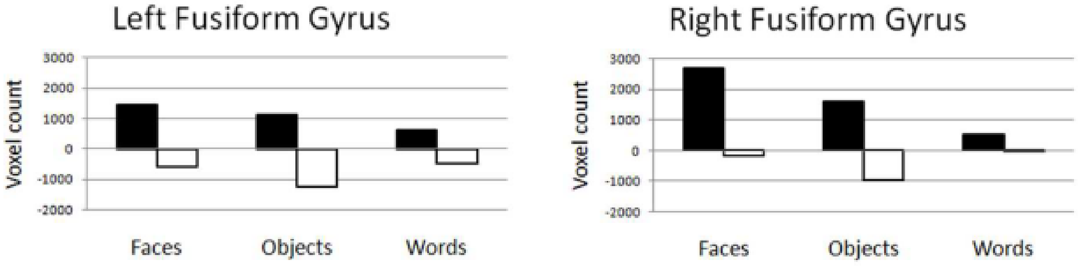


FIGURE 5. In the fusiform gyrus, higher ALE values are observed in the autistics for all processing domains. Between-group differences in effects related to the «FACES», «OBJECTS» and «WORDS» processing domains are shown with bars representing the number of voxels showing higher ALE values (BLACK) and lower ALE values (WHITE) in autistics vs. non-autistics ($p_{FDR} < 0.05$). The voxel counts are presented separately for the left and right hemispheres.



Annexe II. Atypical processing of temporal complexity in Asperger syndrome

Sixteen Asperger (ASP) participants were added to the 13 typically developing (TYP) and 15 autistic (AUT) participants. Age, IQ and manual preference scores for each group were compared using ANOVA and were not different (Table 1). All participants had normal hearing as measured by pure tone audiometry and no formal musical training. The stimuli, task and analysis were the same as those previously described (Chapitre 4).

In terms of behavioural results, we observed no group differences in performance on the sound modulation detection task across the three groups. In terms of imaging results, both within- and between-group effects are reported. First, in each group, contrasts across various condition combinations were used to investigate the effects of spectral and temporal complexity. As for the TYP and AUT group, the ASP group showed spectral and temporal auditory complexity effects in primary and non-primary auditory areas (Figure 1). The additional findings demonstrate the hierarchical architecture of auditory processing in all three participant groups and suggest that autistics and individuals with Asperger syndrome do not differ strongly from typically developing controls with respect to this organization.

To examine differences among groups, linear contrasts were used to identify the regions where the task-related activity varied linearly across the AUT, ASP and TYP groups. The linear comparisons of spectral complexity among groups revealed no suprathreshold voxels for the TYP>ASP>AUT and AUT>ASP>TYP weightings, suggesting that spectral complexity processing did not differ among the groups. Then, linear contrasts (TYP>ASP>AUT and AUT>ASP>TYP) were computed to look at group differences in increasing temporal complexity effects. Theses analyses revealed that the TYP group had the greatest sensitivity to increasing temporal complexity in auditory areas. More specifically, the linear contrast TYP>ASP>AUT showed two peak effects on the STG bilaterally; one in the postero-medial part of HG and another in the STG, lateral and anterior to HG. In sum, while no significant between group difference were observed for processing spectral complexity, increasing temporal complexity showed stronger modulation of non-primary auditory fields in the TYP compared to the AUT and the ASP groups (Figure 2).

To identify linearly varying group differences (TYP>ASP>AUT and AUT>ASP>TYP) in activity associated with spectral and temporal complexity, we extracted the mean signal changes within selected regions of interest. Linear mixed effect models investigating Group x ROI x Task effects were computed with the subject factor treated as a random effect. First, for spectral complexity, a significant Group X ROI X Task interaction was observed, $t(1359) =-2.34, p =.0195$). This interaction corresponded to regionally specific differences in the task variation among the groups (TYP, ASP, AUT). The bar plots in Figure 3 show that activity in PAC in greater in the AUT group. Second, for temporal complexity, a significant Group X ROI X Task interaction was revealed, $t(1359) =-12.18, p <.001$. This interaction indicates significant differences in slopes linearly among the ordered group (TYP, ASP, AUT) among ROIs. The bar plots in Figure 4 show that activity in PAC in greater in the AUT group (AUT>ASP>TYP). This Group by Temporal effect in PAC was confirmed by examining the simple effect, $t(658) =-1.97, p =.0489$. In sum, increases in auditory complexity were associated with greater signal change in primary auditory cortex in the AUT compared to the ASP and TYP groups (Figure 3).

Table 1. Groups were matched on sex, age, Weschler IQ, Raven Progressive Matrices percentile scores and manual preference, which is reported as the Edinburgh score with -100 corresponding to completely left-handed and +100 to completely right-handed. ADI is the Autism Diagnostic Interview. Group differences were assessed using one-way ANOVA (*F,* df=2).

	TYP	AUT	ASP	*p*
Sample size (sex)	13 (2 F, 11 M)	15 (2 F, 13 M)	16 (3 F, 13M)	
Age (y:m)				
Mean (SD)	23:6 (7:5)	24:4 (6:3)	21:4 (6:3)	0.43
Range	16 - 39	14 – 35	14 - 32	
Full-scale IQ				
Mean (SD)	109.6 (10.8)	100.3 (13.9)	105.2 (13.5)	0.19
Range	92 - 131	78 – 126	82 - 129	
Performance IQ				
Mean (SD)	106.3 (13.0)	100.3 (11.8)	101.4 (13.0)	0.44
Range	87 - 133	86 – 117	87 - 128	
Verbal IQ				
Mean (SD)	111.1 (10.7)	100.4 (16.4)	108.4 (14.1)	0.13
Range	93 - 127	72 - 121	81 - 134	
Raven				
Mean (SD)	72.3 (23.2)	70.4 (31.5)	80.4 (14.0)	0.47
Range	19 - 98	6 - 100	46 - 98	
Handedness				
Mean (SD)	+61.2 (41.1)	+71.9 (49.0)	+64.2 (53.9)	0.77
Range	-45 - +100	-100 - +100	-80 - +100	
ADI Score Mean (cut-off)				
Social		24.1(10)	18.4(10)	
Communication		18.2(8)	13.7(8)	
Behavior		7.0(3)	5.9(3)	

Figure 1. (A) BOLD-contrast activity maps associated with spectral complexity effects in ASP group & (B) BOLD activity increases (red) and decreases (blue) associated with increasing temporal complexity effects in ASP group. *T*-statistical maps, using an uncorrected critical threshold of $p < .001$, are superimposed on the SPM5 T1 template. Axial images are shown in the neurological convention with MNI z-coordinate labels.

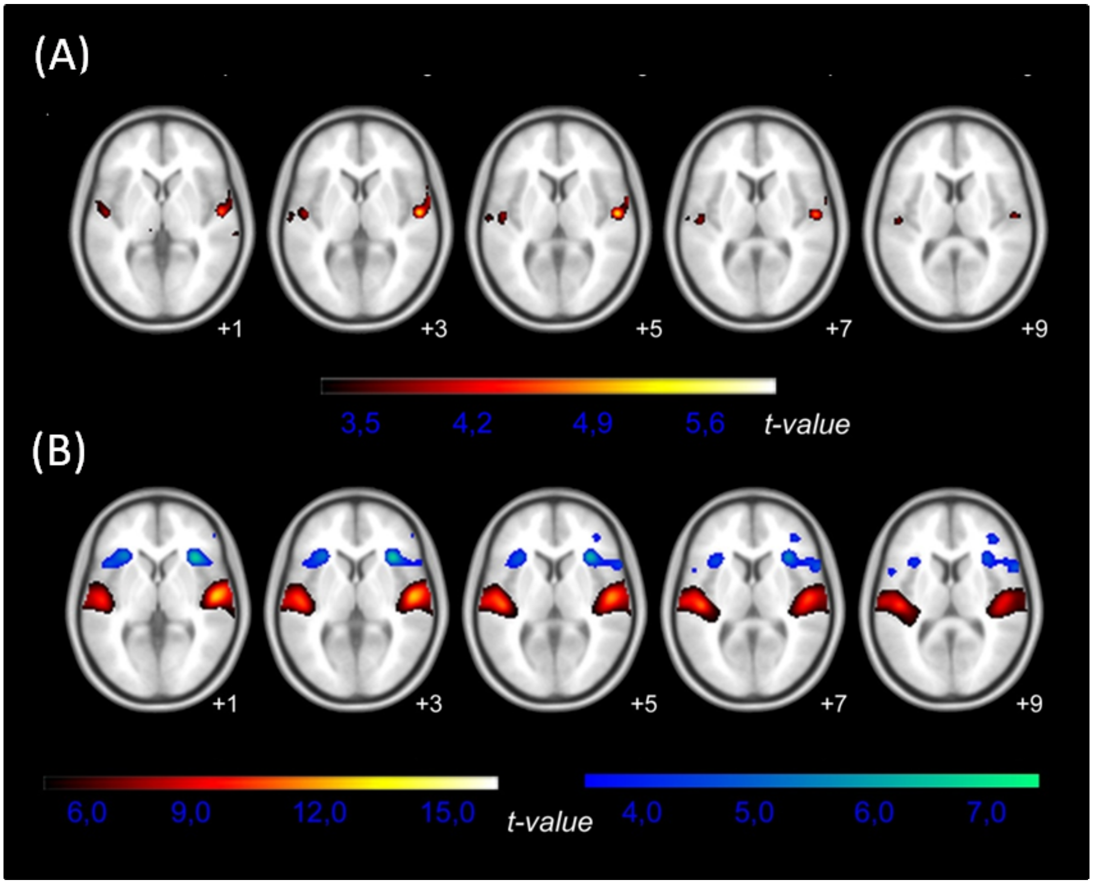


Figure 2. BOLD-contrast activity maps associated with between-group differences (TYP>ASP>AUT) in temporal complexity. *T*-statistical map, using an uncorrected critical threshold of p <.001, is superimposed on the SPM5 T1 template. Axial images are shown using the neurological convention with MNI z-coordinate labels.

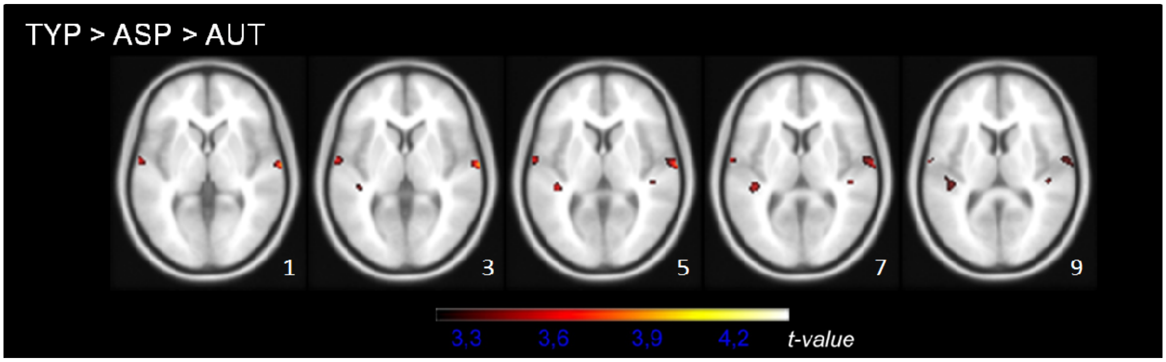
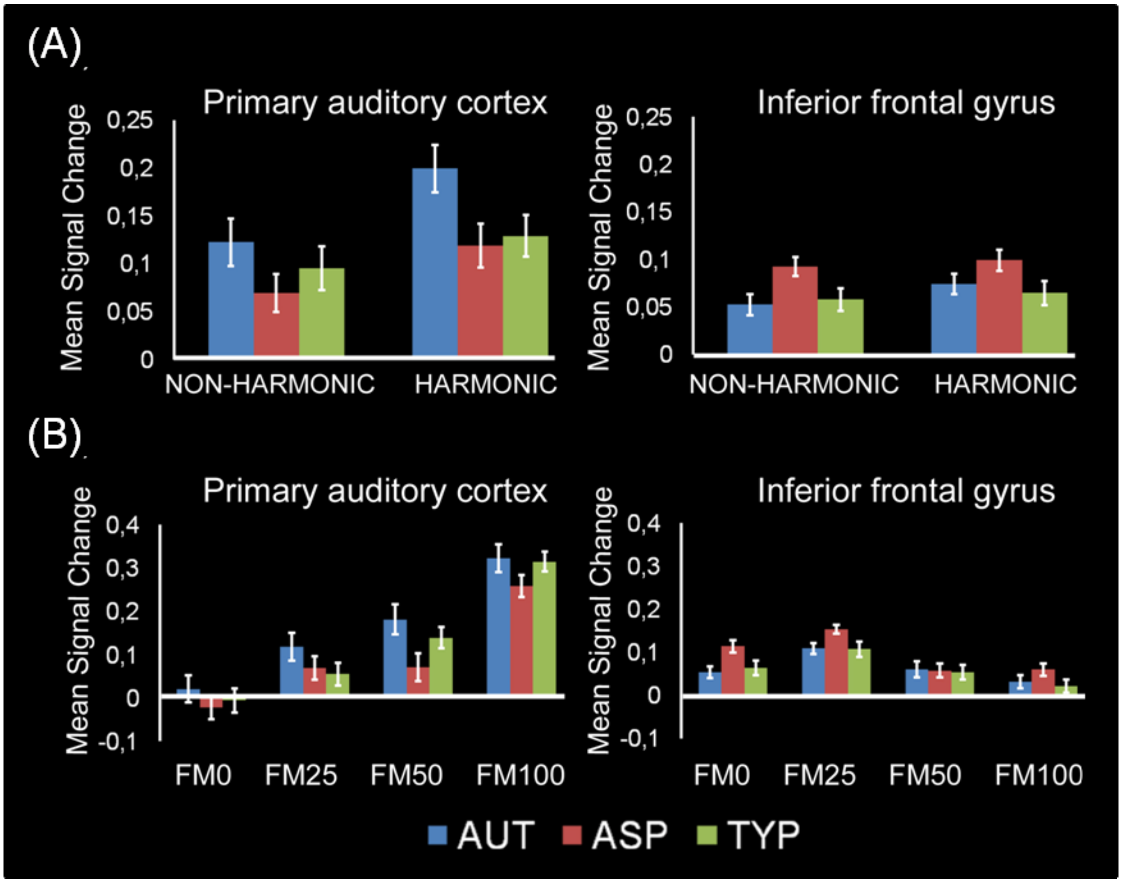


Figure 3. (A) Mean signal change in primary auditory cortex (left) and the inferior frontal gyrus (right) for non-harmonic and harmonic conditions (B) Mean signal change in primary auditory cortex (left) and inferior frontal gyrus (right) for FM0, FM25, FM50 and FM200 conditions. Error bars represent standard errors.



Annexe III. Curriculum vitae abrégé

Cheminement académique

2011 -	Stage postdoctoral, Queen’s University, Kingston, Ontario
2006 - 2011	Ph.D. Sciences biomédicales, Université de Montréal
2005 - 2006	M.Sc. Sciences biomédicales, Université de Montréal, passage direct Ph.D.
2002 - 2004	B.Sc. Sciences biomédicales, Université de Montréal

Expériences professionnelles et de recherche

2009 - 2010	Assistante de recherche, Laboratoire de recherche des troubles neurodéveloppementaux, Hôpital Rivière-des-Prairies
2007 - 2008	Supervision d’un assistant de recherche, Laboratoire de recherche des troubles neurodéveloppementaux, Hôpital Rivière-des-Prairies
2004	Assistante de cours pour séances de laboratoire, Cours de biopathologie générale (niveau baccalauréat), Université de Montréal
2004	Stage de recherche, INSERM U594, Université Joseph-Fourier (France)

Activités parascolaires

2010	Membre du comité organisateur pour la Journée Annuelle de la Recherche du Centre de Recherche Fernand Seguin
2009	Organisation du relais scientifique des étudiants en recherche de l’Hôpital Rivière-des-Prairies
2008 - 2010	Présidente de l’association étudiante de l’Hôpital Rivière-des-Prairies
2008	Organisation du relais scientifique des étudiants en recherche de l’Hôpital Rivière-des-Prairies
2007 - 2010	Représentante des étudiants du laboratoire de recherche des troubles neurodéveloppementaux, Hôpital Rivière-des-Prairies, association étudiante du Centre de Recherche Fernand-Seguin

Publications

Samson, F., Mottron, L., Soulières, I. & Zeffiro, T.A. (2011) Enhanced visual functioniong in autism: an ALE meta-analysis, *Human Brain Mapping*, Epub 4 avril

Samson, F., Zeffiro, T.A., Toussaint, A. & Belin, P. (2011) Stimulus complexity and categorical effects in human auditory cortex: an Activation Likelihood Estimation meta-analysis, *Frontiers in Auditory Cognitive Neuroscience*, 1, 241

Samson, F., Hyde, K.L., Bertone, A., Soulières, I., Mendrek, A., Ahad, P., Mottron, L. & Zeffiro, T.A. (2011) Atypical processing of auditory temporal complexity in autistics, *Neuropsychologia*, 49, 546-555

Hyde, K.L., Samson, F., Evans, A.C. & Mottron, L. (2010) Neuroanatomical differences in young adults with high-functioning autism, *Human Brain Mapping*, 31(4), 556-566

Soulières, I., Dawson, M., Samson, F., Barbeau, E.B., Sahyoun, C., Strangman, G., Zeffiro, T.A. & Mottron, L. (2009) Enhanced perception contributes to fluid reasoning in autism, *Human Brain Mapping*, 30(12), 4082-4107

Samson, F., Mottron, L., Jemel, B., Belin, P. & Ciocca, V. (2006) Can spectro-temporal complexity explains the autistic pattern of performance on auditory tasks? *Journal of Autism & Developmental Disorders*, 36(1), 65-76

Communications (sélection)

Samson, F., Zeffiro, T.A., Soulières, I. & Mottron, L. (2010) Meta-Analysis of Functional Neuroimaging Studies Reveals Enhanced Engagement of Visual System in Autism, International meeting for autism research, Philadelphie (PA)

Samson, F., Zeffiro, T.A., Mendrek, A., Hyde, K.L. & Mottron, L. (2009) Auditory Processing Differences in Autism Spectrum Individuals with and without Language Delay: an fMRI Study. International Meeting for Autism Research, Chicago (IL)

Samson, F., Belin, P., Toussaint, A., Mottron, L. & Zeffiro, T.A. (2008) Regional specialization for processing auditory complexity: ALE meta-analysis and fMRI validation, Organization for Human Brain Mapping, Melbourne, Australie

Samson, F., Zeffiro, T.A., Soulières, I., Ahad, P., Mendrek, A. & Mottron, L. (2008) Spectral and Temporal Auditory Processing in Autism: an fMRI Study, International meeting for autism research, Londres, Angleterre

Bourses au mérite

2011 - 2013	Bourse postdoctorale du FRSQ
2011	Bourse de mention d'honneur au doctorat, CRFS
2009	Bourse d'excellence, Université de Montréal
2008	Bourse d'excellence, Université de Montréal
2007 - 2010	Bourse de doctorat du CRSNG
2007	Bourse de doctorat du FRSQ (refus de l'octroi)
2006	Bourse d'excellence, Université de Montréal
2006 - 2008	Bourse passage direct au doctorat, Université de Montréal
2005	Bourse de maîtrise du «Autism Research Training» Program (IRSC)
2004	Bourse pour stage international, Université de Montréal