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Évaluation électrophysiologique auditive et examen du langage et de l'attention chez l'enfant né prématurément et l'enfant né à terme.

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Résumé

L'objectif de cette thèse est l'étude du développement de l'attention auditive et des capacités de discrimination langagière chez l'enfant né prématurément ou à terme. Les derniers mois de grossesse sont particulièrement importants pour le développement cérébral de l'enfant et les conséquences d'une naissance prématurée sur le développement peuvent être considérables. Les enfants nés prématurément sont plus à risque de développer une variété de troubles neurodéveloppementaux que les enfants nés à terme. Même en l'absence de dommages cérébraux visibles, de nombreux enfants nés avant terme sont à risque de présenter des troubles tels que des retards langagiers ou des difficultés attentionnelles. Dans cette thèse, nous proposons donc une méthode d'investigation des processus préattentionnels auditifs et de discrimination langagière, à l'aide de l'électrophysiologie à haute densité et des potentiels évoqués auditifs (PEAs).

Deux études ont été réalisées. La première visait à mettre sur pied un protocole d'évaluation de l'attention auditive et de la discrimination langagière chez l'enfant en santé, couvrant différents stades de développement (3 à 7 ans, 8 à 13 ans, adultes ; N = 40). Pour ce faire, nous avons analysé la composante de *Mismatch Negativity* (MMN) évoquée par la présentation de sons verbaux (syllabes /Ba/ et /Da/) et non verbaux (tons synthétisés, Ba : 1578 Hz/2800 Hz ; Da : 1788 Hz/2932 Hz). Les résultats ont révélé des patrons d'activation distincts en fonction de l'âge et du type de stimulus présenté. Chez tous les groupes d'âge, la présentation des stimuli non verbaux a évoqué une MMN de plus grande amplitude et de latence plus rapide que la présentation des stimuli verbaux. De plus, en réponse aux stimuli verbaux, les deux groupes d'enfants (3 à 7 ans, 8 à 13 ans) ont démontré une MMN de latence plus tardive que celle mesurée dans le groupe d'adultes. En revanche, en réponse aux stimuli non verbaux, seulement le groupe d'enfants de 3 à 7 ans a démontré une MMN de latence plus tardive que le groupe d'adulte. Les processus de discrimination verbaux semblent donc se développer plus tardivement dans l'enfance que les processus de discrimination non verbaux.

Dans la deuxième étude, nous visions à d'identifier les marqueurs prédictifs de déficits attentionnels et langagiers pouvant découler d'une naissance prématurée à l'aide des PEAs et de la MMN. Nous avons utilisé le même protocole auprès de 74 enfants âgés de 3, 12 et 36 mois, nés prématurément (avant 34 semaines de gestation) ou nés à terme (au moins 37 semaines de gestation). Les résultats ont révélé que les enfants nés prématurément de tous les âges démontraient un délai significatif dans la latence de la réponse MMN et de la P150 par rapport aux enfants nés à terme lors de la présentation des sons verbaux. De plus, les latences plus tardives de la MMN et de la P150 étaient également corrélées à des performances langagières plus faibles lors d'une évaluation neurodéveloppementale. Toutefois, aucune différence n'a été observée entre les enfants nés à terme ou prématurément lors de la discrimination des stimuli non verbaux, suggérant des capacités préattentionnelles auditives préservées chez les enfants prématurés.

Dans l'ensemble, les résultats de cette thèse indiquent que les processus préattentionnels auditifs se développent plus tôt dans l'enfance que ceux associés à la discrimination langagière. Les réseaux neuronaux impliqués dans la discrimination verbale sont encore immatures à la fin de l'enfance. De plus, ceux-ci semblent être particulièrement vulnérables aux impacts physiologiques liés à la prématurité. L'utilisation des PEAs et de la MMN en réponse aux stimuli verbaux en bas âge peut fournir des marqueurs prédictifs des difficultés langagières fréquemment observées chez l'enfant prématuré.

Mots-clés : Prématurité, Enfance, Électroencéphalographie (EEG), Mismatch Negativity (MMN), Potentiels évoqués auditifs (PEA), Développement du langage, Neurodeveloppement

Abstract

The aim of this thesis is to investigate early auditory attention and language development in full-term and preterm children. The last months of pregnancy are particularly important for the child's cerebral development, and the impacts of a premature birth on his/her neurodevelopment can be substantial. Prematurely born children are at higher risk of developing a variety of neurodevelopmental disorders compared to full-terms. Even without visible brain injury, many premature children are at risk of presenting disorders such as language delays and attentional difficulties. In this thesis, we suggest an approach to investigate pre-attentional processes and early language discrimination abilities in infants using high-density electrophysiology and auditory event-related potentials (AERPs).

We conducted two studies. The first one aimed at establishing a paradigm to evaluate auditory attention and language discrimination development in healthy full-term children, over different developmental stages (3 to 7 years, 8 to 13 years, adults; N = 40). To do so, we analyzed the *Mismatch Negativity* (MMN) component in response to speech (spoken syllables /Ba/ and /Da/) and non-speech stimuli (frequency-synthesized tones, Ba: 1578 Hz/2800 Hz; Da: 1788 Hz/2932 Hz). Distinct patterns of activation were revealed according to stimulus type and age. In all groups, non-speech stimuli elicited an MMN of larger amplitude and earlier latency than did the presentation of speech stimuli. Moreover, in response to speech stimuli, both children groups (3 to 7 years, 8 to 13 years) showed a significantly delayed MMN response compared to the adults group. In contrast, in response to non-speech stimuli, only the youngest group (3 to 7 years) showed a significantly delayed MMN compared to the adults. Age-related differences for tone discrimination therefore appear to occur earlier in children's development than do the discriminative processes for speech sounds.

In the second study, we aimed at identifying the electrophysiological markers of auditory attention and language deficits often incurred by a premature birth. We thus presented this paradigm to 74 infants born preterm (before 34 gestational weeks) or full-term (at least 37 gestational weeks), aged 3, 12 and 36 months old. Our results indicated that preterm children of all age groups showed a significantly delayed MMN and P150 responses to speech stimuli compared to full-terms. Moreover, significant correlations were found between the delayed MMN and P150 responses to speech sounds and lower language scores on a neurodevelopmental assessment. However, no significant differences were found between full-term and preterm children for the MMN in response to non-speech stimuli, suggesting preserved pre-attentional auditory discrimination abilities in these children.

Altogether, the findings from this thesis indicate that the neurodevelopmental processes associated with auditory pre-attentional skills occur earlier in childhood compared to language discrimination processes. Cerebral networks involved in speech discrimination are still immature in late childhood. Furthermore, neural networks involved in speech discrimination and language development also appear to be particularly vulnerable to the impacts of prematurity. The use of AERPs and the MMN response to speech stimuli in infancy can thus provide predictive markers of language difficulties commonly seen in premature infants.

Keywords: Prematurity, Electroencephalography (EEG), Mismatch Negativity (MMN), Auditory Evoked Potential (AERP), Language development, Neurodevelopment.

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Liste des sigles et abréviation

AC	Modulation Amplitude
ADHD	Attention Deficit Hyperactivity Disorder
AERPs	Auditory Event-Related Potentials
AG	Age gestationnel
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BA	Brodmann Areas
BRIEF	Behavior Rating Inventory of Executive Function
BRIEF-P	Behavior Rating Inventory for Executive Functioning for Preschool children
BSDI-III	Bayley Scale of Infant Development (Bayley-III)
BOLD	Blood oxygen level dependent
CADS-P	Conners' ADHD/DSM-IV Scale
dB	Décibel
DC	Optical Density
DPF	Differential Path Length Factor
ERP	Event-Related Potential
EEG	Electroencéphalographie / Electroencephalography
fMRI	functional Magnetic Resonance Imaging
fNIRS	function Near-Infrared Spectroscopy
HbO	Oxy-hémoglobine / oxy-heamoglobin
HbR	Déoxy-hémoglobine / deoxy-heamoglobin
HbT	Total hémoglobine
HSD	Honest Significant Difference
Hz	Herzt
IAT	Intracarotide Amobsbital Test
kΩ	Kilo-ohms
LI	Laterality Index
LPV	Leucomalacie Périventriculaire
MANOVA	Multivariate Analysis of Variance
MEG	Magnétoencéphalographie
MMN	Mismatch Negativity
Ms / Msec	Milliseconde
NEPSY	Developmental NEuroPSYchological Assessment
NICU	Neonatal Intensive Care Unit
NIRS	Near-Infrared Spectroscopy
OI	Optical Imaging
OMS	Organisation Mondiale de la Santé

QI	Quotient Intellectuel
PEA	Potentiel Évoqué Auditif
PET	Positron Emission Tomography
ROI	Region of Interest
ROP	Retinopathy of Prematurity
TDAH	Trouble déficitaire de l’attention avec hyperactivité
TEA-Ch	Test of Everyday Attention for Children
TVA	Temporal Voice Area
SD	Standard Deviation
SPIR	Spectroscopie Proche de l’Infrarouge
SPL	Sound Pressure Level
SPSS	Statistical Package for the Social Sciences
STS	Superior Temporal Sulcus
µV	MicroVolt
VEP	Visual Evoked Potential
WHO	World Health Organization
WISC–IV	Weschler Intelligence scale for Children (4th edition)
WPPSI-R	Weschler Preschool and Primary Scale of Intelligence-Revised edition

« You know what the issue is with this world ?
Everyone wants a magical solution to their problem,
and everyone refuse to beleive in magic. »

~ *Alice in Wonderland*

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1. INTRODUCTION

Introduction générale

Les avancements des dernières années dans les unités de néonatalogie et de soins périnataux ont grandement aidé à diminuer la mortalité liée à une naissance avant terme (37 semaines de gestation). Les bébés nés prématurément sont toutefois plus à risque de développer une variété de troubles de la santé et développementaux que les bébés nés à terme. Les complications les plus communes comprennent les difficultés cardio-respiratoires, gastro-intestinales, immunologiques, des problèmes de vision, d'audition et du système nerveux central. En effet, les derniers mois de grossesse sont particulièrement importants pour le développement du système nerveux central de l'enfant et les conséquences d'une naissance prématurée sur le développement neurologique de l'enfant sont considérables. Les troubles du langage et de l'attention figurent parmi les séquelles neurodéveloppementales les plus fréquemment recensées chez les enfants nés prématurément. Toutefois ceux-ci ne sont souvent dépistés que tardivement dans la petite enfance ou à l'âge scolaire, alors que les demandes deviennent plus importantes sur les plans intellectuel, académique et social.

Une prise en charge rapide de ces enfants serait donc hautement pertinente afin de dépister, voire prévenir, ces difficultés neurodéveloppementales. Toutefois, très peu de programmes de dépistage et d'interventions précoces sont disponibles afin de favoriser leur développement à long terme. Étant donné l'ampleur des conséquences potentielles de la prématurité sur le développement de ces enfants, la présente thèse vise à identifier dès la première année de vie de l'enfant les marqueurs électrophysiologiques prédictifs du développement langagier et cognitif. Une méthode d'investigation des processus cognitifs préattentionnels et langagiers à l’aide de l’électrophysiologie et des potentiels évoqués auditifs (PEAs) est ainsi proposée.

D’une part, le premier volet de cette thèse vise à identifier et documenter le développement de l’attention auditive et des capacités de discrimination langagières de l’enfant né à terme, de la petite enfance à l’âge adulte, afin de mettre en place des repères électrophysiologiques développementaux du langage et de l’attention auditive. Ce premier volet permettra la validation du protocole qui sera utilisé auprès d’enfants plus jeunes, nés à terme ou nés prématurément. D’autre part, un deuxième volet vise plus spécifiquement l’identification des marqueurs du développement des capacités auditives langagières et préattentionnelles chez les enfants de trois mois à trois ans, nés à terme ou prématurément, afin de préciser à partir de quel âge il est possible d’identifier les enfants à risque de développer un trouble langagier ou cognitif.

Pour ce faire, quatre chapitres principaux forment le présent manuscrit. Une recension de la littérature permettra dans un premier temps d’obtenir une meilleure compréhension du développement neurologique typique de l’enfant, du concept de la prématurité et de ses effets sur le développement physiologique et cognitif de l’enfant. Les contributions potentielles de l’évaluation électrophysiologique et neuropsychologique du langage et de l’attention auditive chez les enfants nés prématurément ou à terme seront également examinées. Le deuxième chapitre présentera les objectifs principaux de la thèse et les hypothèses spécifiques de chaque étude. Le troisième chapitre exposera les deux articles scientifiques qui composent cette thèse, incluant la méthodologie et les résultats détaillés de chaque publication. Le quatrième chapitre contient la discussion générale et visera l’intégration théorique et clinique des résultats. Ce chapitre de la thèse abordera également les limites de chaque étude ainsi que les perspectives d’études futures. Finalement, en annexe, se retrouveront trois manuscrits additionnels publiés ou soumis parallèlement, investiguant plus largement le développement de la perception de la voix et du langage chez le nouveau-né ainsi que la localisation anatomique en imagerie optique des aires du langage chez l’enfant plus âgé né à terme et chez l’adulte.

Prématurité

Définition, incidence et classification

Selon les lignes directrices de l’Organisation mondiale de la santé (OMS), une naissance est prématurée lorsqu’elle survient avant la 37e semaine de gestation (moins de 259 jours), calculée à partir de la dernière période de menstruation de la mère (American College of Obstetricians and Gynecologists, 2012; March of Dimes, PMNCH, Save the Children, 2012). À ce jour, on estime que plus d’une naissance sur 10 dans le monde survient avant terme, soit près de 15 millions d’enfants qui naissent prématurément chaque année (Beck et al., 2010). Au Canada, ce taux est d’environ 8 % des naissances, soit l’équivalent d’un enfant sur 12 qui nait avant terme (Public Health Agency of Canada, 2008). Selon l’OMS, entre les années 2000 et 2010, les complications liées à la prématurité représentaient la principale cause de mortalité chez les nouveau-nés dans le monde, et la deuxième cause de mortalité chez enfants de moins de 5 ans après la pneumonie (Liu et al., 2012; March of Dimes, PMNCH, Save the Children, 2012). Néanmoins, les probabilités de survie des enfants prématurés ont augmenté au cours des dernières années, notamment grâce à l’amélioration des technologies et des connaissances médicales et scientifiques dans les domaines de l'obstétrique et de la néonatalogie (Beck et al., 2010; McIntire & Leveno, 2008).

Les critères pour classifier une naissance prématurée se basent principalement sur l'âge gestationnel (AG), c'est-à-dire le nombre de semaines entre la conception estimée de l'enfant et sa naissance, ainsi que sur le poids de l'enfant à sa naissance. Le moment de conception de l'enfant est généralement estimé en fonction d'examens d'ultrasonographie (échographies) effectués au cours du premier trimestre de gestation, ou en calculant 14 jours suivant le début des dernières menstruations de la mère (jour de l'ovulation) lorsque l'accès aux techniques d'ultrasonographie est limité (March of Dimes, PMNCH, Save the Children, 2012). Ainsi, une naissance survenant avant la 28e semaine complète de gestation est qualifiée d'extrême prématurité, ce qui correspond à environ 5 % des naissances prématurées. Une naissance survenant entre la 28e et la 32e semaine de gestation est qualifiée de grande prématurité, correspondant à environ 10 % des naissances prématurées. Enfin, une naissance survenant entre la 33e et la 37e semaine de gestation est qualifiée de prématurité moyenne ou tardive et correspond à près de 85 % des naissances prématurées (Blencowe et al., 2012; March of Dimes, PMNCH, Save the Children, 2012). Dans ces conditions, il est d'usage de calculer l'âge corrigé, comme recommandé par *l'American Academy of Pediatrics* (Engle & Committee on Fetus and Newborn, 2004; Wilson-Ching, Pasco, Doyle, & Anderson, 2014). Celui-ci est calculé en soustrayant le nombre de semaines nées prématurément (avant 40 semaines de gestation) de l'âge chronologique (âge réel depuis la naissance), et est généralement utilisé jusqu'à ce que l'enfant atteigne 24 mois d'âge réel. Conjointement à l'âge gestationnel, il est d'usage de classifier une naissance prématurée selon le poids de l'enfant à sa naissance. Ainsi, un enfant prématuré peut être extrêmement petit (né avec un poids < 1000 g), très petit (poids de naissance entre 1000 g et 1500 g) ou petit (poids de naissance entre 1500 g et 2500 g) (March of Dimes, PMNCH, Save the Children, 2012; Public Health Agency of Canada, 2008). Bien que le poids de naissance soit étroitement lié à l'âge gestationnel, cette classification est importante puisqu'un poids de naissance plus petit est souvent associé à des séquelles physiologiques et neurodéveloppementales plus importantes.

Causes et facteurs de risques

Les causes de la prématurité sont multiples. Elles incluent notamment des facteurs environnementaux et sociaux, des caractéristiques maternelles, de même que certains facteurs biologiques et génétiques propres à l'enfant (Committee on Understanding Premature Birth and Assuring Healthy Outcomes Board on Health Sciences Policy, 2007). Ainsi, la rupture prématurée des membranes, la prééclampsie (hypertension artérielle toxique grave chez la mère survenant en deuxième moitié de grossesse), un âge maternel très jeune ou plus âgé, une histoire familiale d'accouchement prématuré, des infections intra-utérines, le tabagisme, la toxicomanie ou la consommation d'alcool, un faible poids de la mère avant la grossesse, un gain ou une perte de poids rapide durant la grossesse, ainsi que les naissances multiples figurent parmi les causes les plus fréquentes d'accouchement prématuré au sein des pays développés (Committee on Understanding Premature Birth and Assuring Healthy Outcomes Board on Health Sciences Policy, 2007; March of Dimes, PMNCH, Save the Children, 2012; Public Health Agency of Canada, 2008). Par ailleurs, le stress maternel est également identifié comme un facteur de risque important d'accouchement prématuré (Dole, Savitz, Hertz-Picciotto, McMahon, & Buekens, 2003), tout comme l'utilisation des techniques de reproduction assistée qui ont mené au cours des dernières années à un surcroit des naissances multiples (Felbertaum, 2007; Public Health Agency of Canada, 2008).

Les coûts médicaux et sociaux liés à la prématurité sont importants, et les impacts socioéconomiques associés s'étendent au-delà des unités néonatales de soins intensifs. En 2005 aux États-Unis, on estimait la charge économique annuelle de la prématurité à plus de 26 milliards de dollars, soit 51 600 $ par enfant né prématurément (Zupancic, 2006). Ces couts comprenaient d'une part l'hospitalisation et les soins médicaux spécialisés prodigués durant la petite enfance, les soins maternels, mais aussi les programmes d'intervention et les services d'éducation spécialisée à plus long terme (Zupancic, 2006). Par ailleurs, à l'âge scolaire les enfants nés prématurément ont des taux plus élevés d'échecs scolaires et de difficultés d'apprentissage que les enfants nés à terme, ils ont besoin plus souvent de services d'éducation spécialisés (Sayeur et al., 2014; Sayeur, Mckerral, & Lassonde, 2011), et les familles ont souvent davantage de dépenses liées aux conséquences de la prématurité (Petrou, 2005).

Conséquences de la prématurité

Développement du système nerveux central

Le développement cortical de l'enfant commence très tôt dans la période intra-utérine et suit une séquence rapide d'évènements cruciaux pour la maturation des systèmes sensoriels, incluant celui du système auditif. Dans les derniers mois de gestation et les premiers mois de vie, l'enfant connait une série d'évènements physiologiques qui seront déterminants dans l'apprentissage du langage, passant par la reconnaissance de la voix humaine à la discrimination des sons et phonèmes qui constituent les fondements de sa langue maternelle [voir Annexe 1 pour une revue plus détaillée des phases du développement de la perception vocale et du langage chez le foetus, le nouveau-né et le jeune enfant]. Brièvement, le premier trimestre de gestation s'étend du moment de la conception jusqu'au troisième mois de grossesse. Durant cette période, la formation initiale de l'organe de Corti se produit, de même que celle des cellules ciliées internes et externes, de la cochlée et du nerf cochléaire (Moore & Linthicum Jr, 2007). À maturité, les cellules ciliées vont convertir les mouvements physiques produits par les vibrations sonores en signaux nerveux qui seront par la suite transmis au cortex auditif par le nerf cochléaire (Graven & Browne, 2008; Hall, 2000; Moore & Linthicum Jr, 2007). L'organe de Corti, la cochlée et le nerf cochléaire continuent de se développer au cours du deuxième trimestre (soit du 4e au 6e mois, inclusivement), et à environ 25-29 semaines de gestation, l'ensemble des structures composant le système auditif est identifiable. Ainsi, dès la fin du sixième mois, la cochlée a établi des connexions axonales entre l'oreille interne, le tronc cérébral et le cortex auditif situé au niveau des aires temporales droite et gauche (Graven & Browne, 2008). C'est également au cours de cette période que les premières indications de perception auditive sont observables chez le fœtus, de même que les premières réponses physiologiques (variations cardiaques) et comportementales (mouvements corporels) à la perception in utero de la voix de la mère (Kisilevsky, Pang, & Hains, 2000; Morris, Philbin, & Bose, 2000).

Par ailleurs, les derniers mois de grossesse sont particulièrement importants pour le développement du système nerveux central de l'enfant. Durant le dernier trimestre de gestation (de 28 à 40 semaines), les synapses deviennent apparentes au sein de la plaque corticale et les circuits sensoriels de certaines zones corticales commencent à se développer et à se spécialiser, notamment au niveau du système auditif (Graven & Browne, 2008; Kostović & Jovanov-Milošević, 2006; Kostovic & Judas, 2010; Rados, Judas, & Kostović, 2006). Parallèlement, la différenciation neuronale et dendritique devient plus importante. Le développement dendritique, la mise en place des afférences corticales et terminaisons axonales qui constituent la matière blanche du cerveau, ainsi que le début du processus de myélinisation des axones, mènent à quatre fois l'augmentation du volume cortical (Hüppi et al., 1998). À maturité, les axones (soit la matière blanche) permettront le transfert rapide et efficace de l'information auditive d'une région à l'autre du cerveau.

Atteintes cérébrales

Les séquelles d'une naissance prématurée sur le développement neurologique de l'enfant sont considérables. L'enfant prématuré est à risque de présenter une hémorragie intraventriculaire et/ou une hydrocéphalie post hémorragique de différents niveaux de sévérité à la naissance ou dans la période périnatale (Huppi, 2004). Par ailleurs, la majorité des lésions cérébrales encourues par une naissance prématurée touchent la matière blanche du cerveau, de façon diffuse ou locale (Huppi, 2004; Volpe, 2009b). Ces atteintes de la matière blanche ont souvent été mises en lien avec la leucomalacie périventriculaire (LPV), une condition particulièrement répandue chez les nourrissons de très petit poids (Huppi, 2004; Volpe, 2008, 2009a, 2009b). La LPV du prématuré réfère à la constellation des lésions de la matière blanche, soit 1) la nécrose focale de celle-ci, particulièrement observée au sein des couches cérébrales plus profondes, et 2) des dommages diffus affectant le développement des oligodendrocites, une cellule responsable de la formation de la gaine de myéline entourant les axones (Volpe, 2009a, 2009b).

De nombreuses études d'imagerie suggèrent que 50 % ou plus des nourrissons nés prématurément et/ou de très faible poids à la naissance montrent des altérations neuronales et axonales importantes (Volpe, 2009a, 2009b). Ces atteintes ont été associées à divers déficits d'ordre perceptif, cognitif, langagier et moteur chez les enfants de très petits poids à la naissance ou nés très prématurément (Chau et al., 2013; Counsell et al., 2003; He & Parikh, 2013; Nosarti et al., 2008; Peterson et al., 2000; S. Rose et al., 2008; Skranes et al., 2007; Volpe, 2009b). Par exemple, une relation linéaire positive a été trouvée entre des valeurs de diffusion plus faibles au niveau du corps calleux, de la commissure antérieure, du cingulum et du fornix chez des enfants prématurés et leur quotient de développement neurologique global à deux ans d'âge corrigé (Counsell et al., 2008). De plus, il semble que certaines de ces altérations persistent jusqu'à l'âge adulte et soient associées à un rendement intellectuel plus faible chez l'adulte né avant 33 semaines de gestation (Allin et al., 2011; Skranes et al., 2007). D'autres études ont souligné des différences volumétriques au niveau de la matière grise chez les sujets prématurés comme une diminution du volume cérébral sous-cortical (thalamus, hippocampe et noyaux caudés), du lobe orbitofrontal, des cortex cingulaire, temporal, et frontal, ainsi que du cervelet (Ball et al., 2012, 2013; Isaacs et al., 2000; Maalouf et al., 1999; Nosarti et al., 2002, 2008). Ces anomalies neuronales ont également été mises en lien avec des atteintes neurodéveloppementales telles que des habiletés langagières et exécutives plus limitées (Ball et al., 2012; Nosarti et al., 2008).

Atteintes neurosensorielles et cognitives

Différents déficits sensoriels d'origine neurologique sont observés chez les enfants prématurés. Par exemple, des déficits visuels sont rapportés, incluant la rétinopathie du prématuré (ROP), perturbant le développement des axones du nerf optique et provoquant une réduction de l'acuité et de la perception visuelles, une perturbation de la fixation oculaire et une mauvaise perception des basses fréquences spatiales ou des stimuli à faible contraste (Dammann et al., 2009; Hammarrenger et al., 2007; Sayeur et al., 2014, 2015; Weinberger, Laskin, Heck, & Laskin, 2002). On note aussi des répercussions de nature psychomotrice chez les enfants nés prématurément : troubles de l'équilibre, difficultés dans la manipulation simple (par exemple, la maîtrise d'un ballon) ou mauvaise dextérité manuelle (de Kieviet, Piek, Aarnoudse-Moens, & Oosterlaan, 2009). Les effets d'un déficit moteur sur le fonctionnement adaptatif de l'enfant ont d'ailleurs été associés à de plus faibles performances cognitives, des difficultés d'apprentissage et des troubles du comportement (Losch & Dammann, 2004; Piek, Dawson, Smith, & Gasson, 2008; Wijnroks & van Veldhoven, 2003). Par ailleurs, les atteintes du traitement auditif ont également une prévalence importante auprès de cette population. Certaines études rapportent une prévalence d'individus nés prématurément présentant une déficience auditive de 6 à 40 fois plus élevée que celle retrouvée parmi la population générale, soit près de 3 % des enfants nés prématurément qui démontrent une déficience auditive d'au moins 50 dB (Ancel, 2004; Cristobal & Oghalai, 2008; Robertson, Hrynchyshyn, Etches, & Pain, 1992; Robertson, Howarth, Bork, & Dinu, 2009).

L'incidence élevée des séquelles neurosensorielles chez les enfants prématurés a définitivement des répercussions considérables au niveau de leur développement cognitif. Les déficits neurodéveloppementaux sont de loin les répercussions négatives dominantes à plus long terme chez l'enfant prématuré ou de faible poids à la naissance (Arpino et al., 2010; Volpe, 2009a). Ces déficits ont été documentés dans une variété de fonctions telles que les habiletés sociales, langagières, mnésiques, visuoperceptuelles, motrices et spatiales, les fonctions exécutives, l'attention et l'ajustement socioémotionnel (Fan, Portuguez, & Nunes, 2013; Sayeur et al., 2011). Malheureusement, la plupart de ces séquelles passent inaperçues dans la petite enfance et ne sont détectées que plus tard dans le cursus de l'enfant, où les exigences cognitives et intellectuelles se font de plus en plus importantes (Anderson & Doyle, 2008; Johnson, Wolke, Hennessy, & Marlow, 2011; Ritter, Perrig, Steinlin, & Everts, 2014). Sur le plan du fonctionnement intellectuel global, des études rapportent des quotients intellectuels (QI) pouvant se situer de 0,5 à 2 écarts-types sous le rendement intellectuel moyen chez les enfants d'âge scolaire nés avant 35 semaines de gestation (Peter Anderson, Doyle, & Victorian Infant Collaborative Study Group, 2003; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Bos & Roze, 2011).

Atteintes langagières

Une conséquence importante possiblement associée aux lacunes neurosensorielles en prématurité est le retard de développement du langage réceptif et expressif qui peut avoir en retour un impact important sur l'acquisition et le développement des habiletés sociales, cognitives et scolaires (Barre, Morgan, Doyle, & Anderson, 2011; Desjardin, Ambrose, Martinez, & Eisenberg, 2009; Durkin & Conti-Ramsden, 2007; Schuymer, Groote, Beyers, Striano, & Roeyers, 2011). Les troubles du langage comprennent les problèmes liés à la capacité de l’enfant à comprendre (langage réceptif), à utiliser et à produire correctement les mots et la grammaire (langage expressif) (Glass, 1999). Ils peuvent inclure des désordres phonologiques, sémantiques, syntaxiques et/ou pragmatiques et se manifestent souvent par des difficultés réceptives (différencier les sons du langage, en comprendre le sens et retenir ce qu’ils ont entendu) et des difficultés de la parole et du langage écrit (Chiat, 2001; Parisse & Maillart, 2004).

La prématurité représente donc un facteur de risque important de troubles du langage à l’âge préscolaire. Environ un grand prématuré sur quatre présente un retard important d’acquisition du langage à l’âge de deux ans et demi, et ce chiffre passe à un enfant sur trois à l’âge de trois ans et demi (Sansavini et al., 2010). Des troubles ou des retards de production et de compréhension du langage ont été documentés à plusieurs reprises chez les enfants et les adolescents ayant eu une naissance prématurée, et ce même en l’absence de dommages cérébraux visibles (Crunelle, Le Normand, & Delfosse, 2003; Guarini et al., 2009; Eira Jansson-Verkasalo et al., 2003; Lee, Yeatman, Luna, & Feldman, 2011; Rizzotto Schirmer, Wetters Portuguez, & Lahorgue Nunes, 2006; Sansavini et al., 2010; Wolke, Samara, Bracewell, Marlow, & EPICure Study Group, 2008). Ainsi, les enfants nés avant terme présentent souvent des scores significativement plus faibles au niveau du quotient verbal, des aptitudes du langage réceptif et expressif, de la compréhension syntaxique, de la vitesse de traitement linguistique, de la mémoire verbale et de la compréhension en lecture (Lee et al., 2011).

La nature spécifique des retards langagiers chez le prématuré est toutefois controversée, compte tenu des nombreux facteurs pouvant l'expliquer (par exemple, le statut socio-économique, une sous-stimulation ou l'impact de déficits associés) (Cusson, 2003). Les enfants ayant des troubles du langage spécifiques présentent des retards d'au moins 12 mois dans le développement du langage (McLean & Cripe, 1997). Ils sont d'une intelligence normale et ne présentent pas de problèmes pouvant avoir une incidence sur le développement langagier (par exemple, une déficience auditive ou neurologique, ou des difficultés émotionnelles ou physiques). Selon une étude de Wolke et collaborateurs (2008) les troubles langagiers et du traitement phonémique observés chez les prématurés extrêmes (moins de 25 semaines de gestation) seraient de nature non spécifique et refléteraient davantage un rendement cognitif global déficitaire plutôt que des atteintes spécifiques du langage (Wolke et al., 2008). Néanmoins, en contrôlant pour les variables intellectuelles et socioéconomiques, Lee, Yeatman, Luna & Feldman (2011) ont trouvé que le degré de prématurité, déterminé par l'âge gestationnel, demeurait un prédicteur important de la vitesse de traitement linguistique, de la mémoire verbale et de la compréhension en lecture (Lee et al., 2011). De même, le développement du langage réceptif de l'enfant à 26 mois d'âge corrigé a été fortement corrélé avec le poids à la naissance et l'âge gestationnel (Cusson, 2003).

Atteintes attentionnelles

En plus des risques de problèmes langagiers et sensoriels, les enfants nés avant 37 semaines gestationnelles présentent une prévalence importante de troubles attentionnels par rapport aux enfants nés à terme (Bhutta et al., 2002; Gustafsson & Källén, 2011). Ainsi, à l'âge de 10 ans, environ 20 % des enfants nés extrêmement prématurés présentent un trouble déficitaire de l'attention avec hyperactivité (TDAH) alors que ce taux est de 8 à 10 % chez les enfants nés à terme (Stjernqvist & Svenningsen, 1999). Dans une étude d'Anderson et collaborateurs (2011) les enfants âgés de 8 ans qui étaient nés très prématurément présentaient des déficits significatifs au niveau de l'attention sélective, soutenue et divisée, ainsi qu'au niveau de la flexibilité attentionnelle, tels que mesurés à l'aide du *Test of Everyday Attention for Children* (TEA-Ch) et de l'échelle d'intelligence pour enfants de Wechsler (WISC–IV). De plus, ces mêmes enfants démontraient davantage de symptômes liés au trouble déficitaire de l'attention avec hyperactivité, mesurés à l'aide du *Behavior Rating Inventory of Executive Function* (BRIEF) et du *Conners' ADHD/DSM-IV Scale* (CADS-P) (Anderson et al., 2011). Ces résultats appuient ceux d'une autre étude effectuée auprès des enfants extrêmement prématurés (moins de 27 semaines gestationnelles) rapportant des performances significativement plus faibles au niveau du contrôle attentionnel et des scores symptomatiques plus élevés sur le *ADHD Rating Scale-IV* (Shum, Neulinger, O'Callaghan, & Mohay, 2008).

L'impact potentiel des mécanismes cognitifs plus généraux comme l'attention sur le développement du langage demeure toutefois ambigu (Cherkes-Julkowski, 1998; Gartstein, Crawford, & Robertson, 2008; Ribeiro et al., 2011; Rose, Feldman, & Jankowski, 2009). Les enfants atteints de troubles spécifiques du langage semblent également avoir davantage besoin d'une utilisation soutenue des ressources attentionnelles lors du traitement de phrases simples (Montgomery, Evans, & Gillam, 2009). Il semble donc primordial de préciser la nature des troubles chez un enfant afin de pouvoir intervenir de façon plus spécifique et efficace. Or, l'évaluation des sphères cognitives, attentionnelles et langagières est limitée en bas âge. Dès lors, l'amélioration des méthodes d'évaluation pourrait nous aider à définir davantage leur développement dans l'espoir de dépister précocement d'éventuels problèmes et par conséquent, mettre en place les stratégies d'intervention appropriées.

Évaluation électrophysiologique de l'attention auditive et du traitement langagier

Les potentiels évoqués auditifs et la *mismatch negativity*

Au cours des dernières années, des études sur le développement cognitif de l'enfant ont souligné la pertinence de l'utilisation de l'électrophysiologie à haute densité (EEG) et des potentiels évoqués auditifs (PEAs) chez les nourrissons et les jeunes enfants. Les PEAs sont produits par la synchronisation de phase neuronale ainsi que l'augmentation du pouvoir spectral de la bande de fréquence oscillatoire thêta (4-7Hz), évoqués par la présentation et la détection d'un stimulus auditif dans l'environnement sonore du sujet (Fuentemilla, Marco-Pallarés, & Grau, 2006). De ce fait, les PEAs permettent d'examiner des processus cognitifs complexes tels que la discrimination linguistique et l'attention auditive sans nécessiter une réponse comportementale spécifique ou le maintien soutenu de l'attention chez l'enfant (Picton & Taylor, 2007; Tampas, Harkrider, & Hedrick, 2005). Plus précisément, grâce à la méthode de *mismatch negativity* (MMN), il est possible d'évaluer les différences d'activations cérébrales obtenues suite à la présentation de stimuli fréquents entrecoupés de stimuli rares. La MMN est une composante électrophysiologique classiquement utilisée pour évaluer la réponse neuronale préattentionnelle à un changement perceptible dans l'environnement auditif du sujet (Näätänen & Winkler, 1999; Näätänen et al., 1997; Näätänen, Paavilainen, Rinne, & Alho, 2007). L'interprétation traditionnelle de la MMN veut que les paramètres d'un stimulus auditif nouveau soient comparés à ceux d'un stimulus fréquent qui auraient été gardés en mémoire sensorielle auditive (Näätänen et al., 2007; Näätänen & Winkler, 1999). Ainsi, la comparaison par soustraction des potentiels évoqués par la présentation d'un stimulus auditif fréquent à ceux obtenus suite à la présentation d'un stimulus auditif rare permet d'observer une négativité dans la courbe différentielle. Cette négativité atteint généralement son maximum au niveau des électrodes fronto-centrales et ce, environ 100 à 250 ms suite à la présentation du stimulus. Cette mesure du fonctionnement attentionnel auditif a été utilisée à de nombreuses reprises pour évaluer le développement auditif attentionnel et langagier normal de l'enfant ainsi qu'auprès de diverses populations cliniques (Rita Ceponiene, Rinne, & Näätänen, 2002; Eira Jansson-Verkasalo et al., 2003; Lovio, Näätänen, & Kujala, 2010; Näätänen et al., 2007). Typiquement, on estime la MMN à l'aide d'une mesure d'amplitude maximale ou d'aire sous la courbe à l'intérieur d'une fenêtre de temps donnée, une fois la moyenne de tous les essais effectuée. Cette méthode constitue un moyen objectif de mesurer les processus préattentionnels auditifs et la discrimination des sons du langage chez des populations de tout âge. De plus, elle est particulièrement adaptée aux jeunes enfants puisqu'elle ne requiert pas leur participation active, pouvant même être administrée lorsqu'ils dorment (Martynova, Kirjavainen, & Cheour, 2003).

Changements électrophysiologiques en lien avec le développement normal

Au cours de l'enfance, d'importants changements structuraux surviennent en lien avec le développement typique, particulièrement au niveau des aires corticales associatives et de haut niveau. Des études récentes en imagerie ont révélé que les aires cérébrales du langage continuent à se développer et se spécialiser durant l'enfance et l'adolescence, jusqu'à l'âge adulte (Casey, Jones, & Todd, 2008; Lidzba, Schwilling, Grodd, Krägeloh-Mann, & Wilke, 2011; Paquette et al., 2010 [voir Annexe 3]; 2015 [voir Annexe 2]; Porter, Collins, Muetzel, Lim, & Luciana, 2011; Su, Kuan, Kaga, Sano, & Mima, 2008). En outre, ces changements liés à l'âge se traduisent par des différences importantes au niveau du signal électrophysiologique (Moore & Linthicum, 2007; Segalowitz, Santesso, & Jetha, 2010). Par exemple, la maturation et la myélinisation des projections thalamo-corticales au sein du cortex auditif atteignent un stade adulte vers l'âge de cinq ans. Plus tard, vers l'âge de six ans, la maturation des couches superficielles du cortex a lieu et leurs connexions atteignent leur pleine efficacité à l'âge de onze ou douze ans (Moore & Guan, 2001). Au cours de la petite enfance, la morphologie des potentiels évoqués corticaux évolue avec la maturation et la myélinisation des projections thalamo-corticales. Bien que la morphologie de la courbe électrophysiologique soit différente chez les très jeunes enfants par rapport à celle d'enfants d'âge scolaire ou d'adultes en raison de l'immaturité du cortex auditif, le cerveau de l'enfant parvient néanmoins à discriminer l'information auditive dès le début du troisième trimestre de vie fœtale (Moore & Linthicum Jr, 2007; Paquette, Dionne-Dostie, Lassonde & Gallagher, soumis [voir en Annexe 1]). De plus, les principales composantes électrophysiologiques positives et négatives (P150, N250, P350, et N450) peuvent déjà être identifiables dans les premiers jours de vie du nourrisson (Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002), suggérant que les générateurs de ces composantes sont fonctionnels à la naissance. En fonction de l'âge, la morphologie de la courbe électrophysiologique augmente progressivement en complexité, c'est-à-dire que la latence des composantes diminue et que leur amplitude augmente (Cheour, Leppanen, & Kraus, 2000; Moore & Linthicum Jr, 2007; Wunderlich, Cone-Wesson, & Shepherd, 2006). D'autres changements du signal EEG coïncident avec la maturation des couches corticales supérieures, entre autres l'apparition de la composante négative N100 (Kraus et al., 1993). Celle-ci s'avère toutefois difficile à détecter durant la petite enfance, mais émerge graduellement de l'âge préscolaire jusqu'à l'âge d'environ neuf ans suite à la maturation de la P100 à une latence d'environ 100 ms (Lippé, Martinez-Montes, Arcand, & Lassonde, 2009; Lippé, Kovacevic, & McIntosh, 2009; Ponton, Eggermont, Kwong, & Don, 2000). Ces changements observés dans les PEAs en réponse aux stimuli fréquents et rares se reflètent sur la morphologie de la courbe différentielle de la MMN et coïncident avec l'acquisition du langage et la capacité croissante de l'enfant à discriminer les sons.

La plupart des études examinant les processus développementaux de la MMN ont toutefois utilisé des stimuli non verbaux (tons simples ou complexes), et peu d'études ont examiné l'évolution spécifique de la MMN en réponse aux stimulations d'origine verbale. Parmi celles-ci, Shafer, Yu, & Datta (2010) ont observé une latence plus tardive de la MMN verbale chez les enfants âgés entre quatre et cinq ans et les enfants âgés entre six et sept ans (entre 300 et 400 ms) comparativement à la latence typiquement observée chez les adultes. De plus, dans leurs échantillons, les enfants plus jeunes avaient tendance à montrer une *mismatch* positive entre 100 et 300 ms de latence, indice de discrimination également retrouvé dans d'autres études effectuées auprès de jeunes enfants (Kushnerenko et al., 2002). Par ailleurs, à notre connaissance, une seule étude s'est intéressée conjointement aux processus développementaux de la MMN verbale et non verbale sur une période couvrant l'enfance, l'adolescence et l'âge adulte (Bishop, Hardiman, & Barry, 2011). Toutefois, la distinction entre le développement de la MMN verbale par rapport à celui de la MMN non verbale n'a pas été étudiée par les chercheurs.

Certains auteurs ont en outre proposé une théorie du traitement parallèle acoustique et phonétique des sons verbaux chez les adultes (Tampas et al., 2005; Winkler et al., 1999). Selon cette théorie, les processus générateurs de la MMN et ceux de la composante P300, associée à l'orientation consciente de l'attention, utilisent à la fois (en parallèle) les représentations acoustiques et phonétiques lors du traitement des sons verbaux, alors que les sons non verbaux sont traités uniquement sur le plan acoustique. La présentation des stimuli verbaux et non verbaux pourrait ainsi permettre de clarifier l'impact des mécanismes préattentionnels auditifs sur le développement des capacités de discrimination langagière de l'enfant, et aider à préciser la nature des retards observés chez l'enfant prématuré. Néanmoins, pour mieux comprendre et préciser le type de déficit encouru par une naissance prématurée à l'aide de la MMN verbale et non verbale, il est tout d'abord indispensable d'avoir au préalable une meilleure compréhension des processus développementaux typiques de la MMN, propres aux traitements des sons verbaux (phonétique) et non verbaux (acoustique).

La MMN comme marqueur du développement langagier et cognitif

Malgré la nature encore méconnue des processus développementaux de la MMN, depuis quelques années la MMN et les PEAs sont utilisés comme mesure du développement cognitif et langagier chez les enfants nés avant terme (Bisiacchi, Mento, & Suppiej, 2009; Gomot, Bruneau, Laurent, Barthélémy, & Saliba, 2007; Eira Jansson-Verkasalo et al., 2010; Maitre, Lambert, Aschner, & Key, 2013; Ortiz-Mantilla & Benasich, 2013). Par exemple, chez les nouveau-nés de moins de 30 semaines de gestation, il est possible d'observer des potentiels évoqués auditifs (PEAs) atypiques ou de plus petites amplitudes que ceux observés chez des enfants nés à terme (Bisiacchi et al., 2009). Fellman et al. (2004) ont observé des PEAs et une MMN de plus petites amplitudes en réponse à des tons harmoniques chez les enfants prématurés comparativement à un groupe d'enfants nés à terme durant la première année de vie. Dans cette étude, la même observation a également été faite chez les nourrissons de petit poids pour l'âge gestationnel par rapport aux enfants de poids approprié pour l'âge gestationnel. De plus, ces réponses atypiques de la MMN et des PEAs mesurés à 12 mois étaient corrélées positivement avec un indice de développement plus faible au *Bayley Scale of Infant Development* à deux ans d'âge corrigé (Fellman et al., 2004). Dans un suivi longitudinal, les chercheurs ont noté que cette réponse atypique de la MMN et celle de la composante P1 (ou P100) étaient également observables à l'âge de cinq ans chez les enfants prématurés (Mikkola et al., 2007). Par ailleurs, l'amplitude de ces composantes était également corrélée avec des indices neuropsychologiques du quotient verbal de l'échelle de Weschler (Weschler Preschool and *Primary Scale of Intelligence-Revised* (WPPSI-R) et du *Developmental NEuroPSYchological Assessment* (NEPSY).

Afin de mieux comprendre le lien entre le traitement des informations auditives et le développement du langage chez cette population, Jansson-Verkasalo et al. (2003) ont étudié la réponse électrophysiologique de discrimination de sons verbaux chez un groupe d'enfants de quatre ans nés avant 33 semaines de gestation et de très petit poids, conjointement avec leur habileté en dénomination d'objets. Ainsi, les enfants nés prématurément qui démontraient des difficultés spécifiques en dénomination présentaient également une réponse électrophysiologique de plus faible amplitude lors de la discrimination de syllabes. En revanche, les enfants prématurés ne présentant pas de difficultés de dénomination n'ont présenté aucune anomalie électrophysiologique lors de la discrimination des syllabes comparativement aux enfants nés à terme (Jansson-Verkasalo et al., 2003). Lorsqu'évalués à nouveau à l'âge de six ans, les enfants ayant démontré des difficultés de dénomination tôt dans la vie démontraient encore une performance de dénomination significativement plus faible par rapport aux enfants nés à terme (Jansson-Verkasalo et al., 2004). Ces résultats appuient la stabilité temporelle et la valeur prédictive des PEAs en lien avec la performance des enfants dans les tâches langagières.

Par ailleurs, des études effectuées auprès d'enfants d'âge scolaire et présentant divers troubles développementaux (tels un trouble déficitaire de l'attention ou la dyslexie) montrent également une MMN atypique, c'est-à-dire de plus faible amplitude ou de plus grande latence, chez ces enfants. Des PEAs et une MMN atypiques en réponse à des stimuli non verbaux (tons) ont ainsi été mis en lien avec un trouble déficitaire de l'attention avec ou sans hyperactivité (TDAH) (Kilpelainen, Partanen, & Karhu, 1999; Rothenberger et al., 2000; Wild-Wall, Oades, & Juran, 2005). D'autres études effectuées auprès d'individus dyslexiques ont identifié des anomalies dans les composantes PEAs suivant la présentation de stimuli verbaux (Froyen, Willems, & Blomert, 2011; Huttunen, Halonen, Kaartinen, & Lyytinen, 2007; Lovio et al., 2010; Shafer, Ponton, Datta, Morr, & Schwartz, 2007; Van Leeuwen et al., 2007). Par exemple, des enfants de six ans à risque de développer une dyslexie (c'est-à-dire ayant une histoire familiale de dyslexie et démontrant une faible performance en lecture) ont également démontré des PEAs et une MMN de plus faible amplitude lors de la discrimination de sons verbaux comparativement aux composantes mesurées auprès d'un groupe d'enfants du même âge sans histoire familiale de troubles neurodévelopementaux (Lovio et al., 2010). En outre, Schulte-Korne, Deimel, Bartling, & Remschmidt (2001) ont distingué la réponse corticale en réponse à des stimuli verbaux de celle obtenue suite à la présentation de tons non verbaux chez des adultes vivant également avec une dyslexie. Leurs résultats suggèrent qu'en comparaison au groupe contrôle, les sujets dyslexiques montrent une MMN d'amplitude plus faible en réponse aux stimuli verbaux, alors qu'aucune différence ne distinguait les deux groupes lorsque des stimuli non verbaux étaient présentés.

En somme, l'utilisation des deux types de stimuli (verbaux et non verbaux) pourrait permettre de distinguer les processus impliqués dans le développement cognitif et langagier de l'enfant. Toutefois, peu d'études chez l'enfant né prématurément ont distingué les réponses corticales aux stimuli verbaux de celles obtenues en réponse aux stimuli non verbaux. Il reste donc difficile de savoir quels types de stimuli (verbaux, non-verbaux, ou les deux) permettraient de mieux évaluer et prédire le développement cognitif et langagier chez les enfants nés prématurément. L'analyse des réponses corticales aux sons verbaux et non verbaux chez les nourrissons prématurés et nés à terme pourrait ainsi aider à mieux caractériser le développement cognitif et du langage chez les enfants prématurés et identifier plus précocement les troubles potentiellement encourus par une naissance prématurée.

2. OBJECTIFS ET HYPOTHÈSES DE RECHERCHE

La revue de la littérature effectuée à ce jour, de même que les résultats mis en lumière précédemment suggèrent que l'investigation des processus préattentionnels, tels que ceux mesurés à l'aide de la MMN, pourrait contribuer à l'identification précoce de déficits cognitifs attentionnels et/ou langagiers. L'objectif spécifique de cette thèse est donc 1) de caractériser l'évolution de la MMN en fonction de l'âge de l'enfant en réponse à une tâche de discrimination verbale et non verbale dans le but de préciser la nature du développement du langage et de l'attention chez l'enfant et 2) permettre d'identifier les marqueurs prédictifs de déficits attentionnels auditifs ou langagiers découlant d'une naissance prématurée, et ce, tôt dans le développement de l'enfant.

Première étude : Marqueurs électrophysiologiques du développement préattentionnel auditif et langagier

Une meilleure compréhension des changements développementaux propres à la MMN verbale et non verbale est nécessaire afin d'établir des comparaisons plus fiables entre le développement cortical auditif typique et atypique. Toutefois, peu d'études se sont intéressées à la caractérisation des processus cérébraux responsables de la discrimination des sons verbaux et non verbaux, tels qu'indexés par la MMN, sur une période allant de la petite enfance à l'âge adulte. **Cette première étude a pour but** de mettre en place un protocole d'évaluation électrophysiologique du langage et de l'attention auprès d'une population de jeunes enfants (3 ans) jusqu'à l'âge adulte. Celle-ci permettra ainsi de mieux identifier les différences temporelles et morphologiques dans la courbe électrophysiologique propre à chaque stade de développement (enfance, adolescence, adulte) ainsi qu'à chaque type de stimulus (verbal, non verbal). Une meilleure connaissance du développement de la réponse électrophysiologique verbale et non verbale permettra ainsi d'identifier avec davantage de certitude une réponse MMN atypique d'une réponse typique en lien avec le développement de l'enfant.

Hypothèse 1 : Sur la base des résultats de l'étude de Shaffer, Yu et Datta (2010) et de Bishop, Hardimann et Barry (2011), nous postulons que les groupes plus jeunes devraient présenter une MMN (verbale et non verbale) de plus grande latence et d'amplitude différente de celle retrouvée chez les adultes.

Hypothèse 2 : Sur la base de la théorie du traitement parallèle acoustique-phonétique (Tampas, Harkrider & Hedrick, 2005; Winckler, 1999), nous postulons que la MMN évoquée par les stimuli verbaux suivra un parcours développemental distinct de la MMN évoquée par les stimuli non verbaux. Plus précisément, la MMN en réponse aux stimuli verbaux sera caractérisée par une trajectoire développementale plus lente (c'est-à-dire une latence plus longue et une amplitude plus petite chez les sujets plus jeunes) par rapport à la MMN en réponse aux stimuli non verbaux.

Deuxième étude : Évaluation électrophysiologique auditive et examen de l'attention et du langage chez les enfants prématurés et nés à terme.

L'utilisation du protocole validé lors de l'étude 1 permettra de comparer l'évolution de la MMN chez des enfants nés prématurément et des enfants nés à terme. En effet, l'analyse des réponses corticales aux stimulations verbales et non verbales chez les nourrissons et les jeunes enfants nés prématurément et nés à terme pourrait permettre de clarifier leur neurodéveloppement et identifier plus précocement les enfants à risque de présenter des troubles langagiers ou cognitifs. **Cette deuxième étude vise donc** à identifier des marqueurs électrophysiologiques précoces du développement langagier et cognitif chez les enfants prématurés et mieux établir à partir de quel âge il est possible de détecter ces troubles par 1) la comparaison des PEAs et de la MMN en réponse à des stimuli verbaux et non verbaux chez les enfants de 3, 12 et 36 mois nés prématurément sans lésion cérébrale majeure et les enfants nés à terme; et 2) l'évaluation de la relation entre les PEAs et la MMN et le développement cognitif et langagier.

Hypothèse 1 : Sur la base des résultats de l'étude de Fellman et al. (2004) et Mikkola et al. (2007), nous postulons que, comparativement aux enfants nés à terme, les enfants prématurés présenteront des PEAs et une MMN atypiques (de latence plus longue et/ou d'amplitude réduite) en réponse aux stimuli verbaux et non verbaux, dès l'âge de trois mois.

Hypothèse 2 : Nous postulons que des PEAs et une MMN atypiques chez les enfants nés prématurément seront corrélés avec des résultats plus faibles aux échelles cognitives et langagières du Bayley-III. Plus précisément, les enfants présentant une réponse électrophysiologique atypique lors de la tâche de discrimination verbale devraient obtenir des scores plus faibles à l'échelle langagière du Bayley-III. De même, les enfants présentant une réponse électrophysiologique atypique aux stimuli non verbaux devraient obtenir des résultats plus faibles à l'échelle cognitive du Bayley-III.

3. MÉTHODOLOGIE ET RÉSULTATS

Article 1 : Neurophysiological correlates of auditory and language development : A mismatch negativity study.

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Neurophysiological correlates of auditory and language development: A mismatch negativity study.

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Abstract

During child development, physiological changes occur in the auditory cortex, which are reflected by differences in the electrophysiological signals. This study aimed to examine the age-related changes of the Mismatch Negativity component (MNN) in response to speech and non-speech stimuli in a cross-sectional design. Results revealed distinct patterns of activation according to stimulus type and age. Age-related differences for tone discrimination occurred earlier in children's development than did the discriminative process for speech sounds. Therefore, networks involved in speech processing are still immature in late childhood and may be more vulnerable to physiological changes.

Key words: Development, Neuropsychology, Electroencephalography (EEG), Mismatch Negativity, Auditory Evoked Potentials, Child, Adolescent, Maturation, Language, Attention.

1. Introduction

In recent years, studies of human cognitive development have highlighted the use of high density electrophysiology (EEG) and auditory event-related potentials (AERPs) in infants and children, as they allow to examine complex cognitive processes such as language discrimination and cognitive development without requiring a specific behavioral response or sustained attention from the child (Ceponiene, Rinne, & Näätänen, 2002; Lippé, Martinez-Montes, Arcand & Lassonde, 2009; Picton & Taylor, 2007; Tampas, Harkrider & Hedrick, 2005, Thierry, 2005; Wunderlich, Cone-Wesson & Shepherd, 2006). An effective index of auditory processing has been widely reported by electrophysiological studies using Mismatch Negativity (MMN), an AERP component corresponding to the automatic detection of a change in the acoustic environment that can be measured in infants, children and adults (Alho & Cheour, 1997; Näätänen, 2003; Näätänen, Paavilainen, Rinnes & Ahlo, 2007). Specifically, this method makes it possible to investigate the differences in brain activations in response to the presentation of frequent stimuli interspersed with rare stimuli. The traditional interpretation of the MMN claims that the parameters of a rare stimulus are compared with those of the frequent stimulus kept in auditory memory (Näätänen & Winkler, 1999). Thus, subtracting the cerebral potentials evoked by the presentation of the frequent stimulus from those obtained by the presentation of the rare stimulus often results in a frontocentral negativity of the differential wave usually reaching its maximum peak amplitude 100-250 ms after stimulus presentation. This measure of preattentional processing has been widely used to assess auditory and language development among normally developing children as well as various clinical populations (Cheour, Leppanen & Kraus, 2000; Näätänen, 2003).

1.1. Structural correlates of the Mismatch Negativity (MMN) maturation

The MMN is generated by at least two subcomponents. The main generator of the MMN is located in the supratemporal auditory cortex (stimulus feature specific), and the other is in the frontal cortex (attention specific) (Molholm, Martinez, Ritter, Javitt & Foxe, 2005). However, during childhood the auditory cortex is marked by important maturational changes, which are likely to be reflected in the morphology of the EEG signal. For instance, the cortical layers that form the auditory cortex are still immature at birth (Moore & Linthicium, 2007). By five years of age, the deeper layers (lower III, IV, V and VI) come to maturation and the myelination of the thalamocortical projections into the deeper auditory cortex reach an adult level. Then, the maturation of the superficial cortical layers (upper III and II) takes place, and their connections become fully efficient around the age of 12 years (Kinney, Brody, Kloman & Gilles, 1988; Moore & Guan, 2001). This maturation coincides with the increasing abilities of the child to process complex auditory stimuli (Ponton, Eggermont, Kwong & Don, 2000; Ponton Eggermont, Khosla, Kwong & Don, 2002).

A growing number of studies report maturational changes in the EEG signal as a consequence of the anatomical maturation of the auditory cortex. For instance, Shafer, Morr, Kreuzer & Kurtzberg (2000), found that the MMN latency in response to tone discrimination decreases at a rate of 11 milliseconds by years of age in children from 4 to 10 year olds. These results, consistent with the development of the superficial cortical layer, support a previous study by Korpilahti and Lang (1994) who found a significant negative correlation between MMN latency and age in children aged between 8 and 13 years in a tone discrimination paradigm. In infants and preschool children, the latency of the MMN in response to a large frequency change in sounds is also negatively correlated with age (Morr, Shafer, Kreuzer & Kurtzberg, 2002). However, when a small frequency change was presented to these children, this negativity could not be recorded, indicating that the brain discriminative response is still immature at this age. Together, these findings, occurring in parallel with the early maturation of the deeper layers VI, V and IV and the late maturation of the superficial layers III and II, suggest that ongoing maturational changes in central auditory processing are reflected by changes in the latency of the brain discriminative response (i.e. the MMN).

Previous studies have mainly used non-speech stimuli (simple or complex tones) to investigate the maturation of the MMN response. Very few aimed to investigate the maturation of the cortical discriminative response to speech sounds from early childhood to adulthood. For instance, using speech sounds, Shafer, Yu & Datta (2010) observed a delayed latency of the MMN response in 4 to 5 and 6 to 7 year-olds when compared to that typically obtained in adults. In their samples, children aged 4 to 5 years and some of the older children also showed a positivity in the differential wave that preceded their MMN. The authors also found that the latency of the MMN-like negativity and the amplitude of the positive mismatch response correlated negatively with increasing age. The latter finding could indicate the ongoing maturational process of the discriminative response in younger children. This positivity in the differential wave has also been reported in other studies investigating speech development in infants and school-aged children (Dehaene-Lambertz, 2000; Kushnerenko, Ceponiene, Balan, Fellman & Naatanen, 2002; Maurer, Bucher, Brem & Brandeis, 2003). Nevertheless, findings regarding cortical response to speech stimuli in young children are inconsistent and the developmental trajectories of the MMN in relation to speech discrimination remain poorly understood.

1.3. Parallel acoustic-phonetic theory and MMN development

On another level, it has been suggested that the processing of acoustic and phonetic stimuli may be parallel (Winkler et al., 1999). Specifically, the parallel acoustic-phonetic theory states that sensory (acoustic) and categorical (phonetic) processing of a speech stimulus occurs simultaneously by independent cognitive processes. This theory was supported by the study of Tampas, Harkrider & Hedrick (2005) in which syllable stimuli and matching frequency glides were differently processed in the same group of participants, despite the fact that the acoustic content of each was similar. To our knowledge, only one study aimed to examine the developmental course of the MMN component to speech sounds conjointly with the MMN to non-speech stimuli in a period covering childhood, adolescence and adulthood. Using traditional averaging methods, Bishop, Hardimann & Barry (2011) found an increase in the MMN amplitude with age for both speech and non-speech stimuli. In addition, using single-trial time-frequency analysis of the mismatch responses, they found a greater synchronization of the theta frequency oscillations (4–7 Hz) in adults than in children, which correlated with behavioral discrimination threshold for both speech and non-speech stimuli. However, the authors reported that no statistical comparisons could be made between the differential maturational process of speech and non-speech stimuli, since the speech and non-speech stimulus conditions contrasted on other dimensions than the frequency difference between standard and deviant stimuli. They reported higher acoustic complexity and greater deviant probability for their speech stimuli.

It is therefore of special interest to better distinguish and describe the respective maturation of networks responsible for speech and non-speech stimulus processing since they putatively engage different processes. Moreover, a better understanding of the maturational changes of the mismatch response is necessary to establish reliable comparisons between typical and atypical auditory cortical development. Previous studies failed to describe the differential maturation of speech and non-speech discrimination as indexed by the MMN responses, over a period covering early childhood to adulthood. Thus, the current study aimed to examine the maturational changes of the MMN in response to speech and non-speech stimuli, which may respectively reflect language and attention processing. To address the methodological issue encountered by Bishop et al. (2011) and to allow the comparison between speech and non-speech MMN responses within each age group, a special attention was given to the spectral and temporal composition of both stimuli type, with only the speech recognition parameters (phonetic processing) accounting for the differentiation of the speech versus the non-speech MMN responses.

Based on the findings of Shafer, Yu & Datta (2010) and Bishop, Hardimann & Barry (2011), we hypothesized that young children will demonstrate an MMN of longer latency and reduced amplitude than that found in adults (to speech and to non-speech stimuli). In addition, based on the parallel acoustic-phonetic theory (Tampas, Harkrider & Hedrick, 2005; Winckler, 1999), we hypothesized that the MMN elicited by speech stimuli would follow a distinct maturational course from the MMN elicited by non-speech stimuli. Hence, the mismatch response to speech stimuli will show a longer maturational rate (longer latency and smaller negativity in younger individuals) compared to the mismatch response to non-speech stimuli, since its elicitation requires both the acoustical and categorical representations of the stimuli.

2. Materials and Methods

2.1 Participants

A total of 40 healthy French-speaking participants aged from 3 to 32 years were recruited. Based on previous developmental studies, participants were grouped into three age bands covering different developmental stages: early childhood (3 to 7 years), late childhood (8 to 13 years), and adults (16 years and older). Table 1 shows the demographic characteristics of the sample. Participants or their parents first had to read carefully and then sign a consent form providing detailed information about the experimental procedure. Prior to testing, a screening session was carried out using interviews and parental developmental questionnaires to ensure that all participants were healthy with no history of hearing, speech, language or developmental disorders. In addition, we controlled for normal attentional and executive functioning in our children sample using the Behavior Rating Inventory of Executive Function (BRIEF) and its preschool version for children younger than 5 years (BRIEF-P) (Gioia, Espy, & Isquith, 2003; Gioia, Isquith, Guy, & Kenworthy, 2000). In order to be included in the study, all participants also needed to display on EEG an exogenous stimulus-related response, characterized by a large positivity followed by a negativity (P1-N2 complex in children or the N1-P2 complex in adults), as these components reflect normal auditory processing (Novak, Kurtzberg, Kreuzer & Vaughan 1989). Data from two participants (a 10-year-old girl and one male adult) were withdrawn from the original sample because of excessive movement artifacts during the ERP recordings. Therefore, the subsequent analyses and results included 38 participants.

Insert Table 1 here

2.2 Stimuli

Stimuli consisted of five blocks of speech stimuli and five blocks of non-speech stimuli presented in a counter-balanced order between subjects. Speech stimuli were a frequent syllable /Da/ and a rare syllable /Ba/, recorded from a female speaker using Adobe Audition 3 software (Adobe Systems Incorporated, 2007). Non-Speech stimuli were frequency-synthesized, keeping only the second and third formants of the speech stimuli (Ba: 1578 Hz, 2800 Hz; Da: 1788 Hz, 2932 Hz) using Praat software (Boersma, 2001). All stimuli were presented using a passive auditory oddball paradigm consisting of a series of frequent sounds (85% presentation rate) interspersed with rare ones (15% presentation rate), where any rare stimulus was preceded by at least three frequent stimuli. Stimuli were 170 ms in duration including a 5 ms rise and fall time. They were presented binaurally at 70 dB sound pressure level (SPL) through loudspeakers located at equidistance (30 centimeters) from the participant's head. Each block was made of 400 trials with a stimulus onset asynchrony (time interval between the onsets of 2 consecutive stimuli) of 710 ms, thus keeping the Interstimulus interval at 540 ms. The total duration of each recording session was kept within 1 hour including the set-up of the EEG net and pauses according to individual needs. The stimulus sequences were generated using E-Prime Psychology Software (Psychology Software Tools Inc., Pittsburgh, USA), on a DELL computer located in an adjacent room.

2.3 Procedure

The recording sessions took place in a dark and soundproof Faraday room. Participants were seated in a comfortable chair or on their parent's lap. To divert their attention from the stimuli, a silent movie was presented during recordings. Electrophysiological data were acquired with a high-density recording system using a 128-channel HydroGel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OH, USA) at a sampling rate of 250 Hz, using a band pass filter of 0.1-100H, and a Cz reference. Electrode impedance was kept below 50 kΩ and the data were recorded using NetStation EEG Software (Electrical Geodesics Inc., Eugene, OH, USA) on a Macintosh computer. All participants were monitored through an infrared camera equipped with an integrated speaker and an experimenter located in an adjacent room constantly monitored their alert state.

2.4 Data analysis

The raw data were digitally filtered off-line with a 1-30 Hz bandwidth (24 dB ⁄ octave) and re-referenced to the average of left and right mastoids using the BrainVision Analyzer program (Brain products, Germany). EEG epochs of 600 ms (including 100 ms prestimulus) were averaged after semi-automatic artifact rejection (threshold of ±100 μV), ocular and baseline corrections. No ERP averages were based on less than 70 trials. Table 2 shows the trial retention rates for each stimulus type and age group. Individual MMN responses were computed by subtracting the standard from the deviant waveforms independently for each condition (speech, non-speech). The individual MMN components were defined using an automatic peak amplitude detection in which latencies of the most negative peaks in the difference waves were measured between 100 and 300 ms after stimulus onset. Visual inspection of detected peaks was carried out subsequently by three researchers (N.P., P.V., A.G.) with experience in electrophysiology. An inter-rater agreement of 0.9 was obtained. This procedure was repeated on the data recorded on the four frontocentral electrodes (Afz, Fz, FCz, and Cz), where the largest differences in the EEG response (i.e., MMN) were found when examining the topographical distribution of the MMN responses.

Insert Table 2 here

Statistical analyses were carried out using the SPSS statistics program, version 19.0 (SPSS Inc., Chicago, IL, USA) on the mean amplitudes of the MMN within a 25 ms time window of the MMN previously identified by the automatic and visual peak detection, and the corresponding latencies. Between-group differences were tested for MMN amplitude and latency using a mixed between-within subject analysis of variance (ANOVA) with group as a between-subjects factor (3 to 7 year-olds, 8 to 13 year-olds, adults), and condition (speech, non-speech) and electrode (Afz, Fz, FCz, Cz) as within-subject factors. Greenhouse-Geisser adjustments were performed (corrected p values are reported). Tukey's post-hoc HSD tests were used to identify significant interactions and correction for multiple comparisons was done using the Bonferroni procedure.

3. Results

3.1. Behavioral results

Mean scores on the BRIEF inventory showed that executive functioning for both younger children (mean t-score 43.09; SD 8.58) and older children (mean t-score 41.23; SD

7.45) were within the normal range. Unpaired T-test analysis also showed no significant difference between the two groups (*t* (22) -0.57, *p* = .58).

3.2. Electrophysiological results

For each individual and condition, the presence of the MMN as a negative deflection in the differential curve could reliably be confirmed and an inter-rater agreement was obtained. Table 3 shows the group average for MMN peak latency and amplitude (and standard deviations) at each electrode location and Figure 1 displays individual data recorded at FCz. Group average ERPs to frequent and rare stimuli and to differential waveforms are illustrated in Figures 2 and 3, respectively for speech and non-speech condition. Topographic representations at the peak latencies are represented next to their corresponding waveforms with the amplitude scale adjusted for each group and condition.

Insert Table 3 here

Insert Figures 1, 2, and 3 here

3.3. MMN amplitude to speech and non-speech stimuli

When both conditions were taken together, a significant between-group effect ($F_{2,\ 35}$ = 5.83, P < 0.01) was found on the MMN amplitude. Tukey post-hoc analyses revealed significant differences between adults (-4.52, SD = 0.43 μV) and young children (-2.46, SD = 0.46 μV) (P < 0.01) and between adults and older children (-2.92, SD 0.44 μV) (P < 0.05). A similar comparison between young and older children was not significant (P > 0.05).

A significant main effect for condition was also found for all groups ($F_{1, 35} = 61.89$, $P < 0.01$) with speech stimuli elicited a smaller negativity (- 1.6, SD = 0.25 μV) than did the non-speech stimuli (-5, SD = 0.41 μV). Pair-wise comparisons calculated using the Bonferroni correction showed that this effect was present in all groups ($p < 0.01$). However, the group by condition interaction was not significant ($F_{2, 35} = 2.06$, $P = 0.14$).

A significant condition by electrode interaction ($F_{1.6, 56} = 12.65$, $P < 0.01$) was found on mean MMN amplitude, with a significant main effect for electrode ($F_{1.6, 58.44} = 15.29$, $P < 0.01$). Pair-wise comparisons revealed that the amplitude of the MMN recorded at Cz was significantly smaller than that recorded at the other three electrodes (AFz, Fz, FCz) in response to the non-speech stimuli ($P < 0.05$). In contrast, response to speech stimuli did not differ in amplitude in all four electrodes ($P > 0.05$). The electrode by group ($F_{3.04, 53.12} = 1.79$, $P = 0.16$) interaction was not significant.

3.4. MMN latency to speech and non-speech stimuli

When all groups were taken together, a significant main effect for condition ($F_{1, 35} = 142.34$, $P < 0.001$) was found with the non-speech stimuli eliciting an MMN at an earlier latency (145.57, SD 3.45 ms) than did the speech stimuli (241.52, SD 6.57 ms). Pair-wise comparisons calculated using the Bonferroni correction showed that this effect was present in all groups ($p < 0.01$). A significant between-group effect ($F_{2, 35} = 19.13$, $P < 0.01$) and a significant group by condition interaction ($F_{2, 35} = 4.01$, $P < 0.05$) were also found.

Pair-wise comparisons for the group by condition interaction further showed that when speech stimuli were used, the response recorded in adults (197, SD 11.23 ms) occurred significantly earlier than in younger (271.25, SD 11.69 ms) ($P < 0.01$) and older children (256.31, SD 11.23 ms) ($P < 0.01$), although a similar comparison between younger and older children was not significant ($P > 0.05$). Regarding the non-speech condition, only the younger children group (157.33, SD 6.14 ms) showed a significantly longer latency compared to the adult group (133, SD 5.9 ms) ($P < 0.05$). The older children group (146.39, SD 5.9 ms) did not significantly differ from the younger children or from the adult groups ($P > 0.05$).

Mains effects for electrode ($F_{2.47,\ 90.1} = 2.53$, $P = 0.07$), electrode by group interactions ($F_{5.15,\ 90.1} = 2.13$, $P = 0.07$) or condition by electrode interactions ($F_{2.34,\ 81.97} = 0.81$, $P = 0.46$) computed on the mean MMN latencies were not significant.

4. Discussion

Previous studies have often linked speech MMN responses to language processing in various populations (clinical and typically developing) (Lovio, Naatanen & Kujala, 2010 ; Naatanen et al., 1997). Similarly, other studies investigating attentional processes have used the MMN in response to different tones (simple or complex) to assess pre-attentional processes in children and adults (Escera, Alho, Schröger & Winkler, 2000 ; Kilpelainen, Partanen & Karhu, 1999). An in-depth characterization of the auditory discriminative processes through development is critical in understanding maturation of the central auditory pathways involved in language processing and attentional functions. In the present study, we aimed to investigate the age-related changes in the morphology of the MMN responses to speech and non-speech sounds over different developmental stages. Using a cross-sectional design, we presented speech and non-speech stimuli in a passive oddball paradigm to healthy French-speakers aged from 3 to 32 years old. Physical differences between frequent and rare stimuli were carefully controlled as recommended in Pettigrew et al. (2004) and inter-rater agreement of the MMN peaks was used to assess the mismatch responses. Therefore, mismatch responses could reliably be computed for each stimulus type. Age-related differences in auditory responses were determined by contrasting MMN amplitude and latency at each developmental stage (early childhood, late childhood and adulthood).

4.1. MMN amplitude

Age-related differences in the MMN amplitude were not specific to speech or non-speech stimuli. Our results indicate that non-speech stimuli elicited a greater negativity than did speech stimuli in all age groups. These results suggest that speech and non-speech stimuli are processed differently by the auditory nervous system, indicating that attentional and speech processes are also categorized differently. They also support findings from Tampas, Harkrider & Hedrick (2005) suggesting a categorical representation of speech and non-speech stimuli at the level of another electrophysiological component, the P300 generators. In this study, we show that a categorical representation of speech and non-speech stimuli occurs also at the level of the MMN, an electrophysiological component that is thought to reflect pre-attentional processes (Naatanen, 2007). This was found within each age group. In addition, our results show a greater negativity in response to non speech MMN than to speech MMN found in all groups, suggesting that even though the acoustic content of each was similar, the non speech stimuli were perceptually more salient and processed more easily than the speech stimuli. These results are consistent with previous findings of speech and non-speech sound categorization using auditory ERPs in children and adults (Ceponiene, Alku, Westerfield, Torki, & Townsend, 2005; Ceponienë, Torki, Alku, Koyama, & Townsend, 2008; Ceponiene, Shestakova, Balan & al., 2001; Harkrider & Hedrick, 2005)

When conditions (speech and non-speech) were taken together, adults showed a greater negativity than did the children groups, and the older children showed a greater negativity than did the younger children. Therefore, increase in the negativity of the MMN was found with the increasing age of the subjects, regardless of the stimulus type. These age-related differences are consistent with the increasing auditory discrimination skills in children as reported by previous behavioral and electrophysiological studies (Ceponiene, Rinne & Näätänen, 2002; Ceponiene et al., 2005; Gomes, Molholm, Christodoulou, Ritter, & Cowan, 2000).

4.2. MMN latency

Our results also confirm distinct developmental patterns of cerebral activations according to stimulus type (speech versus non-speech). Both children groups showed a significant delay in their MMN response to speech stimuli compared to adults. In contrast, when non-speech stimuli were presented, only the younger children group showed a significantly delayed MMN compared to adults. The latency of the MMN elicited in the older children group did not significantly differ from that elicited in the adults or in the young children group. This result suggests the ongoing maturation of the MMN response to non-speech sounds in older children, while young children still show a delayed response. Moreover, within-groups differences were found for all groups. Non-speech sounds elicited an MMN at an earlier latency than did speech sounds. Because speech sound analysis is thought to require both acoustic and phonetic processing, according to the parallel acoustic-phonetic theory, a more complex categorization occurs. The latter requires additional cognitive resources whereas non-speech sounds require only an acoustic categorization (Winkler et al., 1999). This could explain the longer latency of the MMN in response to speech sounds in comparison to the MMN in response to non-speech sounds in all groups. This theory could also explain the slower maturation of the MMN for speech sounds.

These findings support previous work showing a delayed response to speech (Dehaene-Lambertz, 2000; Kushnerenko, Ceponiene, Balan, Fellman & Naatanen, 2002; Maurer, Bucher, Brem, & Brandeis, 2003) and non-speech (Lippé et al., 2009; Morr et al., 2002; Shafer et al., 2000; Wunderlich, Cone-Wesson, & Shepherd, 2006) stimuli in children when compared to that found in adults. These results also support studies suggesting that a shift in latencies of the discriminative responses could be used as a reliable electrophysiological marker of the cortical auditory maturation using either speech of non-speech stimuli (Bishop, Hardimann and Barry, 2011; Korpilahti and Lang, 1994; Shafer, Yu, & Datta, 2010; Shafer et al., 2000).

4.3. Differential maturation of speech and non-speech MMN responses

The differential maturation of speech versus non-speech discriminative responses found in this study is consistent with a parallel processing for acoustic and phonetic sounds in children or in adults. According to this theory, speech sounds are processed both acoustically and phonetically whereas non-speech sounds are processed only acoustically. Supporting evidence for this theory is still sparse since very few studies have investigated the differential response to speech and non-speech stimuli in light of different processing systems. For instance, Tampas, Harkrider & Hedrick (2005) showed an MMN response to non-speech stimuli, but not to matched-syllable stimuli, even though the acoustic content of both types of stimuli was equivalent. Acoustic differences between the two within-category speech stimuli were not detected by the MMN, supporting the categorical representation of the MMN to speech stimuli rather than a purely acoustic discrimination process. Differential acoustic-phonetic processes in adults and children were also found in a study by Ceponiene & al. (2005), where tone stimuli evoked larger earlier ERPs (N1 and P2) while syllable stimuli elicited larger later ERPs (N2 in adults and N4 in children). Furthermore, categorization differences have even been found in infants as young as 4-month-old where a distinct topography within the temporal lobe was found in response to syllables compared to tones contrasts (Dehaene-Lambertz, 2000), suggesting distinct neural networks for the MMN in response to these two types of stimuli. The latter results support the acoustic-phonetic theory previously reported and further suggests an anatomical basis to acoustic and phonetic parallel processing within the auditory cortex.

Taken as a whole, these differences in maturation of cortical responses to speech and non-speech stimuli might reflect the central auditory development involved in attention and language processing. This maturational course for tone discrimination occurs earlier in children’s life than does the discriminative process for speech sounds, the networks involved in speech processing still being immature in late childhood and requiring both the acoustical and categorical representations of the stimuli.

4.4. Electrophysiological markers of the cortical auditory development

As pointed out earlier, the auditory cortex is marked by important maturational changes during childhood (Ponton, Eggermont, Kwong, & Don, 2000; Ponton, Eggermont, Khosla, Kwong, & Don, 2002). The structural maturation of the deeper and superficial auditory cortical layer is likely to account for the age-related differences in latencies and amplitude of the discriminative response to speech and non-speech stimuli in this study, especially in the younger subjects. Another possible explanation of these results may lie in electrophysiological alterations during adolescence that coincide with changes in gray and white matter volume (Segalowitz, Santesso & Jetha, 2010; Moore, & Linthicum, 2007; Paus, 2005). An important neural reorganization occurring during adolescence is synaptic pruning, which refers to the elimination of unnecessary synapses and associated neuropils (Casey, Jones & Todd, 2008; Paus, 2005; Segalowitz, Santesso & Jena, 2010). This reorganization coincides with a general decline of EEG power of all bands with age and a more efficient information processing (Bishop et al., 2011). This could also account for the better categorization of non-speech sounds in our older children groups compared to the younger ones. Moreover, the delayed response for speech categorization found in both groups of children compared to adults could also be consistent with synaptic reorganization occurring latter in the anatomical networks specific to phonetic in contrast to the networks specific to acoustic processing suggested by Dehaene-Lambertz (2000). Therefore, it could be possible that synaptic reorganization influences those networks at different moments in the course of the child development. Nevertheless, the impact of synaptic pruning in the adolescent brain on language and attentional functions remains poorly understood. It will be of special interest for future works to assess the specific relationship between structural and functional maturation and changes in electrophysiological potentials recorded during this period.

4.5. Study limitations

Conclusions about age-related differences reported in this study are based on a cross-sectional design. Longitudinal studies of human development could provide more reliable information about the specific maturation of the speech and non-speech cortical responses. In addition, we focused our analyses on age-related changes in the MMNs responses. In a current study, we are interested in further investigating changes and cerebral sources of the ERP components that are elicited by both the standard and the deviant stimulus since these peaks could provide valuable information about the sensory development and auditory obligatory responses.

Conclusions

This study demonstrated age-related differences in the amplitude and latency of the MMN responses and provided evidence of speech non-speech differences. Overall, our results can serve as a basis to investigate language and attentional development among normally developing children and special populations. Further investigations could clarify the relationship between structural cortical maturation and changes in electrophysiological potentials.

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Tables and Figures

Table 1. Mean age (standard deviation in parentheses), total number of subjects, males and mean T-score per group

Group	*N*	*Mean Age (SD)*	*Males*	*BRIEF Scores (SD)*
Children 3–7	12	5.21 (1.75)	5	43.09 (8.58)
Children 8–13	14	11.33 (1.74)	5	41.23 (7.45)
Adults (16–32)	14	23.69 (3.83)	8	n/a

Table 2. Mean (standard deviation in parentheses) trials retention for each stimuli and conditions by group

	Speech Stimuli		*Non-Speech Stimuli*	
Group	*Deviant (SD)*	*Standard (SD)*	*Deviant (SD)*	*Standard (SD)*
Children 3–7 years	131.43 (25.39)	749.57 (99.47)	144 (32.3)	770.43 (69.87)
Children 8–13 years	126.5 (22.29)	673.5 (157.8)	129.42 (18)	723.5 (99.29)
Adults	110.08 (25.97)	599 (155.65)	102.42 (24.18)	525.75 (146.17)

Table 3. Mean (standard deviation in parentheses) peak amplitude and latency of the difference wave by groups at Afz, Fz, FCz and Cz electrodes site

		MMN Speech			MMN Non Speech		
		Children 3-7 y	Children 8-13 y	Adults	Children 3-7 y	Children 8-13 y	Adults
AFz	Latency (SD) msec	272.33 (53.49)	255.69 (44.85)	193.85 (14.84)	157 (31.04)	147.38 (19.92)	132 (9.38)
	Amplitude (SD) µV	-0.84 (1.58)	-0.74 (1.80)	-3.39 (1.50)	-4.12 (2.53)	-5.35 (3.02)	-6.11 (2.44)
Fz	Latency (SD) msec	271.67 (53.41)	256.31 (45.24)	196.92 (17.97)	157.67 (30.68)	147.08 (20.34)	133.54 (8.57)
	Amplitude (SD) µV	-0.67 (1.54)	-0.64 (1.71)	-3.36 (1.51)	-4.29 (2.36)	-5.59 (3.26)	-6.13 (2.40)
FCz	Latency (SD) msec	270 (52.70)	255.69 (44.08)	197.54 (18)	156.33 (30)	145.23 (19.55)	133.23 (8.70)
	Amplitude (SD) µV	-0.89 (1.30)	-0.62 (1.72)	-3.36 (1.61)	-4.2 (2.10)	-5.40 (3.35)	-5.88 (2.45)
Cz	Latency (SD) msec	271 (53.34)	257.54 (40.81)	199.69 (17.70)	158.33 (31.05)	145.85 (19.30)	133.23 (11.59)
	Amplitude (SD) µV	-1.1 (1.41)	-0.59 (1.52)	-3.05 (1.56)	-3.59 (1.74)	-4.44 (2.51)	-4.89 (2.09)

Figure Legend

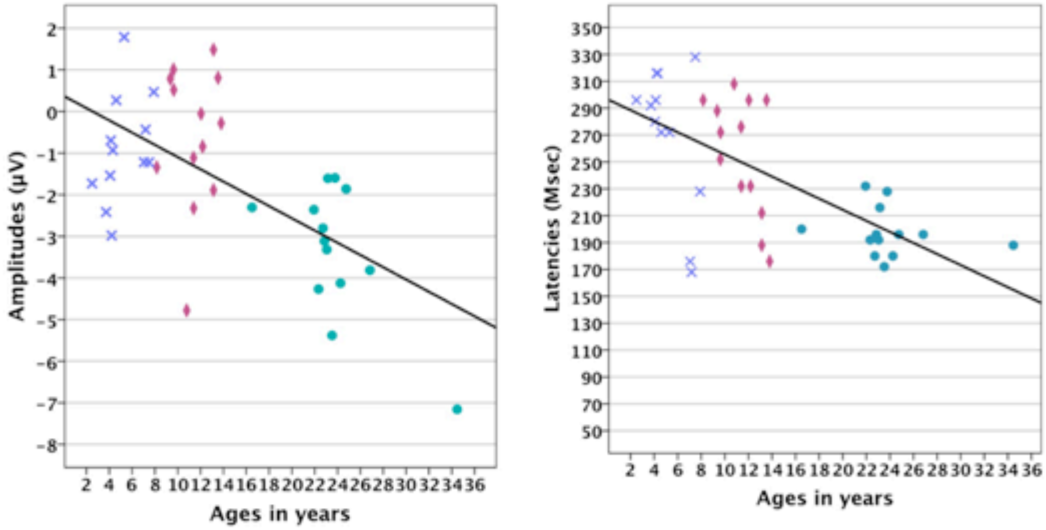
Figure 1. Individuals MMN latencies and amplitudes (at FCz) in response to a) speech and b) non-speech stimuli.

Figure 2. Differential waveforms (black) and grand average ERPs elicited by frequent (blue) and deviant (red) speech stimuli recorded at AFz, Fz, FCz and Cz electrode locations for each group. Topographic representation of the MMN responses are presented for each group next to their corresponding waveforms.

Figure 3. Differential waveforms (black) and grand average ERPs elicited by frequent (blue) and deviant (red) non-speech stimuli recorded at AFz, Fz, FCz and Cz electrode locations for each group. Topographic representation of the MMN responses are presented for each group next to their corresponding waveforms**.**

Figure 1. Individuals MMN latencies and amplitudes at FCz

a) Speech stimuli



b) Non-speech stimuli

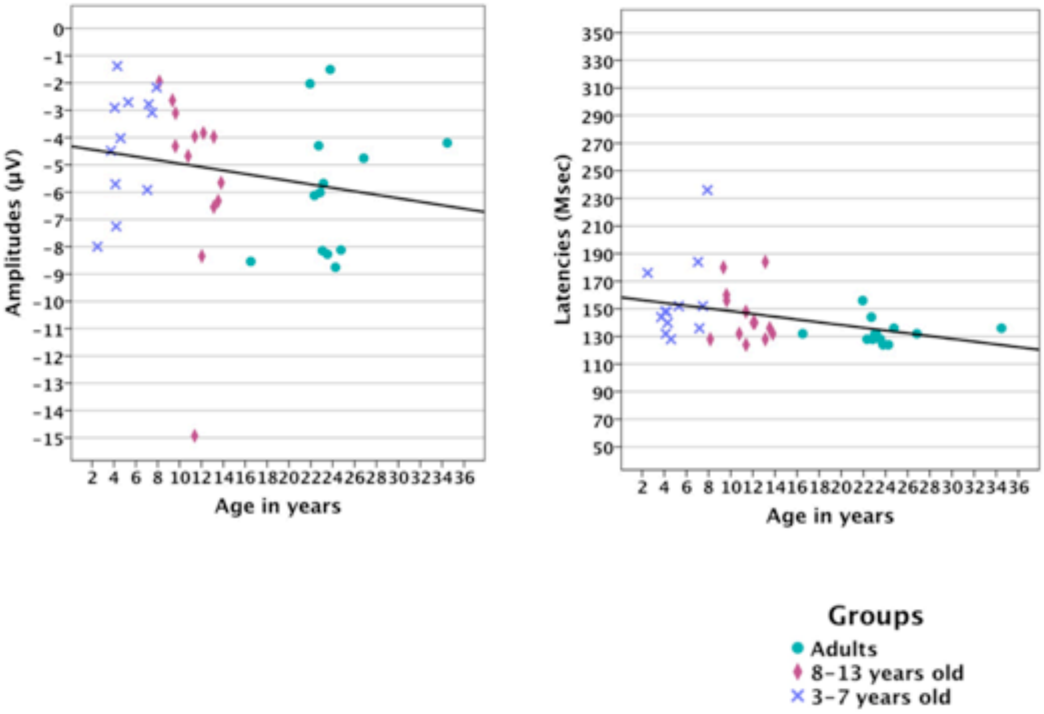


Figure 2. Differential waveforms and grand average ERPs to speech stimuli

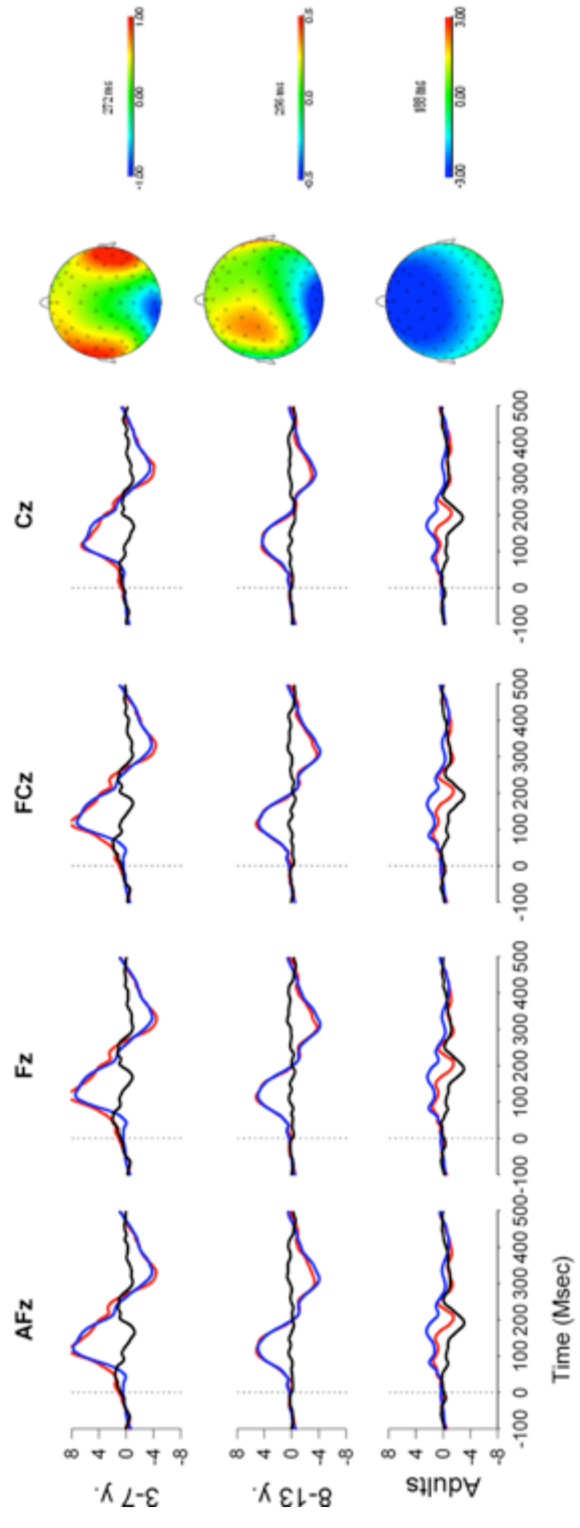
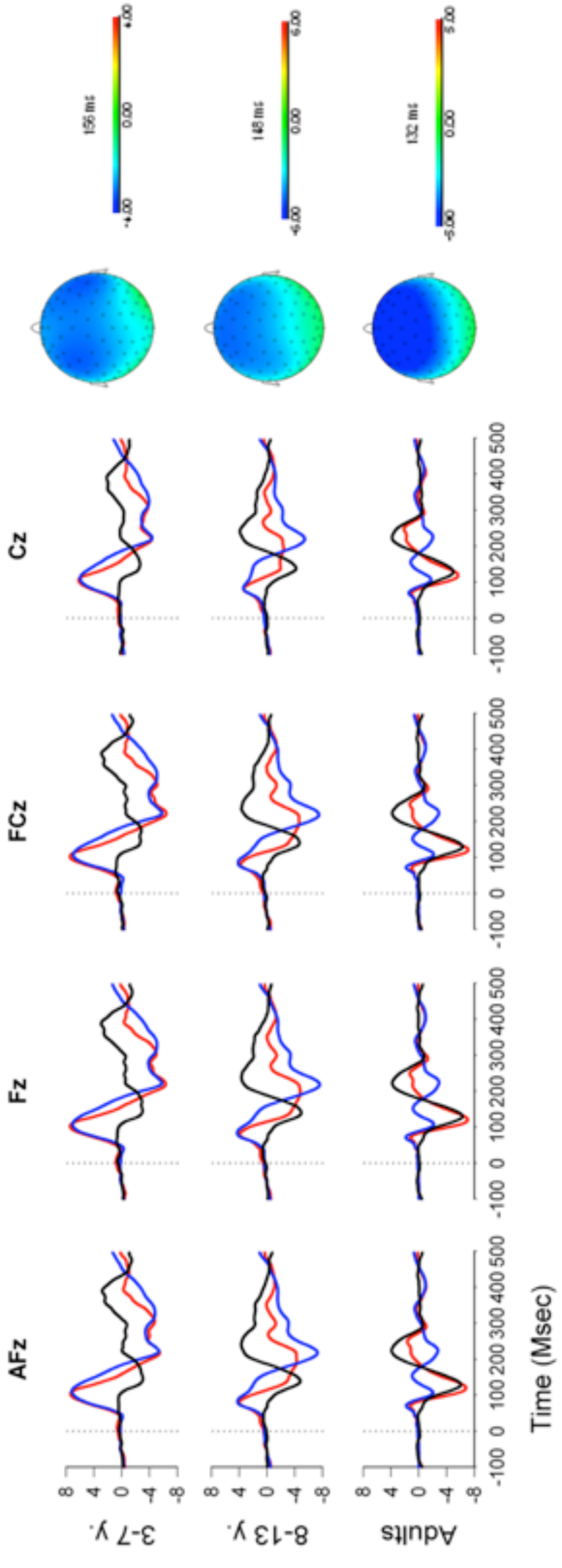


Figure 3. Differential waveforms and grand average ERPs to non-speech stimuli



Article 2 : Early electrophysiological markers of atypical language processing in prematurely born infants.

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Early electrophysiological markers of atypical language processing in prematurely born infants.

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Abstract

Because nervous system development may be affected by prematurity, many prematurely born children present language or cognitive disorders at school age. The goal of this study is to investigate whether these impairments can be identified early in life using electrophysiological auditory event-related potentials (AERPs) and mismatch negativity (MMN). Brain responses to speech and non-speech stimuli were assessed in prematurely born children to identify early electrophysiological markers of language and cognitive impairments. Participants were 74 children (41 full-term, 33 preterm) aged 3, 12, and 36 months. Pre-attentional auditory responses (MMN and AERPs) were assessed using an oddball paradigm, with speech and non-speech stimuli presented in counterbalanced order between participants. Language and cognitive development were assessed using the Bayley Scale of Infant Development, Third Edition (BSID-III). Results show that preterms as young as 3 months old had delayed MMN response to speech stimuli compared to full-terms. A significant negative correlation was also found between MMN latency to speech sounds and the BSID-III expressive language subscale. However, no significant differences between full-terms and preterms were found for the MMN to non-speech stimuli, suggesting preserved pre-attentional auditory discrimination abilities in these children. Identification of early electrophysiological markers for delayed language development could facilitate timely interventions.

Key words: Prematurity; Children; Electroencephalography (EEG); Language development; Mismatch negativity (MMN).

1. Introduction

1.1. Neurodevelopmental and cognitive sequelae of premature birth

According to the World Health Organization, 15 million infants are born before term every year. In 2010, the rate of preterm birth (less than 37 gestational weeks) in developed countries was of 8.6% (March of Dimes, PMNCH, Save the Children, 2012). It has been clearly shown that premature birth substantially impacts child development. Even in the absence of visible cerebral damage, cognitive and language impairments are among the most frequently reported negative outcomes in prematurely born children (Barre, Morgan, Doyle, & Anderson, 2011; Cusson, 2003; Guarini et al., 2009; Jansson-Verkasalo et al., 2003; Rizzotto Schirmer, Wetters Portuguez, & Lahorgue Nunes, 2006; Saigal & Doyle, 2008; Sansavini et al., 2006; Sayeur, Mckerral, & Lassonde, 2011). Preterm children are at much higher risk for language impairment than their full-term peers: about one out of three shows significant delay in language acquisition at age 3 years (Sansavini et al., 2010). Delayed development of expressive and receptive language in preschool children has been shown to negatively impact interpersonal skills, social functioning, and academic achievement (Durkin & Conti-Ramsden, 2007; Johnson, Wolke, Hennessy, & Marlow, 2011). Furthermore, cognitive and academic problems in preschool- and school-aged preterm children (Baron, Erickson, Ahronovich, Baker, & Litman, 2011; Gartstein, Crawford, & Robertson, 2011) have been shown to persist in adolescence and adulthood (Anderson, Doyle, & Victorian Infant Collaborative Study Group, 2003; Hack et al., 2002; Lefebvre, Mazurier, & Tessier, 2005; Northam et al., 2012; Saigal, Hoult, Streiner, Stoskopf, & Rosenbaum, 2000; Saroj Saigal & Doyle, 2008; Skranes et al., 2007; Wolke, Samara, Bracewell, Marlow, & EPICure Study Group, 2008). Prematurity is a growing socioeconomic and educational concern. Early intervention therefore appears to be critical in order to limit the negative consequences of prematurity for cognitive, academic, and social functioning.

1.2. Electrophysiological indicators of auditory and speech processing in infants.

Recently, high-density electroencephalography (EEG) and auditory event-related potentials (AERPs) have been increasingly used to study cognitive development in infants and young children (Thierry, 2005; Picton & Taylor, 2007). AERPs are produced by neural phase synchronization and increases in spectral power following presentation of an auditory stimulus, allowing to measure the timing and strength of the individual cortical responses (Fellman & Huotilainen, 2006; Lippé, Martinez-Montes, Arcand, & Lassonde, 2009). They are used to examine complex cognitive processes such as pre-attentional auditory processes and language discrimination without requiring a specific response or sustained attention from the child (Tampas et al., 2005; Picton & Taylor, 2007). Although, morphology of the AERPs waveform is known to be different in very young children compared to adults due to the immaturity of the auditory cortex, the ability of the infant's brain to discriminate auditory information is thought to be present from the second trimester of foetal life (Moore & Linthicum, 2007). Moreover, the main positive and negative peaks of the infant waveform (P150, N250, P350, and N450) are already identifiable in the first days of life (Kushnerenko, Ceponiene, Balan, Fellman, Huotilainen, et al., 2002), suggesting that the generators of the infantile AERP components are already functional at birth. As a function of age, AERPs waveform gradually increases in complexity, the latencies of the AERP components decreases and the amplitudes increase (Marie Cheour, Leppanen, & Kraus, 2000; Moore & Linthicum Jr, 2007; Wunderlich, Cone-Wesson, & Shepherd, 2006).

The mismatch response (MMN) can be elicited very early in infancy and has been used to study speech sound and auditory discrimination in neonates and infants in the first months of life (Marie Cheour et al., 1998, 2002; Martynova, Kirjavainen, & Cheour, 2003). Specifically, mismatch negativity (MMN), which provides an indication of pre-attentional auditory discrimination ability, is a negative differential wave obtained by subtracting brain responses elicited by frequent (or standard) auditory stimuli from those evoked by rare (or deviant) ones (Cheour, Leppanen, & Kraus, 2000; Näätänen, Paavilainen, Rinne, & Alho, 2007; Näätänen & Winkler, 1999; Näätänen, 2003; Trainor, Samuel, Desjardins, & Sonnadara, 2001). In adults, this negativity generally peaks in the fronto-central electrodes at approximately 100–250 ms after stimulus presentation. However, in very young children and infants, a positive rather than a negative mismatch at 100–300 ms latency has been reported, suggesting the presence of a pre-attentional discrimination process, albeit immature (Kushnerenko, Ceponiene, Balan, Fellman, Huotilainen, et al., 2002; Shafer, Yu, & Datta, 2010).

1.3. Speech versus non-speech auditory stimuli

Atypical AERPs and MMN to auditory speech and non-speech stimuli have been documented in prematurely born children, suggesting alterations in cortical processing of auditory information (Bisiacchi, Mento, & Suppiej, 2009; Lavoie, Robaey, Stauder, Glorieux, & Lefebvre, 1997; Léveillé, Robaey, Ge, & Lefebvre, 2002). For instance, using non-speech harmonic tones, it was shown that AERPs obtained in preterm children differed from those measured in full-term children during the first year of life (Fellman et al., 2004). Specifically, compared to full-term children, preterm children born with low birth weight showed AERPs of lower amplitude and no significant MMN, whereas preterm children with appropriate birth weight for gestational age showed a positive rather than a negative mismatch. Moreover, absent or positive MMN and smaller AERP responses measured at age 12 months were positively correlated with a lower cognitive functioning at age 2 years, corrected for age (Fellman et al., 2004). In a longitudinal follow up, this atypical MMN and P1 responses to non-speech stimuli were also present at age 5 years (Mikkola et al., 2007). In addition to various cognitive impairments observed in these children (lower attention, sensory- and visuo-motor, language and memory scores), the lower amplitude of the AERPs and the MMN components correlated positively with lower language results, suggesting that atypical AERPs can be used as indicators of lower language functioning in infants and children.

To better understand the relationship between language development and auditory processing in preterm children, object naming ability and electrophysiological responses to auditory discrimination of syllables were examined in 4-year-old preterm children (Jansson-Verkasalo et al., 2003). Results showed that preterm children who had specific problems naming objects also had lower MMN amplitudes on a syllable discrimination task. However, no electrophysiological abnormalities were found in children with normal objects naming ability (Jansson-Verkasalo et al., 2003). In addition, lower MMN amplitudes in response to speech stimuli subsequently correlated with objects naming skills at age 6 years, demonstrating the temporal stability and predictive value of the MMN response (Jansson-Verkasalo et al., 2004). Atypical or longer AERPs latencies have also been reported in prematurely born infants or in children at risk for specific language impairment (Cheour et al., 1998; Friedrich, Weber, & Friederici, 2004; Pasman, Rotteveel, de Graaf, Maassen, & Visco, 1996; Ribeiro & Carvallo, 2008). For instance, Jansson-Verkasalo et al. (2010) found a significantly longer MMN latency in very prematurely born infants at the age of six months (corrected age) compared to same age full-terms in a native phoneme discrimination task, suggesting slower language discrimination in these infants. Although previous studies mainly reported amplitude differences in AERP and MMN components between preterm and full-term children, latency analysis could also provide valuable information about children's language discrimination processes and pre-attentional development.

Nevertheless, it remains unclear which types of stimuli (speech, non-speech, or both) could better indicate lower cognitive and language development in these children. Previous studies failed to describe the differential maturation of speech and non-speech responses in preterm and full-term born children and their relationship with cognitive and language development. Analyzing cortical responses to speech and non-speech sounds could thus help to clarify cognitive and language development in premature children and early identify impairments incurred following premature birth. The current study therefore aims to identify early electrophysiological markers of language and cognitive impairments in preterm children and to better establish from what age it is possible to detect these impairments by 1) comparing AERP responses to speech and non-speech stimuli in 3-, 12-, and 36-month-old children born prematurely without neonatal brain injury and in children born at term; and 2) assessing the relationship between AERPs and cognitive and language development. Based on the findings by Fellman et al. (2004) and Mikkola et al. (2007), we postulate that preterm children as young as 3-month-old will show atypical AERPs (longer latency and/or reduced amplitude of the P150, N250 and MMN components) in response to speech and non-speech stimuli. We also hypothesize that AERP responses in both groups will be correlated with neurodevelopment outcomes on the BSID-III.

2. Methods

2.1. Participants

The study participants were 74 children aged 3, 12, and 36 months and born prematurely or at term. These age groups were selected based on language developmental milestones in the first years of life and to investigate from what age it is possible to identify early AERP abnormalities and their relationship with neurodevelopmental outcomes on the BSID-III (Bates, Thal, Finlay, & Clancy, 1992; Gervain & Mehler, 2010). Specifically, the ages of 3 and 12 months were selected because it is possible to start measuring language and cognitive development using standardized tools such as the BSID-III at those ages as opposed to younger ones. Moreover, the age of 36 months was chosen as it becomes possible to objectively assess language delays and impairement at that age. Corrected age was used for 3- and 12-month-old preterm infants, as recommended by the American Academy of Pediatrics, calculated by subtracting the number of weeks born before 40 gestation weeks (based on the mother's last menstrual period and ultrasound examinations) from the chronological age (Engle, 2004; Wilson-Ching, Pasco, Doyle, & Anderson, 2014). Preterm infants were born from 22 to 34 postconceptional weeks, had no cranial ultrasound abnormalities (grade III or IV intraventricular hemorrhage, periventricular leukomalacia), and had normal hearing-screening test results in a routine perinatal follow-up. Full-term children were born at from 37 to 41 gestational weeks and had birth weight > 2,500g and Apgar score > 7 at 1 min. To be included in the control group, full-term infants had unremarkable maternal and perinatal history, no major infectious syndromes during gestation, and no congenital, neurological, or chromosomal anomalies. All children were born to French-speaking parents, and French was spoken at home and at the day-care facility. Data from two 3-month-old infants (one preterm girl and one full-term boy) were excluded from the analysis due to excessive movements during recording or abnormal EEG signals. Informed written parental consent was obtained for each participant, and the study was approved by the Sainte-Justine Hospital's Research Ethics Committee. Table 1 presents the sociodemographic and clinical characteristics of the sample.

Insert table 1 here.

2.2. Neurodevelopmental assessment

All children underwent a neurodevelopmental assessment using the language and cognitive subscales of the BSID-III (Bayley, 2006). Language scale items assess receptive and expressive communication skills such as responding to names and words, following directions, understanding tense, babbling, vowel-consonant or syllable combinations, word approximation, objects, picture naming, and story telling. The cognitive scale assesses skills such as precursor of attention and anticipatory behavior, exploration of environment, simple problem solving, numeracy, and relational and imaginary play. The BSID-III has been widely used in developmental and longitudinal studies in typically developing children and in children with various developmental disabilities (Luttikhuizen dos Santos, de Kieviet, Königs, van Elburg, & Oosterlaan, 2013; Milne, Mcdonald, & Comino, 2012). It is designed to identify areas of relative impairment or delay in children 1 to 42 months old. Scores are age-adjusted and follow a normal distribution, with a mean of 100 and standard deviation of 15 (mean scaled score 10, standard deviation ± 3). The BSID-III was administered during the AERP recording session or the following week if the child was feeling too tired after the EEG testing. A graduate student in clinical neuropsychology (NP) with training and experience in administrating the BSID-III performed the neurodevelopmental assessment, and interscorer agreement was obtained with another trained examiner.

2.3. Stimuli and AERP recording

All children were tested while sitting on their parent's lap and watching a silent cartoon video in a soundproof and electromagnetically shielded Faraday room at Sainte-Justine Hospital. The stimulus parameters (speech, non-speech) and electrophysiological recording procedures used in this experiment are described in detail in elsewhere (Paquette et al., 2013). Briefly, four blocks of 200 speech stimuli and four blocks of 200 non-speech stimuli (all 170 ms in duration; 540 ms interstimulus interval) were presented using an auditory oddball paradigm in counterbalanced order across participants. Speech stimuli were the syllables /Da/ (frequent or standard, stimulus; 85% presentation rate) and /Ba/ (rare or deviant, stimulus; 15% presentation rate). Non-speech stimuli were synthesized using the second and third formants of the speech stimuli. As described elsewhere (Paquette et al., 2013), EEG data were acquired using a 128-channel HydroGel Geodesic Sensor Net on a Macintosh computer equipped with NetStation EEG Software (Electrical Geodesics Inc., Eugene, OH, USA). The acquisition used a sampling rate of 250 Hz, a band pass filter of 0.1–100 Hz, and a Cz reference.

2.4. EEG Data analysis

EEG data were analyzed using BrainVision Analyzer software version 2 (Brain Products, Germany). Preprocessing included offline digital filtering of the 1–30 Hz bandwidth (24 dB/octave) and re-referencing to an average left and right mastoid. Ocular correction was performed using the Gratton and Coles algorithm in BrainVision Analyzer (G. Gratton, Coles, & Donchin, 1983). Data were then segmented into 700-ms epochs (including 100 ms baseline: -100–600 ms) and averaged independently for each stimulus type after artifact rejection (amplitude ±150 μV) and baseline corrections (-100–0 ms). All AERP averages were based on at least 75 trials.

Automatic peak amplitude detection was used to identify local maximum peaks corresponding to AERP and MMN components independently for each condition (speech, non-speech), as recommended by Luck (2005). Individual P150 components were defined as the most positive peak within 50–250 ms after stimulus onset in the waveform obtained for deviant stimuli, and N250 responses as the most negative peak within 150–350 ms. Mismatch responses were defined as the maximum positive or negative peak in the difference wave within 100-300 ms. The polarity of the mismatch responses (positive or negative) was determined according to the local maximal difference between the deviant and the frequent waveforms and a visual validation of the MMN polarity was performed by superimposing the MMN, the deviant, and the frequent waveforms. This procedure was repeated for data recorded at the four frontocentral electrodes: AFz, Fz, FCz, and Cz (electrodes E16, E11, E6 and E129 on the EGI Sensor Net), where the largest differences in MMN responses were observed in the topographical distribution of responses. This procedure has been used previously in studies on children's auditory development (Gomot, Giard, Roux, Barthélémy, & Bruneau, 2000; Mikkola et al., 2007; Paquette et al., 2013; Ponton, Eggermont, Kwong, & Don, 2000). Detected peaks were visually inspected and reviewed by two of the authors (NP, PV) with expertise in electrophysiology (an inter-rater agreement of 0.9 was obtained). Peak amplitudes (3 time-points before and after each peak, corresponding to the mean amplitude in a 28 msec time-window centered on the peak) and corresponding latencies for the P150, N250, and MMN responses were then exported to SPSS software for further statistical analyses.

2.5. Statistical analysis

Statistical analyses were carried out using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). First, between-group (preterm, full-term) sociodemographic differences were assessed using parametric multivariate analyses of variance (MANOVA) on maternal age at childbirth and maternal education years. Non-parametric Mann-Whitney U tests were performed on the categorical variables annual familial income and parental marital status. Mixed between-within subject, repeated-measures analyses of variance (ANOVAs) were performed on the latencies and amplitudes for the P150, N250, and MMN components to test for significant variation across age (3, 12, 36 months), group (preterm, full-term), electrode (AFz, Fz, FCz, Cz) and stimulus condition (speech, non-speech). Neurodevelopmental data were tested using multivariate analysis of variance (MANOVA) with individual standardized scaled scores (cognitive, receptive language, and expressive language subscale indices) as dependent variables and age (3, 12, 36 months) and group (preterm, full-term) as between-subject factors. Greenhouse-Geisser adjustment for violation of sphericity was performed when necessary, and corrections for multiple comparisons were made using Bonferroni's procedure (corrected *p* values reported). Tukey's post-hoc HSD tests were used to identify significant interactions, with significance set at $p < 0.05$.

In addition, to assess the relationship between AERPs to speech and non-speech stimuli and early language and cognitive development, correlations between EEG parameters recorded at the FCz electrode and neurodevelopmental results were tested using Pearson's correlation coefficients. This electrode was chosen based on previous AERP and MMN studies in children and adults (Lippé, Martinez-Montes, Arcand, & Lassonde, 2009; Pakarinen, Rinne, Takegata, & Na, 2004). Moreover, visual inspection of the topographical distributions revealed that this electrode site yielded the most consistent AERP responses across groups and conditions. Gestational age (weeks) and birth weight (grams) were also included in the correlations. In order to minimize the likelihood of Type I errors when computing multiple correlations without increasing the risk of Type II errors, the alpha significance level was adjusted to $p < 0.01$, and 0.05 probability was considered a trend (Feise, 2002; Proschan & Waclawiw, 2000).

3. Results

3.1. Sociodemographic and clinical characteristics of the children

MANOVAs calculated on maternal age at birth and maternal education revealed no significant differences between preterm and full-term children ($F_{(1, 69)} = 2.12$, $p = .150$; $F_{(1, 69)} = 2.64$, $p = .109$, respectively). Moreover, the nonparametric Mann-Whitney U test revealed that the two groups were equivalent in terms of familial income and parental marital status ($U = 541.50$, $p = 0.377$; $U = 536.50$, $p = 0.248$, respectively).

3.2. Neurodevelopmental results

Neurodevelopmental results showed performance within international standards for all groups (Table 1). However, the preterm groups scored significantly lower than full-term children on the cognitive ($F_{(1,\ 65)} = 5.06$, $p = .028$) (preterms: 10.19 ± 0.3; full-terms: 11.08 ± 0.26) and expressive language scales ($F_{(1,\ 65)} = 8.23$, $p = .006$) (preterms: 8.63 ± 0.35; full-terms: 9.97 ± 0.31). Main effects of age and the age-by-group interaction on the cognitive scale were not significant. However, significant main effects of age were found on the expressive ($F_{(2,\ 65)} = 4.45$, $p = .015$) and receptive language scales ($F_{(2,\ 65)} = 18.15$, $p < 0.001$). Specifically, on the expressive language scale, 36-month-olds performed significantly better than 3- and 12-month-olds ($p = .026$ and $p = .044$, respectively) (3-month-olds: 8.77 ± 0.38; 12-month-olds: 8.83 ± 0.41; 36-month-olds: 10.3 ± 0.42). On the receptive language scale, 12-month-olds scored significantly lower than 3- and 36-month-olds ($p = .011$ and $p < .001$, respectively), and 3-month-olds scored significantly lower than 36-month-olds ($p = .006$) (3-month-olds: 10.19 ± 0.43; 12-month-olds 8.30 ± 0.46; 36 months: 12. 27 ± 0.48). Age-by-group interactions for both receptive and expressive language results were not significant.

3.3. Electrophysiological results

In preterm and full-term children of all ages, standard and deviant stimuli elicited an identifiable P150-N250 complex in both speech and non-speech conditions (Figure 1 and Figure 2, grey and black solid lines). Similarly, the deviant-standard difference waveforms showed identifiable mismatch peaks in all children and in both conditions (Figure 1 and Figure 2, black dotted lines). Mean amplitude and latency of the P150, N250, and MMN components recorded at each electrode (AFz, Fz, FCz, Cz) for each group and age are available in supplementary material (supplementary Table 1 for the speech condition and supplementary Table 2 for the non-speech condition).

Insert Figure 1 about here.

Insert Figure 2 about here.

Trial retention values (mean and standard deviation) on the deviant and standard stimulus are displayed in Table 2 and 3 respectively for each group, age, and condition. An age-by-group ANOVA performed on the deviant and standard average trials retention for both conditions revealed that each group and age were equivalent in term of trial retention. Specifically, on the deviant trials retention, no main effect for age ($F_{(2,66)}= .39$, $p = .679$), group ($F_{(1,66)}= 1.07$, $p = .315$), or group-by-age interaction ($F_{(2,66)} = .20$, $p = .816$) were found using speech stimuli. Likewise, using non-speech stimuli, main effect of age ($F_{(2,65)}= .06$, $p = .940$), group ($F_{(1,65)}= .30$, $p = .587$), and group-by-age interaction ($F_{(2,65)} = .96$, $p = .388$) were not significant. On the standard trials retention, no main effect for age ($F_{(2,66)}= .30$, $p = .745$), group ($F_{(1,66)}= 1.18$, $p = .281$), or group-by-age interaction ($F_{(2,66)} = .18$, $p = .838$) were found using speech stimuli. Using non-speech stimuli, main effect of age ($F_{(2,65)}= .21$, $p = .815$), group ($F_{(1,65)}= .06$, $p = .804$), and group-by-age interaction ($F_{(2,65)} = .37$, $p = .693$) were also not significant.

Insert Table 2 about here.

Insert Table 3 about here.

As expected upon visual inspection of the standard waveforms for each group and age, between-group differences on standard P150 and N250 components were not significant, although age-related differences were found on the latency of the standard P150, and the lantency and amplitude of the standard N250. In the interest of clarity, only AERPs (P150 and N250 components) recorded on the deviant waveform are reported here; detailed results from the standard AERPs can be found in supplementary appendix A.

3.3.1 MMN latency

The latency analysis revealed a main effect of group ($F_{(1,\ 65)} = 5.18$, $p = .026$), along with a significant condition-by-group interaction ($F_{(1,\ 65)} = 6.48$, $p = .013$), whereby preterm infants of all ages responded later than full-terms only when speech stimuli were used (preterms: 219.88 ±4.44; full-terms: 190.92 ±4.00 ms). A main effect of age was also found ($F_{(2,\ 65)} = 47.51$, $p < .001$): 3-month-old infants showed longer latency than 12- and 36-month-olds (3-month-olds: 239.31 ± 4.90; 12-month-olds: 185.32 ± 5.15; 36-month-olds: 174.42 ± 5.15 ms) ($p < .001$). The main effects of condition and electrode, and age- or group-by-electrode, or –condition interactions were not significant.

3.3.2. MMN amplitude

The MMN amplitude analysis revealed main effects of condition ($F_{(2,\ 65)} = 37.12$, $p < .001$) and age ($F_{(2,\ 65)} = 6.15$, $p = .004$), along with a significant condition-by-age interaction ($F_{(2,\ 65)} = 6.43$, $p = .003$). Pairwise comparisons showed that, taken together, the mismatch found in 3-month-olds was of significantly higher amplitude than the mismatch measured in

12- and 36-month-olds (p < .001) (3-month-olds: 1.92 ± 0.47; 12-month-olds: -2.17 ± 0.50; 36-month-olds: -2.85 ± 0.50 µV). A significant main effect of electrode was also found ($F_{(2.28, 148.03)}$ = 3.58, p = .025): in all children, amplitude recorded at Cz (-2.59 ± 0.32 µV) tended to be smaller than that recorded at Fz (-4.95 ± 0.34µV) (p = .068). The main effect of group, group-by-condition or -age, and electrode-by-group or -age interactions were not significant.

3.3.3. P150 latency

The latency analysis showed a main effect of group ($F_{(1, 65)}$ = 3.94, p = .051): both conditions taken together, preterm of all ages showed longer latency than full-term children (preterms: 152.48 ±3.22; full-terms: 142.92 ±3.57ms). Main effects of age ($F_{(2, 65)}$ = 61.26, p < .001) and condition ($F_{(1, 65)}$ = 61.36, p < .001) were also found, along with a significant condition-by-age interaction ($F_{(2, 65)}$ = 11.44, p < .001). Pairwise comparisons revealed that, when speech stimuli were used, latencies decreased across all ages (3-month-olds: 209.25 ± 3.91; 12-month-olds: 152.95 ± 4.11; 36-month-olds: 124.82 ± 4.11 ms). However, when non-speech stimuli were used, only 3-month-old infants showed longer latency compared with 12- and 36-months-olds (3-month-olds: 156.11 ± 36.07; 12-month-olds: 129.33 ± 6.37; 36-month-olds: 113.75 ± 6.37 ms) (p = .010 and p < .001, respectively). In addition, a significant group-by-electrode interaction ($F_{(2.14, 138.80)}$ = 3.66, p = .026) was found on the latencies of the P150 component. Pairwise comparisons indicated that latencies recorded at AFz, Fz and FCz electrodes (166.27 ± 3.35 ms) were significantly longer in preterm infants (AFz: 153.40 ± 3.67; Fz: 153.11 ± 3.65 and FCz: 152.48 ± 3.62 ms) than those recorded in full-term infants (AFz: 143.23 ± 3.31; Fz: 142.62 ± 3.29 and FCz: 142.62 ± 3.27 ms) (p = .044, p = .036 and p

= .047, respectively). Main effect of electrode as well as age-by-electrode and group-by–condition interactions were not significant.

3.3.4. P150 amplitude

The amplitude analysis revealed a significant condition-by-age interaction ($F_{(2,\ 65)} = 3.38$, $p = .040$): in 3-month-olds only, the P150 component was of higher amplitude when speech stimuli were presented (7.18 ± 0.68 μV) than that recorded when non-speech stimuli were presented (5.66 ± 0.97 μV). A main effect of electrode was also found ($F_{(2.44,\ 158.74)} = 30.04$, $p < .001$), along with a significant electrode-by-group interaction ($F_{(2.44,\ 158.74)} = 4.81$, $p = .006$). Pairwise comparisons revealed that, in full-term infants, amplitudes recorded at Cz and AFz (AFz: 6.09 ± 0.62; Cz: 5.70 ± 0.57 μV) were significantly lower than those recorded at Fz and FCz (Fz: 6.48 ± 0.63; FCz: 6.77 ± 0.59 μV) (AFz: $p = .002$ and $p = .003$, respectively; Cz: all $p < .001$). In contrast, in preterm infants, amplitude recorded at Cz (5.57 ± 0.63 μV) was lower than amplitude recorded at all three other electrodes (AFz: 6.79 ± 0.69; Fz: 6.86 ± 0.70; FCz: 6.66 ± 0.65 μV). Main effects of condition, group and age, or group-by-age or –condition, and age-by-electrode interactions were not significant.

3.3.5. N250 latency

The latency analysis showed a main effect of age ($F_{(2,\ 65)} = 45.51$, $p < .001$) and condition ($F_{(1,\ 65)} = 52.68$, $p < .001$), along with a significant age-by-condition interaction ($F_{(2,\ 65)} = 18.19$, $p < .001$). Pairwise comparisons revealed that, preterms and full-terms taken together, latencies decreased with age when speech stimuli were presented (3-month-olds: 316.77 ± 6.97; 12-month-olds: 247.04 ± 7.37; 36-month-olds: 202.93 ± 7.32 ms) ($p < .001$). In turn, when non-speech stimuli were presented, only 3-month-old infants showed longer latencies than 12- and 36-month-old children (3-month-olds: 231.09 ± 7.82; 12-month-olds: 203.63 ± 7.82 ms) (*p* = .040). Main effects of group and electrode, group-by-age or -condition, and electrode-by-age or –condition or -group interactions were not significant.

3.3.6. N250 amplitude

The amplitude analysis showed a main effect of age ($F_{(2, 65)} = 8.41$, $p < .001$) and condition ($F_{(1, 65)} = 15.35$, $p < .001$), along with a significant age-by-condition interaction ($F_{(2, 65)} = 6.90$, $p = .002$). Pairwise comparisons indicated that, when speech stimuli were presented, amplitude of the N250 component was more negative in 12-month-olds compared to 3-month-olds (3-month-olds: 0.27 ± 0.80; 12-month-olds: -2.91 ± 0.84 μV) (p = .023). However, when non-speech stimuli were used, the N250 amplitudes were more negative in both 12- and 36-month-olds compared to 3 month-old infants (3-month-olds: 0.52 ± 1.18; 12-month-olds: -5.33 ± 1.24; 36-month-olds: -6.42 ± 1.24 μV). A main effect of electrode ($F_{(2.19, 142.28)} = 3.91$, $p = .019$) was also found, together with an electrode-by-age ($F_{(4.38, 142.28)} = 3.99$, $p = .003$), an electrode-by-condition ($F_{(2.20, 143.02)} = 3.43$, $p = .031$) and an electrode-by-age-by-condition interaction ($F_{(4.40, 143.02)} = 2.61$, $p = .033$). In the interest of clarity, all pairwise comparisons (n = 47) are shown in supplementary material (Supplementary Table 3). Main effects of group, group-by-age or -condition interactions were not significant.

3.4. Correlations between neurodevelopmental results and AERP parameters

Pearson's correlations between neurodevelopmental results, AERP parameters at the FCz electrode (which, on visual inspection of the topographical distribution, appeared to yield the most consistent AERP amplitudes across groups and conditions), gestational age, and birth weight are presented in Table 4. Significant correlations were found between expressive language scores and gestational weeks (*r* = .35, *p* = .002), birth weight (*r* = .35, *p* = .002), and P150, N250, and MMN latencies for speech stimuli (*r* = -.34, *p* = .002; *r* = -.34, *p* = .002 and *r* = -.39, *p* = .001, respectively). A trend was also found for the correlations between expressive language scores and P150 and N250 amplitudes for speech stimuli (*r* = .23, *p* = .038 and *r* = .23, *p* = .041, respectively). Receptive language scores correlated positively with N250 latency responses to speech stimuli (*r* = .34, *p* = .002), and tended to correlate with P150 and MMN latencies for speech stimuli (*r* = -.25, *p* = .025; and *r* = -.26, *p* = .020, respectively). In addition, cognitive language scores correlated significantly with birth weight (*r* = .32, *p* = .005), and a trend was found between gestational weeks and N250 latency responses to non-speech stimuli (*r* = .24, *p* = .036 and *r* = -.26, *p* = .022, respectively). To illustrate the brain-behavior relationships, scatterplots with regression lines for significant correlations between birth data and neurodevelopmental results, and between AERP parameters and neurodevelopmental results are shown in Figures 3 and 4, respectively.

Insert Table 4 here.

Insert Figure 3 here

Insert Figure 4 here

4. Discussion

In this cross-sectional study, we aimed to investigate whether the MMN and AERPs components could be used as an electrophysiological indicator for language and/or cognitive delays in order to help identify as early as possible which prematurely born children are at risk for developing such impairments. We thus analyzed cortical responses to speech and non-speech sounds across ages (3-, 12- and 36-months-old) and groups (preterm, full-term), as well as their relationship to behavioral responses in both groups in order to help clarify cognitive and language development in premature and full-term children and to early identify impairments incurred following premature birth. Using speech and non-speech stimuli, a delayed P150 response was observed in prematurely born children aged 3, 12, and 36 months. Moreover, preterms of all ages showed a delayed MMN response compared to full-term children, specifically when speech stimuli were presented. The use of EEG and auditory event-related potentials (AERPs) in preterm children is of particular interest as it provides a quick, objective, and noninvasive method that can be used routinely in neonatal intensive care unit (NICU) and hospital settings to assess potential cognitive sequelae incurred by premature birth. In a previous study, we demonstrated that visual development in preterm children aged from 3 to 12 months, corrected for age, could be examined using EEG and visual evoked potentials (VEPs) (Tremblay et al., 2014). More specifically, we found that 3-month-old preterm infants showed developmental delays (longer VEP latencies) associated with the magnocellular system, a delay that gradually diminished with age. Developmental vulnerabilities of the magnocellular pathways have been reported in various developmental disabilities such as developmental dyslexia (for a review, see Stein, 2001). In the present study, we show that AERPs and MMN can also be used in infants as young as 3-month-old to help examine early language development in premature children.

Our findings concur with previous electrophysiological studies that found atypical or delayed AERP or MMN components in prematurely born children, adolescents, and adults (Fellman et al., 2004; Gomot, Bruneau, Laurent, Barthélémy, & Saliba, 2007; Jansson-Verkasalo et al., 2010; Kilpelainen et al., 1999; Maitre, Lambert, Aschner, & Key, 2013; Mikkola et al., 2007). However, in these studies, the distinction between the MMN responses to speech and non-speech stimuli as an electrophysiological marker for language and cognitive impairments was not clearly established. Another concern in these studies is the inclusion of children who underwent major complications in the perinatal period and early cerebral damage, such as periventricular leukomalacia or intracranial hemorrhages, which have also been associated with auditory processing impairment and language delays (for reviews, see Pavlova & Krägeloh-Mann, 2013; Volpe, 2009). In order to overcome these limitations, in the current study we used both speech and non-speech stimuli and included prematurely born infants without major neonatal brain injuries. Therefore, altered MMN responses to speech stimuli in the preterm group suggest that these children have impaired language discrimination ability, which is probably related to premature birth. Overall, our results add to the body of literature by exploring the electrophysiological markers of language development in premature infants at risk for language impairments using AERP and MMN responses to speech and non-speech sounds.

4.1. Delayed MMN and P150 responses

The present study observed prematurity-related effects on peak latency only, while prior studies mainly reported amplitude effects. Latency measures, however, can provide valuable information about the development of children's perceptual, discriminative and cognitive abilities. Delayed AERPs have been found in studies investigating auditory discrimination in children at risk for language impairment (Friedrich et al., 2004) as well as in auditory brainstem responses in preterm children (Hasani & Jafari, 2013; Pasman et al., 1996; Ribeiro & Carvallo, 2008). In developing children, latency decreases of AERPs have been associated with increase in myelination and in synaptic density in the auditory cortex (Eggermont, 1985; Eggermont & Ponton, 2003; Ponton, Eggermont, Khosla, Kwong, & Don, 2002). Furthermore, this maturation has been shown to coincide with the increasing abilities of the child to process complex auditory stimuli (Moore & Linthicum Jr, 2007; Ponton et al., 2000).

The most probable explanation for delayed MMN and P150 latency responses in prematurely born children is the impact of premature birth on myelin and white matter development. It is likely that delayed MMN and P150 latencies are associated with diffuse damage to the white matter, which is common in very prematurely born infants (Counsell et al., 2003; Volpe, 2009). Diffusion imaging studies have shown that alterations in the white matter were associated with various perceptual, cognitive, and motor skills deficits in preterm children (Peterson et al., 2000; Rose et al., 2008; Skranes et al., 2007; Stewart et al., 1999). For instance, a linear relationship between lower diffusion in the corpus callosum, anterior commissure, cingulum, and fornix, as well as a lower overall developmental quotient was found in preterm infants aged 2 years, corrected for age (Counsell et al., 2008). Moreover, in a prospective cohort of very preterm infants without major congenital anomalies, significant correlations between white matter volume abnormalities and BSID-III scores for language and cognition were found at 2 years of corrected age (He & Parikh, 2013). Specifically, atypical volume of cortical projection and association fibers in the periventricular region of preterm infants was correlated with lower language and cognitive scores on the BSID-III. Thus, atypical cognitive and language development in premature children might be partly explained by alterations in myelin and axonal development, which typically peaks during the last few weeks of gestation and the first few weeks after birth.

Another possible explanation would be alterations in functional cerebral connectivity, which refers to the synchronization of activation across spatially separate cortical regions (Raichle & Snyder, 2007). Such alterations have previously been found in prematurely born infants, children, and adolescents using investigations of spontaneous brain activity or resting state functional connectivity analysis (Cohen et al., 2008; Fair et al., 2008, 2010; Fox & Raichle, 2007; Fransson, Åden, Blennow, & Lagercrantz, 2011; Smith et al., 2009). For instance, in a study investigating resting-state cerebral connectivity during sleep, full-term infants showed enhanced connectivity between left temporal and parietal areas, whereas preterm infants showed enhanced connectivity between bilateral temporal and parietal regions (Fuchino et al., 2013). Alternatively, in a cohort of 12-year-old adolescents performing a lexical-semantic processing task, it was shown that preterm adolescents engaged language networks differently than their full-terms peers, and they had significantly reduced left frontal and bilateral temporal white matter volumes. In fact, in preterm adolescents, the language network was shown to involve the temporal area together with the sensorimotor association cortex. However, in full-term adolescents, this network instead involved the left inferior frontal gyrus together with right inferior frontal gyrus and right middle temporal gyrus (Schafer et al., 2009). Although this hypothesis related to functional brain connectivity could explain the delayed MMN and P150 latency responses found in prematurely born children, it was not directly investigated in the present study. Further studies are therefore needed to fully understand developmental changes in resting state and functional connectivity and their clinical implications for examining the networks associated with language and cognitive development in premature children.

Surprisingly, group analyses on the N250 component amplitude and latency were not significant between preterm and full-term children. As previously reported by others, the N250 component is the most predominant and robust negative auditory obligatory AERPs associated with auditory perceptual process in children (Ceponiene, Rinne, & Näätänen, 2002; Jing & Benasich, 2006). In accordance with our results, its amplitude is known to gradually increase and its latency to decrease as a function of age (Ceponiene et al., 2002; Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002; C. W. Ponton et al., 2000). Our findings might indicate that the auditory perceptual process associated with the N250 component is rather preserved in healthy preterm children and less sensitive to speech and/or non-speech discrimination impairments than the P150 and MMN components.

4.2. Age-related differences in AERPs and MMN

In addition to differences in AERPs and MMN components between children born preterm and full-term, significant age-related differences were found when the two groups were taken together. Using speech stimuli, we found that P150 and N250 latency significantly decreased with age, suggesting neural and axonal maturation, which would allow more timely and efficient information processing (Nagy, Westerberg, & Klingberg, 2004; Ponton, Eggermont, Khosla, Kwong, & Don, 2002; Ponton et al., 2000). In contrast, when non-speech stimuli were used, only 3-month-old infants showed longer AERP latencies compared with

12- and 36-month-old children. These results suggest that response to non-speech stimuli mature earlier in the infant's life compared to the discriminative process for speech sounds. A significant effect of age was also found on MMN amplitude to speech stimuli, with 3-month-old infants showing a positive mismatch and 12- and 36-month-old children showing a negative mismatch. Positive mismatches in typically developing infants and in children with language impairment when using speech stimuli have been previously reported by others (Ahmmed, Clarke, & Adams, 2008; G. Dehaene-Lambertz, 2000; Kushnerenko, Ceponiene, Balan, Fellman, Huotilainen, et al., 2002; Maurer, Bucher, Brem, & Brandeis, 2003; Morr, Shafer, Kreuzer, & Kurtzberg, 2002; Shafer et al., 2010; Weber, Hahne, Friedrich, & Friederici, 2004). Although the interpretation of this component in infants and children remains debatable, one of the main explanations is that it reflects a more immature discriminative response, whereas a more mature, adult-like, negative MMN response was observed in school-aged children (Shafer et al., 2010). Overall, age-related differences found in this study suggest specific ongoing maturation of auditory discriminative skills in response to speech and non-speech stimuli in young children (Dehaene-Lambertz, 2000; Kushnerenko et al., 2002; Lippé, Kovacevic, & McIntosh, 2009; Paquette et al., 2013; Shafer et al., 2010).

In the present study, an unexpected result was the lower scores on the receptive language scale of the BSID-III observed in 12-month-olds compared to 3-month-olds. This age difference could be accounted for by the behavioral assessment, as it is more difficult to objectively assess receptive language at 12 months. Thus, a combination of different assessment tools and high interrater agreement might enable a more precise receptive language assessment at this age. Additional studies are needed to better interpret this result.

4.3 Electrophysiological markers of language impairments using speech vs. non-speech stimuli

One important finding of this study is the significant correlations observed between longer latencies of the MMN, P150 and N250 components in response to speech stimuli and lower expressive language scores on the BSID-III. However, when non-speech stimuli were used, only a weak correlation was found between the N250 latency and lower cognitive scores. In a previous study, distinct patterns of brain activation according to stimulus type (speech vs non-speech) and age were found in healthy full-term children aged 3 to 13 years-old and adults (Paquette et al., 2013). Specifically, age-related differences for tone discrimination (non-speech stimuli) occurred earlier in childhood (around 8 to 13 years-old) than did the discriminative process for speech sounds (after 13 years-old), suggesting that networks involved in speech discrimination are still immature until late childhood. It is thus possible that networks involved in speech discrimination may also be more vulnerable to physiological and cognitive differences associated with prematurity. Likewise, the brain-behavior correlation results of the current study suggests that the MMN response to speech stimuli may be more sensitive to language delays identification in preterm children and could provide a stronger marker than non-speech stimuli in detecting such impairments.

4.4. Methodological considerations and further directions

In this study, the conclusions drawn about group- and age-related differences are based on a cross-sectional design and a relatively small sample size. Longitudinal studies of human development and larger cohorts could provide more reliable information on cognitive and language development and the predictive value of AERPs in preterm and full-term children. Similarly, additional evidence regarding reliability of MMN latencies in infants is needed in order to better establish their predictive value. It is challenging to assess neurodevelopment in very young children, and it requires a combination of tools and good interrater agreement. Future studies could investigate which language subdomains might be specifically affected by premature birth, such as phonological awareness, discourse, and pragmatic comprehension. In our experiments, the non-speech stimuli were created by deleting a formant from speech recordings. This led to a difference in the frequency spectrum of the speech and non-speech stimuli. By using non-speech stimuli created in a different way, future research could better distinguish whether it is frequency content per se, or a distinction between speech and non-speech that drives differences in AERPs.

5. Conclusion

Overall, our findings revealed delayed AERP and MMN responses to speech sounds in prematurely born children. These responses correlated with lower language scores on the BSID-III, suggesting that AERPs and MMN can be used for early identification of children at risk for language impairment as young as 3 months old. Better and earlier identification of the incurred deficits and the establishment of electrophysiological biomarkers of language development could allow clinicians to better target rehabilitation interventions and reduce the long-term medical and psychosocial needs of these children. Improved assessment methods could also help to further clarify normal and abnormal development of preterm children in the hope of detecting potential problems earlier and more accurately.

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Figure and tables

Table 1. Sociodemographic, clinical characteristics, and performances on the BSID-III of preterm and full-term children

	Preterms			**Full-terms**		
	3 months old	**12 months old**	**36 months old**	**3 months old**	**12 months old**	**36 months old**
Demographic characteristics and birth data						
Age at testing[a]	3.44 (.53)	13.24 (1.96)	38.27 (1.81)	3.22 (.21)	13.56 (1.05)	38.03 (3.71)
N (girls; boys)	13 (7; 6)	10 (5; 5)	10 (5; 5)	15 (7; 8)	13 (7; 6)	13 (6; 7)
Gestational weeks	29.7 (3.4)	29.5 (3.6)	29.4 (3.0)	39. 9 (1.0)	39.1 (1.4)	39.7 (1.1)
Birth weight (g)	1571 (597)	1498 (682)	1408 (444)	3642 (527)	3201 (606)	3377 (460)
Cesarean deliveries [*n* (%)]	6 (46)	4 (40)	7 (70)	4 (27)	4 (31)	4 (31)
Apgar score, 1 min	5.3 (3.4)	7 (2.6)	5.8 (1.9)	9 (.4)	8.8 (.4)	9 (.5)
Apgar score, 5 min	6.7 (2.0)	8.1 (1.4)	7.6 (1.1)	9.1 (.3)	9.2 (.4)	9.1 (1.5)
Neonatal complications						
Respiratory distress syndrome [*n*]	3	1	3	0	0	0
Retinopathy of prematurity [*n*]	3	1	0	–	–	–
Neonatal icterus (jaundice) [*n*]	7	7	3	1	2	0
Bronchopulmonary dysplasia [*n*]	3	1	4	0	0	0
Maternal and familial characteristics						
Maternal age at child birth (years)	28.92 (4.54)	31.8 (4.32)	27.5 (5.93)	31.33 (4.70)	29.67 (4.14)	31.83 (5.92)
Maternal education (years)	14.62 (2.53)	15.8 (2.53)	13.3 (2.79)	15.8 (3.03)	16.77 (4.46)	14.5 (2.47)
Familial income (in CAD) (n)						
0 – $15,000	1	0	0	0	0	1
$15,000–$35,000	0	1	1	0	1	0
$35,000–$55,000	3	0	4	2	2	2
$55,000$–$75,000	1	1	4	2	2	3
> $75,000	8	8	1	11	7	6
N/A	0	0	0	0	1	1
Parental marital status						
Married [*n*]	3	8	0	4	6	6
Common law partner [*n*]	9	2	7	11	7	6
Separated/divorced [*n*]	0	0	2	0	0	0
Single-parent	1	0	1	0	0	0
N/A	0	0	0	0	0	1
Neurodevelopmental results on the BSID-III						
Cognitive score	9.83 (.47)	10.3 (.51)	10.44 (.54)	11.07 (.44)	11.31 (.45)	10.85 (.45)
Expressive language score	8.25 (.56)	8.20 (.61)	9.44 (.65)	9.29 (.52)	9.46 (.54)	11.15 (.54)
Receptive language score	10.08 (.63)	8.00 (.69)	12.22 (.73)	10.29 (.59)	8.54 (.61)	12.31 (.61)

Mean values are presented with ± standard deviation in parenthesis, unless otherwise stated.
CAD=Canadian dollars.

[a] Corrected age used for 3- and 12-month-old preterm infants.

Table 2. Retention trial values on the deviant (rare) trials (standard deviation in parenthesis)

		Speech condition	Non-speech condition
Full-terms	3 months old	134.20 (11.51)	138.19 (11.20)
	12 months old	133.06 (11.94)	122.83 (11.20)
	36 months old	140.94 (11.94)	128.92 (11.20)
Preterms	3 months old	115.88 (12.43)	114.50 (11.65)
	12 months old	130.55 (13.62)	129.05 (12.76)
	36 months old	130.68 (13.62)	130.60 (12.76)

Table 3. Retention trial values on the standard (frequent) trials (standard deviation in parenthesis)

		Speech condition	Non-speech condition
Full-terms	3 months old	744.96 (63.28)	712.00 (64.64)
	12 months old	737.21 (65.67)	682.08 (64.64)
	36 months old	777.42 (65.67)	710.17 (64.64)
Preterms	3 months old	643.98 (68.36)	632.33 (67.28)
	12 months old	717.55 (74.88)	709.70 (73.70)
	36 months old	714.33 (74.88)	720.60 (73.70)

Table 4. Pearson's correlations between AERPs, MMN, and BSID-III scores

			Cognitive scores	Expressive lang. score	Receptive lang. score
Birth data		Gestational weeks	.24*	**.35****	.07
		Birth weight	**.32****	**.35****	.08
Speech condition	MMN	Latency (ms)	−.13	−**.39*****	−.26*
		Amplitude (μV)	−.05	−.10	.05
	P150	Latency (ms)	−.16	−**.34****	−.25*
		Amplitude (μV)	.10	.23*	.14
	N250	Latency (ms)	−.15	−**.34****	−**.34****
		Amplitude (μV)	.10	.23*	.17
Non-speech condition	MMN	Latency (ms)	−.14	−.19	−.11
		Amplitude (μV)	.06	. 09	.13
	P150	Latency (ms)	−.18	−.18	−.21
		Amplitude (μV)	−.05	.16	.12
	N250	Latency (ms)	−.26*	−.22	−.14
		Amplitude (μV)	−.07	−.10	−.11

All tests two-tailed. Corrected age used for 3- and 12-month-old preterm infants In bold: significant correlation at the adjusted alpha level (.01).

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Figures Legend

Figure 1. Grand average standard (solid grey line), deviant (solid black line) and differential waveforms (dotted black line) in response to speech stimuli for each group and age. The y axis indicates the amplitude of the response (in microvolts, μV); the x axis indicates the response time in ms. Responses from FCz are illustrated.

Figure 2. Grand average standard (solid grey line), deviant (solid black line), and differential waveforms (dotted black line), in response to non-speech stimuli for each group and age. The y axis indicates the amplitude of the response (in microvolts, μV); the x axis indicates the response time in ms. Responses from FCz are illustrated.

Figure 3. Scatterplots and regression lines for significants correlations at $p < .01$ between birth data (birth weight and gestationals weeks) and individual neurodevelopmental scores.

Figure 4. Scatterplots and regression lines for significants correlations at $p < .01$ between AERPs and MMN parameters (latency and amplitude) and individual neurodevelopmental scores.

Figure 1. Grand average standard, deviant and differential waveforms to speech stimuli

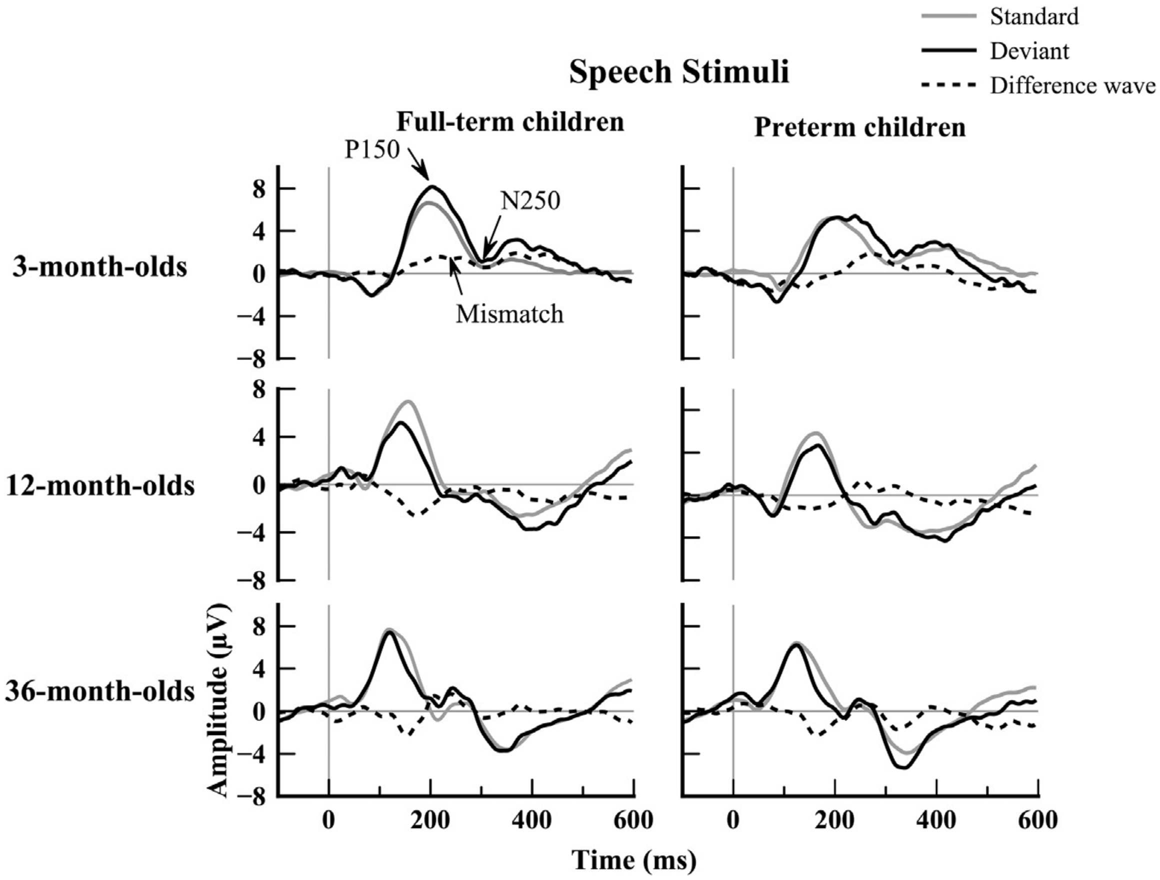


Figure 2. Grand average standard, deviant and differential waveforms to non-speech stimuli

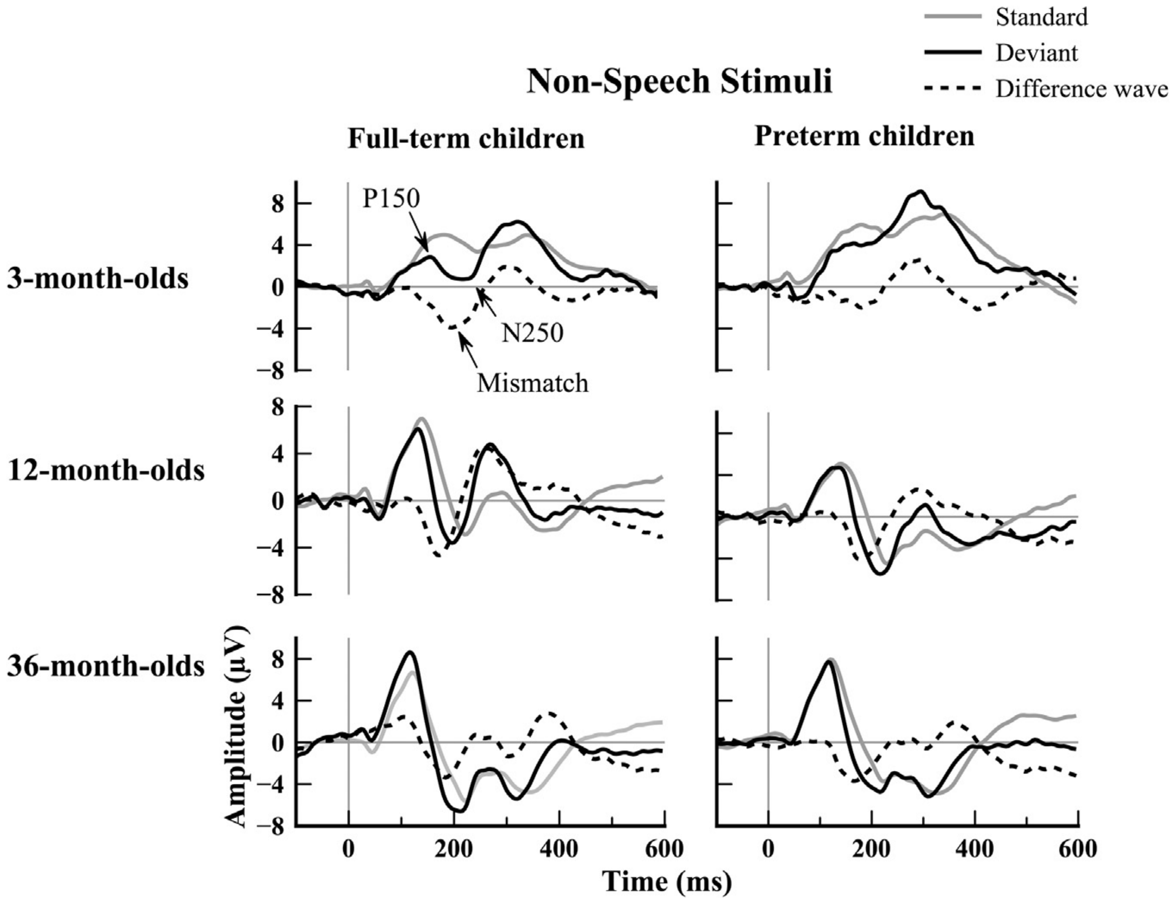


Figure 3. Scatterplots for correlations between birth data and neurodevelopmental scores

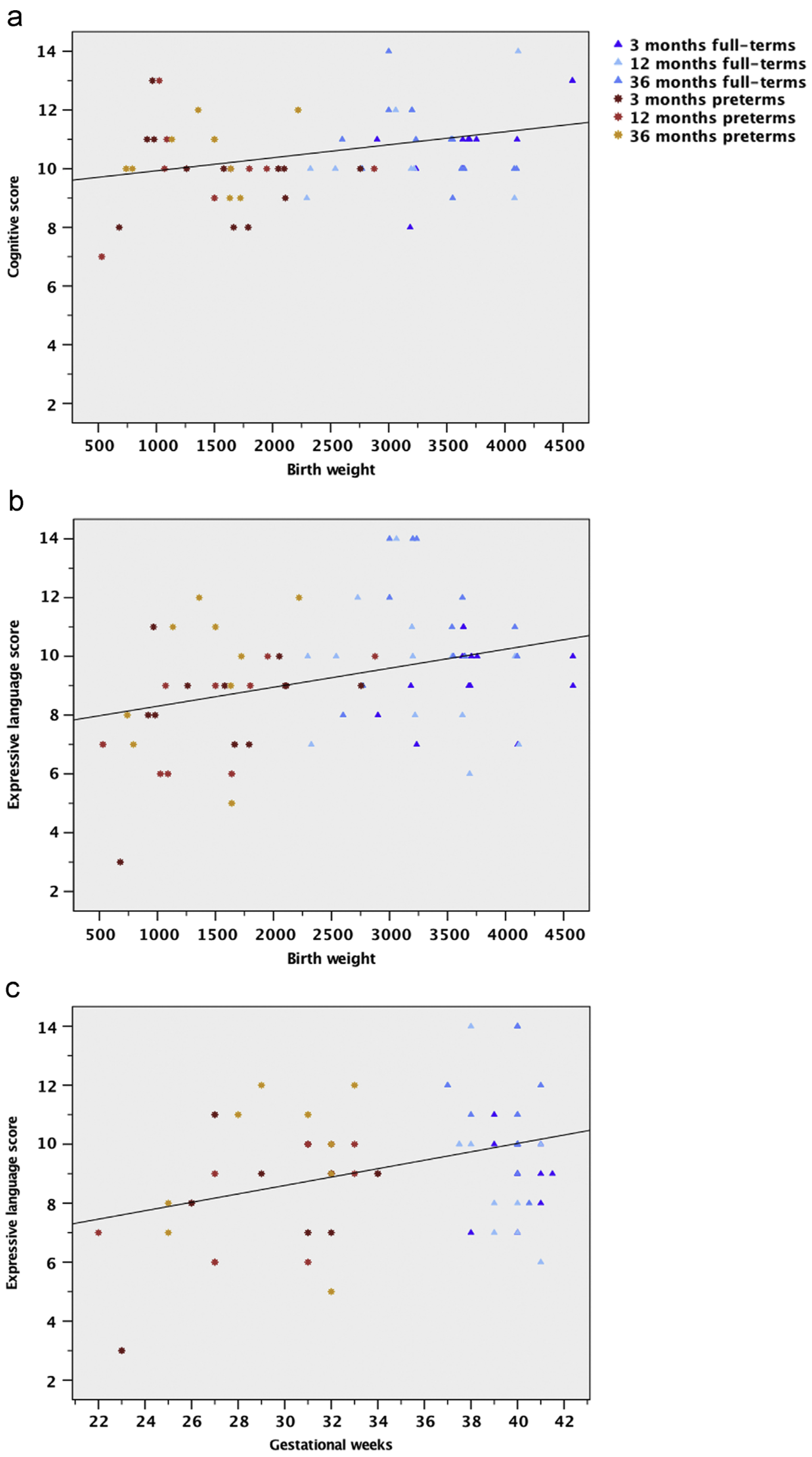
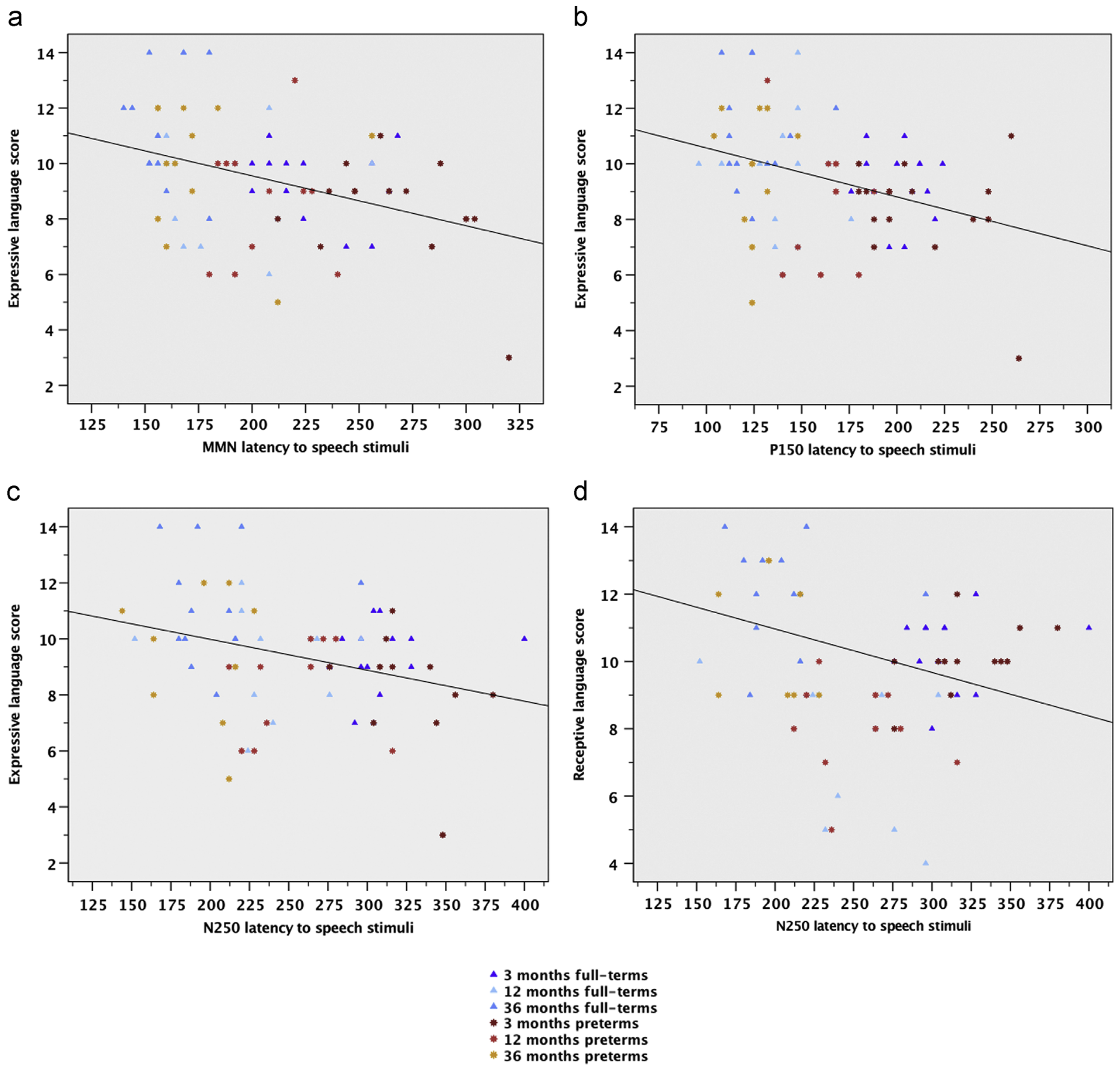


Figure 4. Scatterplots for correlations between AERPs and MMN parameters, and neurodevelopmental scores



Supplementary materials

Appendix A - AERPs results in response to the standard stimuli

P150 latency

The latency analysis on the P150 component showed a main effect of condition ($F_{(1,\ 65)} = 16.78$, $p < .001$). When all children were taken together, recorded P150 latencies on the standard stimuli were longer when speech stimuli were used compared to non-speech stimuli (speech: 160.30 ± 3.25; non-speech: 148.66 ± 3.37 ms). Moreover, a main effect of age ($F_{(2,\ 65)} = 37.64$, $p < .001$) indicated that, for both conditions, latencies decreased across ages (3-month-olds: 188.19 ± 5.01; 12-month-olds: 149.07 ± 5.26; 36-month-olds: 126.17 ± 4.26 ms). A main effect of electrode ($F_{(2.38,\ 154.35)} = 4.04$, $p = .014$) was also found; latency recorded at Cz tended to be shorter than that recorded at AFz (Cz: 154.03 ± 2.98; AFz 154.87 ± 3.00). The main effect of group, as well as group-by-age, -electrode or -condition and age-by-electrode or –condition interactions were not significant.

P150 amplitude

The amplitude analysis revealed a significant main effect of electrode ($F_{(1.65,\ 107)} = 58.88$, $p < .001$). Pairwise comparisons revealed that, when both group were taken together, amplitude recorded at Cz was significantly lower than amplitude recorded at all three other electrodes, and that amplitude recorded at AFz was lower than that recorded at Fz (AFz: 6.66 ± 0.40; Fz: 6.78 ± 0.40; FCz: 6.77 ± 0.39; Cz: 5.81 ± 0.34 µV). Main effects of condition, group and age, or group-by-age, –condition or -electrode, and age-by-electrode or –condition interactions were not significant.

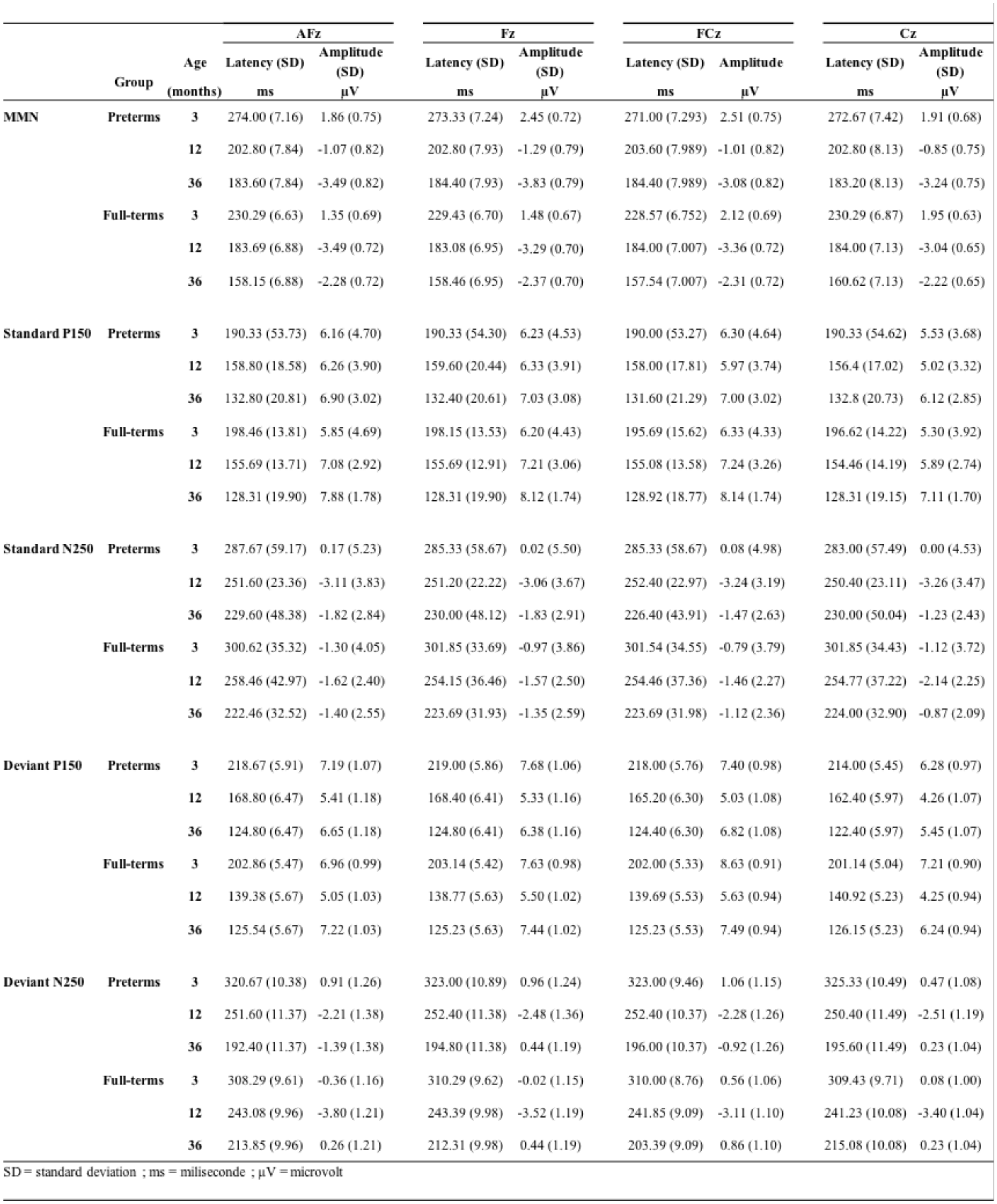
N250 latency

The latency analysis showed a main effect of age ($F_{(2, 65)} = 16.02$, $p < .001$) and condition ($F_{(1, 65)} = 17.03$, $p < .001$), along with a significant age-by-condition interaction ($F_{(2, 65)} = 4.01$, $p = .023$). Pairwise comparisons revealed that, in 3- and 12-month-olds, latency of the N250 component was significantly longer in response to speech stimuli (3-month-olds: 293.40 ± 8.08; 12-month-olds: 254.43 ± 8.49 ms) compared to non-speech stimuli (3-month-olds: 264.63 ± 7.09; 12-month-olds: 229.56 ± 7.45 ms). Main effects of group and electrode, group-by-age or -condition, and electrode-by-age or –condition or -group interactions were not significant.

N250 amplitude

The amplitude analysis showed a main effect of age ($F_{(2, 65)} = 16.80$, $p < .001$), along with significant age-by-condition ($F_{(2, 65)} = 25.91$, $p < .001$), age-by-electrode ($F_{(3.08, 100.01)} = 9.60$, $p < .001$) and age-by-condition-by-electrode interactions ($F_{(3.39, 125.86)} = 11.09$, $p < .001$). Pairwise comparisons indicated that when non-speech stimuli were used, amplitude of the N250 component was significantly lower in 3-month-old children than those recorded in 12- and 36-month-olds, on all four electrodes (for clarity, all pairwise comparisons are displayed in **Supplementary Table 4**). Main effects of electrode and group, as well as group-by-age or -condition interactions were not significant.

Supplementary Table 1. Mean (standard deviation in parenthesis) peak latency and amplitude for the MMN, P150 and N250 components in response to speech stimuli



			AFz		Fz		FCz		Cz	
	Group	Age (months)	Latency (SD) ms	Amplitude (SD) µV	Latency (SD) ms	Amplitude (SD) µV	Latency (SD) ms	Amplitude µV	Latency (SD) ms	Amplitude (SD) µV
MMN	**Preterms**	**3**	274.00 (7.16)	1.86 (0.75)	273.33 (7.24)	2.45 (0.72)	271.00 (7.293)	2.51 (0.75)	272.67 (7.42)	1.91 (0.68)
		12	202.80 (7.84)	-1.07 (0.82)	202.80 (7.93)	-1.29 (0.79)	203.60 (7.989)	-1.01 (0.82)	202.80 (8.13)	-0.85 (0.75)
		36	183.60 (7.84)	-3.49 (0.82)	184.40 (7.93)	-3.83 (0.79)	184.40 (7.989)	-3.08 (0.82)	183.20 (8.13)	-3.24 (0.75)
	Full-terms	**3**	230.29 (6.63)	1.35 (0.69)	229.43 (6.70)	1.48 (0.67)	228.57 (6.752)	2.12 (0.69)	230.29 (6.87)	1.95 (0.63)
		12	183.69 (6.88)	-3.49 (0.72)	183.08 (6.95)	-3.29 (0.70)	184.00 (7.007)	-3.36 (0.72)	184.00 (7.13)	-3.04 (0.65)
		36	158.15 (6.88)	-2.28 (0.72)	158.46 (6.95)	-2.37 (0.70)	157.54 (7.007)	-2.31 (0.72)	160.62 (7.13)	-2.22 (0.65)
Standard P150	**Preterms**	**3**	190.33 (53.73)	6.16 (4.70)	190.33 (54.30)	6.23 (4.53)	190.00 (53.27)	6.30 (4.64)	190.33 (54.62)	5.53 (3.68)
		12	158.80 (18.58)	6.26 (3.90)	159.60 (20.44)	6.33 (3.91)	158.00 (17.81)	5.97 (3.74)	156.4 (17.02)	5.02 (3.32)
		36	132.80 (20.81)	6.90 (3.02)	132.40 (20.61)	7.03 (3.08)	131.60 (21.29)	7.00 (3.02)	132.8 (20.73)	6.12 (2.85)
	Full-terms	**3**	198.46 (13.81)	5.85 (4.69)	198.15 (13.53)	6.20 (4.43)	195.69 (15.62)	6.33 (4.33)	196.62 (14.22)	5.30 (3.92)
		12	155.69 (13.71)	7.08 (2.92)	155.69 (12.91)	7.21 (3.06)	155.08 (13.58)	7.24 (3.26)	154.46 (14.19)	5.89 (2.74)
		36	128.31 (19.90)	7.88 (1.78)	128.31 (19.90)	8.12 (1.74)	128.92 (18.77)	8.14 (1.74)	128.31 (19.15)	7.11 (1.70)
Standard N250	**Preterms**	**3**	287.67 (59.17)	0.17 (5.23)	285.33 (58.67)	0.02 (5.50)	285.33 (58.67)	0.08 (4.98)	283.00 (57.49)	0.00 (4.53)
		12	251.60 (23.36)	-3.11 (3.83)	251.20 (22.22)	-3.06 (3.67)	252.40 (22.97)	-3.24 (3.19)	250.40 (23.11)	-3.26 (3.47)
		36	229.60 (48.38)	-1.82 (2.84)	230.00 (48.12)	-1.83 (2.91)	226.40 (43.91)	-1.47 (2.63)	230.00 (50.04)	-1.23 (2.43)
	Full-terms	**3**	300.62 (35.32)	-1.30 (4.05)	301.85 (33.69)	-0.97 (3.86)	301.54 (34.55)	-0.79 (3.79)	301.85 (34.43)	-1.12 (3.72)
		12	258.46 (42.97)	-1.62 (2.40)	254.15 (36.46)	-1.57 (2.50)	254.46 (37.36)	-1.46 (2.27)	254.77 (37.22)	-2.14 (2.25)
		36	222.46 (32.52)	-1.40 (2.55)	223.69 (31.93)	-1.35 (2.59)	223.69 (31.98)	-1.12 (2.36)	224.00 (32.90)	-0.87 (2.09)
Deviant P150	**Preterms**	**3**	218.67 (5.91)	7.19 (1.07)	219.00 (5.86)	7.68 (1.06)	218.00 (5.76)	7.40 (0.98)	214.00 (5.45)	6.28 (0.97)
		12	168.80 (6.47)	5.41 (1.18)	168.40 (6.41)	5.33 (1.16)	165.20 (6.30)	5.03 (1.08)	162.40 (5.97)	4.26 (1.07)
		36	124.80 (6.47)	6.65 (1.18)	124.80 (6.41)	6.38 (1.16)	124.40 (6.30)	6.82 (1.08)	122.40 (5.97)	5.45 (1.07)
	Full-terms	**3**	202.86 (5.47)	6.96 (0.99)	203.14 (5.42)	7.63 (0.98)	202.00 (5.33)	8.63 (0.91)	201.14 (5.04)	7.21 (0.90)
		12	139.38 (5.67)	5.05 (1.03)	138.77 (5.63)	5.50 (1.02)	139.69 (5.53)	5.63 (0.94)	140.92 (5.23)	4.25 (0.94)
		36	125.54 (5.67)	7.22 (1.03)	125.23 (5.63)	7.44 (1.02)	125.23 (5.53)	7.49 (0.94)	126.15 (5.23)	6.24 (0.94)
Deviant N250	**Preterms**	**3**	320.67 (10.38)	0.91 (1.26)	323.00 (10.89)	0.96 (1.24)	323.00 (9.46)	1.06 (1.15)	325.33 (10.49)	0.47 (1.08)
		12	251.60 (11.37)	-2.21 (1.38)	252.40 (11.38)	-2.48 (1.36)	252.40 (10.37)	-2.28 (1.26)	250.40 (11.49)	-2.51 (1.19)
		36	192.40 (11.37)	-1.39 (1.38)	194.80 (11.38)	0.44 (1.19)	196.00 (10.37)	-0.92 (1.26)	195.60 (11.49)	0.23 (1.04)
	Full-terms	**3**	308.29 (9.61)	-0.36 (1.16)	310.29 (9.62)	-0.02 (1.15)	310.00 (8.76)	0.56 (1.06)	309.43 (9.71)	0.08 (1.00)
		12	243.08 (9.96)	-3.80 (1.21)	243.39 (9.98)	-3.52 (1.19)	241.85 (9.09)	-3.11 (1.10)	241.23 (10.08)	-3.40 (1.04)
		36	213.85 (9.96)	0.26 (1.21)	212.31 (9.98)	0.44 (1.19)	203.39 (9.09)	0.86 (1.10)	215.08 (10.08)	0.23 (1.04)

SD = standard deviation ; ms = miliseconde ; µV = microvolt

Supplementary Table 2. Mean (standard deviation in parenthesis) peak latency and amplitude for the MMN, P150 and N250 components in response to non-speech stimuli

			AFz		Fz		FCz		Cz	
	Group	Age	Latency (SD)	Amplitude (SD)	Latency (SD)	Amplitude (SD)	Latency (SD)	Amplitude	Latency (SD)	Amplitude (SD)
		(months)	ms	μV	ms	μV	ms	μV	ms	μV
MMN		**3**	226.67 (12.59)	-3.88 (1.34)	226.67 (12.44)	-3.76 (1.38)	227.00 (12.89)	-3.72 (1.33)	225.67 (12.66)	-3.01 (1.27)
		12	178.40 (13.79)	-4.48 (1.47)	179.60 (13.63)	-4.58 (1.51)	178.40 (14.12)	-4.59 (1.45)	177.60 (13.86)	-4.92 (1.39)
		36	174.40 (13.79)	-4.20 (1.47)	175.60 (13.63)	-4.23 (1.51)	176.40 (14.12)	-4.21 (1.45)	175.20 (13.86)	-3.44 (1.39)
	Full-terms	**3**	224.92 (12.10)	-5.61 (1.29)	226.46 (11.95)	-5.42 (1.32)	231.08 (12.38)	-5.50 (1.27)	228.00 (12.16)	-5.35 (1.22)
		12	176.92 (12.10)	-5.40 (1.29)	177.23 (11.95)	-5.57 (1.32)	175.69 (12.38)	-5.64 (1.27)	174.46 (12.16)	-4.43 (1.22)
		36	181.85 (12.10)	-5.16 (1.29)	181.85 (11.95)	-4.98 (1.32)	185.85 (12.38)	-4.60 (1.27)	185.23 (12.16)	-4.35 (1.22)
Standard P150	**Preterms**	**3**	183.00 (60.09)	8.28 (6.56)	181.67 (59.19)	8.21 (6.55)	181.00 (59.75)	7.74 (6.18)	181.67 (57.68)	6.94 (5.39)
		12	141.20 (11.16)	5.28 (2.77)	140.40 (12.14)	5.37 (2.80)	141.60 (11.50)	5.25 (2.68)	140.80 (12.19)	4.55 (2.43)
		36	122.8 (10.16)	8.01 (3.59)	122.80 (10.16)	8.18 (3.66)	122.80 (10.16)	8.18 (3.43)	122.00 (10.37)	6.92 (2.88)
	Full-terms	**3**	184.00 (27.91)	5.33 (4.41)	184.62 (29.52)	5.30 (4.38)	183.08 (27.19)	5.78 (4.19)	182.15 (27.21)	4.90 (3.77)
		12	141.85 (9.33)	6.37 (2.75)	141.85 (9.33)	6.64 (2.78)	142.15 (9.33)	6.77 (2.80)	141.54 (9.60)	5.44 (2.57)
		36	121.23 (8.23)	6.46 (1.57)	121.54 (8.25)	6.55 (1.62)	120.92 (8.67)	6.53 (1.75)	121.23 (7.55)	6.05 (1.71)
Standard N250	**Preterms**	**3**	266.00 (63.00)	4.43 (4.84)	264.33 (62.21)	4.35 (4.77)	263.00 (62.37)	3.89 (4.67)	259.67 (63.65)	3.34 (4.04)
		12	234.40 (23.03)	-5.03 (2.23)	234.4 (23.03)	-4.95 (2.24)	234.80 (22.94)	-4.7 (2.16)	234.00 (23.50)	-4.44 (2.13)
		36	228.40 (38.94)	-5.05 (4.28)	228.00 (36.71)	-4.96 (4.28)	227.60 (37.07)	-4.37 (3.83)	231.20 (40.43)	-3.61 (3.28)
	Full-terms	**3**	266.15 (39.11)	2.06 (4.80)	265.54 (39.07)	1.91(4.98)	265.54 (38.04)	2.31 (4.66)	266.77 (38.93)	1.40 (4.03)
		12	225.23 (9.71)	-3.2 (3.29)	224.62 (9.78)	-3.15 (3.25)	224.92 (9.82)	-2.81 (3.00)	224.00 (7.30)	-2.74 (2.82)
		36	222.15 (12.18)	-5.77 (2.66)	222.15 (12.18)	-5.89 (2.58)	221.85 (11.15)	-5.6 (2.41)	222.77 (10.76)	-4.78 (2.39)
Deviant P150	**Preterms**	**3**	163.33 (8.73)	7.59 (1.44)	161.67 (8.76)	7.61 (1.47)	161.67 (8.77)	7.30 (1.43)	160.67 (8.88)	6.47 (1.32)
		12	132.00 (9.57)	5.79 (1.58)	133.20 (9.59)	5.66 (1.61)	133.20 (9.61)	5.44 (1.56)	131.60 (9.73)	4.20 (1.45)
		36	112.80 (9.57)	8.11 (1.58)	111.60(9.59)	8.52 (1.61)	112.40 (9.61)	7.00 (1.56)	114.40 (9.73)	6.76 (1.45)
	Full-terms	**3**	150.46 (8.39)	3.78 (1.38)	149.23 (8.41)	4.16 (1.42)	150.15 (8.43)	4.66 (1.37)	151.69 (8.54)	3.69 (1.27)
		12	126.77 (8.39)	5.84 (1.38)	126.46 (8.41)	6.13 (1.42)	125.23 (8.43)	6.24 (1.37)	126.15 (8.54)	5.31 (1.27)
		36	115.08 (8.39)	8.04 (1.38)	114.46 (8.41)	8.32 (1.42)	114.46 (8.43)	8.52 (1.37)	114.77 (8.54)	7.83 (1.27)
Deviant N250	**Preterms**	**3**	235.00 (10.84)	2.20 (1.82)	234.67 (10.97)	2.28 (1.81)	234.33 (11.01)	1.67 (1.68)	233.00 (10.36)	1.85 (1.59)
		12	212.40 (11.88)	-6.09 (1.99)	210.80 (12.01)	-5.99 (1.98)	211.20 (12.06)	-5.76 (1.84)	209.20 (11.35)	-6.08 (1.74)
		36	205.20 (11.88)	-5.63 (1.99)	205.20 (12.01)	-5.60 (1.98)	204.80 (12.06)	-5.28 (1.84)	205.20 (11.35)	-3.90 (1.74)
	Full-terms	**3**	226.15 (10.42)	-0.90 (1.74)	227.39 (10.54)	-0.75 (1.74)	229.85 (10.58)	-0.67 (1.61)	228.31 (9.96)	-1.47 (1.53)
		12	196.00 (10.42)	-4.95 (1.74)	196.00 (10.54)	-4.97 (1.74)	197.85 (10.58)	-4.77 (1.61)	195.69 (9.96)	-4.05 (1.53)
		36	202.77 (10.42)	-8.41 (1.74)	202.15 (10.54)	-8.33 (1.74)	202.15 (10.58)	-7.58 (1.61)	201.54 (9.96)	-6.58 (1.53)

Supplementary Table 3. Pairwises comparisons for the electrode-by-age-by-condition interaction on the deviant (rare) N250 amplitudes

Condition	Electrodes	Age 1	Age 2	Mean Difference (Age 1 - Age 2)	Std. Error	*p* value
Speech	**Afz**	3	12	3.125*	1.263	.048
			36	0.683	1.263	1
		12	3	-3.125*	1.263	.048
			36	-2.442	1.294	.190
		36	3	-0.683	1.263	1
			12	2.442	1.294	.190
	Fz	3	12	3.291*	1.243	.030
			36	0.941	1.243	1
		12	3	-3.291*	1.243	.030
			36	-2.35	1.273	.208
		36	3	-0.941	1.243	1
			12	2.35	1.273	.208
	FCz	3	12	3.287*	1.143	.016
			36	0.612	1.143	1
		12	3	-3.287*	1.143	.016
			36	-2.674	1.171	.077
		36	3	-0.612	1.143	1
			12	2.674	1.171	.077
	Cz	3	12	3.036*	1.082	.020
			36	0.46	1.082	1
		12	3	-3.036*	1.082	.020
			36	-2.576	1.109	.070
		36	3	-0.46	1.082	1
			12	2.576	1.109	.070
Non-speech	**Afz**	3	12	6.167*	1.825	.004
			36	7.670*	1.825	< .001
		12	3	-6.167*	1.825	.004
			36	1.503	1.87	1
		36	3	-7.670*	1.825	< .001
			12	-1.503	1.87	1
	Fz	3	12	6.244*	1.817	.003
			36	7.733*	1.817	< .001
		12	3	-6.244*	1.817	.003
			36	1.489	1.861	1
		36	3	-7.733*	1.817	< .001
			12	-1.489	1.861	1
	FCz	3	12	5.768*	1.688	.003
			36	6.935*	1.688	< .001
		12	3	-5.768*	1.688	.003
			36	1.167	1.729	1
		36	3	-6.935*	1.688	< .001
			12	-1.167	1.729	1
	Cz	3	12	5.252*	1.599	.005
			36	5.429*	1.599	.004
		12	3	-5.252*	1.599	.005
			36	0.176	1.638	1
		36	3	-5.429*	1.599	.004
			12	-0.176	1.638	1

Supplementary Table 4. Pairwises comparisons for the electrode-by-age-by-condition interaction on the standard (frequent) N250 amplitude.

Condition	Electrodes	Age 1	Age 2	Mean Difference (Age 1 - Age 2)	Std. Error	*p* value
Speech	Afz	3	12	1.796	1.05	0.275
			36	1.045	1.05	0.970
		12	3	-1.796	1.05	0.275
			36	-0.752	1.075	1
		36	3	-1.045	1.05	0.970
			12	0.752	1.075	1
	Fz	3	12	1.841	1.059	0.260
			36	1.113	1.059	0.891
		12	3	-1.841	1.059	0.260
			36	-0.728	1.085	1
		36	3	-1.113	1.059	0.891
			12	0.728	1.085	1
	FCz	3	12	1.996	0.971	0.131
			36	0.942	0.971	1
		12	3	-1.996	0.971	0.131
			36	-1.054	0.994	0.879
		36	3	-0.942	0.971	1
			12	1.054	0.994	0.879
	Cz	3	12	2.144	0.929	0.073
			36	0.492	0.929	1
		12	3	-2.144	0.929	0.073
			36	-1.652	0.952	0.262
		36	3	-0.492	0.929	1
			12	1.652	0.952	0.262
Non-speech	Afz	3	12	7.361*	1.115	< .001
			36	8.655*	1.115	< .001
		12	3	-7.361*	1.115	< .001
			36	1.294	1.142	0.783
		36	3	-8.655*	1.115	< .001
			12	-1.294	1.142	0.783
	Fz	3	12	7.177*	1.118	< .001
			36	8.556*	1.118	< .001
		12	3	-7.177*	1.118	< .001
			36	1.378	1.146	0.700
		36	3	-8.556*	1.118	< .001
			12	-1.378	1.146	0.700
	FCz	3	12	6.857*	1.051	< .001
			36	8.088*	1.051	< .001
		12	3	-6.857*	1.051	< .001
			36	1.231	1.077	0.771
		36	3	-8.088*	1.051	< .001
			12	-1.231	1.077	0.771
	Cz	3	12	5.962*	0.936	< .001
			36	6.564*	0.936	< .001
		12	3	-5.962*	0.936	< .001
			36	0.602	0.958	1
		36	3	-6.564*	0.936	< .001
			12	-0.602	0.958	1

4. DISCUSSION GÉNÉRALE

La présente thèse s'intéressait à l'étude du développement de l'attention auditive et des capacités de discrimination langagière chez l'enfant né à terme et né prématurément. Dans cette optique, deux études ont été réalisées à l'aide de l'électroencéphalographie de haute densité et ont été publiées dans deux journaux scientifiques avec révisions par des comités de pairs. Le premier objectif de la thèse était de mettre sur pied un protocole permettant d'examiner l'évolution de la composante MMN en réponse à une tâche de discrimination verbale et non verbale chez des enfants et adultes nés à terme dans le but de préciser le développement typique des capacités préattentionnelles auditives et de discrimination du langage. Par la suite, nous visions à utiliser ce même protocole auprès de nourrissons et jeunes enfants nés prématurément et nés à terme afin d'identifier des marqueurs électrophysiologiques de difficultés cognitives et langagières émanant d'une naissance prématurée. Parallèlement, l'étude du développement normal du langage chez les enfants, les adolescents et les adultes en santé et sans trouble connu du développement a également mené à la réalisation de trois autres publications présentées en annexe de cette thèse, dont deux articles scientifiques réalisés à l'aide de l'imagerie optique et publiés dans des revues avec comité de pairs [voir en Annexe 2 et Annexe 3] et une recension des écrits soumise sous forme de chapitre de livre [voir en Annexe 1]. Dans les sections qui suivent, les résultats des deux études principales de la thèse seront résumés, discutés et mis en contexte avec la littérature scientifique actuelle.

Rappel des objectifs et principaux résultats

Étude 1

Dans un premier temps, nous avons voulu déterminer les changements électrophysiologiques spécifiques à la discrimination des sons verbaux et non verbaux en lien avec différents stades du développement de l'enfant. Les études antérieures ont souvent associé les réponses de la MMN verbale et non verbale (par exemple des tonalités simples ou complexes) à l'efficience du traitement langagier auprès de diverses populations cliniques et typiques (Ahmmed, Clarke, & Adams, 2008; Bishop & Hardiman, 2010; Fellman et al., 2004; Jansson-Verkasalo et al., 2004; Lovio et al., 2010; Näätänen et al., 1997). D'autres études portant plus spécifiquement sur le développement attentionnel ont utilisé la MMN non verbale en réponse à des tonalités simples ou complexes afin d'évaluer les processus préattentionnels auditifs chez les enfants et les adultes (Escera, Alho, Schroger, & Winkler, 2000; Kilpelainen et al., 1999). Toutefois, peu d'études se sont intéressées aux processus développementaux distincts de la MMN verbale et non verbale. Une caractérisation plus approfondie des processus de discrimination auditive dans le développement de l'enfant apparait donc essentielle pour mieux comprendre le développement des aires auditives respectivement impliquées dans le traitement des sons du langage et celui des processus préattentionnels auditifs. À l'aide d'un plan d'étude transversal et d'un paradigme *oddball*, nous avons présenté des stimuli verbaux (les syllabes Ba et Da) et non verbaux (tons synthétisés à partir des deuxièmes et troisièmes formants des stimuli verbaux, Ba : 1578 Hz/2800 Hz; Da : 1788 Hz/2932 Hz) à des participants en santé, âgés de 3 à 32 ans. Les participants ont été répartis en trois groupes selon leur âge (jeunes enfants de 3 à 7 ans; enfants d'âge scolaire de 8 à 13 ans et adultes). Les différences liées à l'âge ont été examinées en contrastant l'amplitude et la latence de la MMN verbale et non verbale entre les groupes d'âge.

Les résultats obtenus indiquent que la discrimination des stimuli non verbaux a évoqué une négativité de plus grande amplitude que celle évoquée par les stimuli verbaux chez tous les groupes d'âge. De plus, des effets liés à l'âge des participants ont été trouvés. Quel que soit le type de stimulus présenté, une augmentation de l'amplitude de la MMN a été trouvée avec l'âge croissant des sujets. Les différences de latence en fonction du type de stimulus présenté et de l'âge des participants se sont également révélées significatives. Ainsi, lors de la présentation des stimuli verbaux, les deux groupes d'enfants ont montré une latence plus tardive de la MMN que les adultes. Ce résultat suggère une certaine immaturité de la réponse de discrimination verbale à l'âge préscolaire et scolaire. En revanche, lors de la présentation des stimuli non verbaux, seul le groupe d'enfants plus jeunes a démontré une réponse significativement plus tardive que celles des adultes, alors que la latence de réponse des enfants d'âge scolaire ne différait pas significativement de celle des adultes, indiquant une réponse préattentionnelle auditive plus mature à cet âge.

Étude 2

La deuxième étude de cette thèse visait plus spécifiquement à déterminer si la MMN et les PEAs en réponse aux stimuli verbaux et non verbaux pouvaient être utilisés comme marqueurs du développement préattentionnel auditif et langagier de l'enfant né prématurément afin d'aider à identifier rapidement les enfants à risque de retards langagiers ou cognitifs. En utilisant le protocole validé lors de la première étude, nous avons analysé les réponses corticales d’enfants âgés de 3, 12 ou 36 mois, nés prématurément (âge corrigé pour les enfants de 3 et 12 mois, âge réel pour les enfants de 36 mois) et à terme, en réponse aux stimuli verbaux et non verbaux. Pour clarifier le lien entre les réponses électrophysiologiques et le développement cognitif et langagier de l’enfant, nous avons également analysé les corrélations entre les paramètres des composantes électrophysiologiques et les résultats de chaque enfant obtenus suite à une évaluation du langage et de la cognition à l’aide du Bayley-III.

L’utilisation de ce protocole et la présentation des stimuli verbaux et non verbaux ont permis de mesurer une réponse P150 de latence plus tardive chez les enfants nés prématurément de tous les âges comparativement aux enfants nés à terme. Ces enfants ont également montré une MMN de latence plus tardive que les enfants nés à terme, mais uniquement lorsque les stimuli verbaux ont été présentés. De plus, les latences tardives de la MMN, la P150 et la N250 en réponse aux stimuli verbaux, un âge gestationnel et un poids à la naissance plus petit, corrélaient significativement avec des scores plus faibles à l’échelle du langage expressif du Bayley-III.

Par ailleurs, des effets liés à l’âge ont également été observés lorsque les réponses des deux groupes ont été analysées conjointement. En réponse aux sons verbaux et non verbaux, les enfants âgés de 3 mois ont démontré des réponses MMN significativement plus tardives que celles mesurées chez les enfants âgés de 12 et 36 mois. Les résultats ont également montré qu’en réponse aux stimuli verbaux, les latences des composantes P150 et N250 diminuent progressivement avec l’âge (3 mois > 12 mois > 36 mois). En revanche, lorsque les stimuli non verbaux ont été utilisés, seuls les enfants âgés de 3 mois ont montré des latences de la P150 et de la N250 plus tardive que les enfants de 12 et 36 mois.

Intégration théorique et clinique des résultats

Marqueurs électrophysiologiques du développement préattentionnel et langagier

Que ce soit chez les enfants nés à terme ou nés prématurément, les résultats liés à l'âge soutiennent les conclusions de Tampas et al. (2005) et Winkler et al. (1999) qui suggèrent une représentation cérébrale en parallèle des stimuli verbaux et non verbaux observés à l'aide des PEAs et de la MMN. Ainsi, dans la première étude, les stimuli non verbaux ont évoqué une MMN de latence plus rapide chez tous les groupes d'âge comparativement à celle évoquée par les stimuli verbaux. De plus, les résultats des analyses sur la latence confirment des patrons différents de développement cérébral entre les processus de discriminations verbale et non verbale. La latence de la MMN en réponse aux stimuli verbaux était encore immature chez le groupe d'enfant d'âge scolaire (8 à 13 ans), alors qu'aucune différence ne les distinguait des adultes lors de la présentation des stimuli non verbaux. La latence plus longue mesurée en réponse aux stimuli verbaux suggère donc que leur catégorisation requiert à la fois le traitement acoustique et phonétique des sons.

De même, dans la deuxième étude, des différences significatives liées à l'âge et au type de stimulus ont été observées. La latence des composantes P150 et N250 en réponse aux stimuli verbaux chez les groupes d'enfants nés à terme ou prématurément diminue de façon significative avec l’âge, reflétant probablement la maturation axonale et neuronale qui permettrait ainsi un traitement plus rapide et plus efficace de l'information langagière (Nagy, Westerberg, & Klingberg, 2004; Ponton et al., 2002; Ponton et al., 2000). Toutefois, lorsque les stimuli non verbaux ont été présentés, seuls les nourrissons âgés de 3 mois ont montré des PEAs de latences plus longues comparativement aux enfants de 12 et de 36 mois. En accord avec les conclusions de la première étude (Paquette et al., 2013), ces résultats démontrent que la réponse corticale des jeunes enfants lors de la présentation et de la discrimination des stimuli non verbaux se développe plus rapidement que celle des processus de discrimination langagière. De plus, un effet significatif de l'âge a été trouvé sur l’amplitude de la MMN en réponse aux stimuli verbaux, les nourrissons de 3 mois démontrant une réponse de polarité positive alors qu’une réponse de polarité négative était observée chez les enfants de 12 et de 36 mois. Une MMN positive a déjà été observée chez les nourrissons et les très jeunes enfants nés à terme et en santé, de même que chez les enfants à risque de présenter des troubles du langage (Ahmmed et al., 2008; Dehaene-Lambertz, 2000; Kushnerenko et al., 2002; Maurer, Bucher, Brem, & Brandeis, 2003; Morr, Shafer, Kreuzer, & Kurtzberg, 2002; Shafer et al., 2010; Weber, Hahne, Friedrich, & Friederici, 2004). Bien que l’interprétation et la signification clinique de la polarité positive de la MMN demeurent peu investiguées à ce jour, l'une des principales hypothèses est que celle-ci reflète une réponse de discrimination plus immature, tandis qu’une réponse négative de la MMN, comme celle observée chez l’adulte, peut être mesurée de façon plus stable dès l’âge préscolaire.

Le développement différentiel de la MMN et des PEAs en réponse aux sons verbaux et non verbaux observé dans les études constituant cette thèse est compatible avec la théorie du traitement parallèle acoustique et phonétique des sons verbaux (Tampas et al., 2005; Winkler et al., 1999). Selon cette théorie, la catégorisation des sons du langage exige un traitement parallèle sur les plans acoustique et phonétique, alors que la catégorisation des sons non verbaux exige uniquement le traitement acoustique des sons. Bien que cette notion puisse paraitre relativement intuitive, la littérature appuyant cette théorie chez l'enfant est encore pauvre. En effet, peu d'études se sont intéressées à décrire la réponse différentielle aux stimuli verbaux et non verbaux en fonction des systèmes distincts de traitement cognitif et peu d'entre elles ont considéré différents stades développementaux. L'implication clinique de cette théorie revêt pourtant une importance indéniable dans l'étude des populations à risque de développer un trouble du langage ou de l'attention, puisque celle-ci influence la spécificité des protocoles d'évaluation utilisés auprès de ces enfants et la nature des processus examinés. Parmi les études recensées, Ceponiene, Alku, Westerfield, Torki, & Townsend (2005) ont examiné les processus de discrimination acoustique et phonétique chez des enfants en santé âgés entre 7 et 10 ans et des adultes. Des patrons d'activation distincts ont été observés dans chaque groupe en réponse aux stimuli verbaux (syllabes ba-da-ga) et non verbaux (tons synthétisés à partir de la fréquence fondamentale des stimuli verbaux). La présentation des stimuli non verbaux a évoqué des réponses N100 (chez l'adulte) et P200 (chez l'enfant d'âge scolaire et l'adulte) de plus grande amplitude que la présentation des sons verbaux. En revanche, la présentation des stimuli verbaux a évoqué des réponses N200 et N400 (chez l'enfant et l'adulte) de plus grande amplitude que celles évoquées par les stimuli non verbaux. Les auteurs suggèrent en outre que les premières composantes (N100 et P200) reflèteraient l'orientation automatique de l'attention et la détection acoustique des sons alors que les composantes plus tardives (N200 et N400) reflèteraient davantage le traitement du contenu phonétique des sons verbaux

(Ceponiene et al., 2005). Des différences dans la discrimination des stimuli verbaux et non verbaux ont également été observées chez les nourrissons âgés de 3 mois, alors que des topographies différentes ont été observées au niveau du lobe temporal en réponse à des syllabes comparativement à des tons complexes (Dehaene-Lambertz, 2000), indiquant des réseaux neuronaux distincts dans les processus discriminatifs de ces deux types de stimuli. Dans les deux études de cette thèse, la présentation des stimuli non verbaux a évoqué des PEAs (P150 et N250) et des MMNs de plus grande amplitude et de latence plus courte que celle des stimuli verbaux, tant chez les enfants nés à terme que les enfants nés prématurément. En ajout, des patrons de développement différents ont été observés en réponse aux stimuli verbaux par rapport aux stimuli non verbaux, supportant l'hypothèse de processus différents engendrés par la discrimination des stimuli verbaux et non verbaux.

Dans l'ensemble, les différences d'âge observées dans les patrons de réponses corticales aux stimuli verbaux et non verbaux reflètent le développement des aires cérébrales respectivement impliquées dans les processus langagiers et préattentionnels. Durant l'enfance, le système auditif est marqué par des changements structuraux importants qui peuvent être reflétés dans la morphologie du signal EEG (Eisermann, Kaminska, Moutard, Soufflet, & Plouin, 2013). Les connexions axonales qui s'étendent au cœur des couches corticales profondes sont encore immatures à la naissance et arrivent à maturité vers l'âge de cinq ans, alors que le développement des couches corticales supérieures culmine entre l'âge de 6 et 12 ans (Moore & Guan, 2001; Moore & Linthicum Jr, 2007). Le développement des couches corticales profondes et supérieures est donc susceptible de rendre compte de certaines différences d'âge observées dans les mesures de latences et d'amplitudes de la MMN et des PEAs verbaux et non verbaux, particulièrement auprès des enfants plus jeunes.

Cette maturation corticale coïncide avec les capacités croissantes de l'enfant à traiter et discriminer les stimuli auditifs complexes. En effet, les études indiquent des changements développementaux dans le signal électrophysiologique de l'enfant en lien avec le développement anatomique du cortex auditif. Par exemple, Shafer, Morr, Kreuzer, & Kurtzberg (2000), ont constaté que la latence de la MMN en réponse des tons complexes diminue d'environ 11 millisecondes par année d'âge entre 4 et 10 ans. Ces résultats coïncident avec le développement des couches corticales supérieures et concordent avec les études révélant une corrélation négative significative entre une latence plus courte de la composante MMN et un âge plus avancé chez des nourrissons et des enfants d'âge préscolaire (Morr et al., 2002) ou chez des enfants plus âgés (Korpilahti, Krause, Holopainen, & Lang, 2001; Korpilahti & Lang, 1994). Ainsi, les changements liés à l'âge dans la morphologie de la courbe EEG et observables par une diminution de latence de la réponse de discrimination dans les deux études de cette thèse correspondent avec la maturation des couches profondes VI, V et IV et le développement des couches superficielles III, II, et I. Ces résultats suggèrent également que les processus préattentionnels recrutés dans la discrimination des tons se développent plus rapidement dans l'enfance que ceux responsables de la discrimination des sons verbaux, indiquant que les réseaux neuronaux impliqués dans le traitement langagier sont encore immatures à l'âge scolaire. Finalement, ces résultats suggèrent également qu'une variation de latence des réponses de discrimination peut être utilisée en tant que marqueur électrophysiologique de la maturité des processus attentionnels auditifs et langagiers, ce qui a été évalué dans le deuxième article de la présente thèse.

L'EEG dans l'étude du développement du bébé prématuré

L'utilisation de l'EEG et des PEAs chez les enfants nés prématurément est d'un intérêt particulier, car cette méthode peut fournir un moyen rapide, objectif et non invasif pouvant être utilisé de façon routinière dans les milieux hospitaliers afin d'évaluer le risque de séquelles encourues par une naissance prématurée. Dans des études antérieures menées dans notre laboratoire, il a été démontré que le développement des processus visuels chez les enfants prématurés pouvait être examiné en bas âge en utilisant l'EEG et les potentiels évoqués visuels (PEVs) à 3, 6 et 12 mois d'âge corrigé (Sayeur et al., 2015; Tremblay et al., 2014). Plus spécifiquement, nous avons constaté que les nourrissons âgés de 3 mois nés prématurément ont montré des retards de latence des PEVs associés avec le développement du système magnocellulaire. Ce type de retard au niveau des voies magnocellulaires a fréquemment été relié à la manifestation de troubles neurodéveloppementaux tels que les troubles du langage écrit (dyslexie) (Stein, 2001). Dans la présente étude, nous montrons que la MMN et les PEAs peuvent également être utilisés chez les nourrissons et les jeunes enfants nés prématurément dès l'âge de 3 mois afin d'étudier le développement attentionnel auditif et langagier.

Dans la deuxième étude, nous avons observé des effets liés à la prématurité principalement sur la latence des composantes P150 et MMN, alors que les études antérieures ont souvent rapporté des effets d'amplitude (Fellman et al., 2004; Gomot et al., 2007; Jansson-

Verkasalo et al., 2004; Jansson-Verkasalo et al., 2003). Il est possible que les mesures d'amplitude de la MMN et de la P150 soient plus sensibles à la variabilité interindividuelle qui est particulièrement importante chez les très jeunes enfants que les mesures de latence. En effet, des différences individuelles au niveau du développement neuroanatomique (par exemple, le diamètre de la tête, l'épaisseur de la boite crânienne et l'impédance de la peau), ont pu affecter à divers degrés l'amplitude du signal EEG enregistré et masquer certaines différences entre les groupes d'enfants prématurés et nés à terme (J J Eggermont & Salamy, 1988; Hasani & Jafari, 2013; Holland, Haas, Norman, Brant-Zawadzki, & Newton, 1986; Li, Chen, Wilkinson, & Jiang, 2011). Des études supplémentaires, effectuées auprès de cohortes d'enfants plus grandes et incluant des mesures quantitatives du développement neuroanatomique, pourraient permettre d'éclaircir cette question. Les mesures de latence peuvent toutefois fournir des informations importantes et fiables sur le développement des capacités perceptuelles et discriminatives en lien avec le traitement attentionnel auditif et langagier de l'enfant. Par exemple, des PEAs de latences tardives ont été observées dans les études portant sur la discrimination auditive chez des enfants nés à terme, mais présentant un risque de troubles du langage oral ou écrit (Friedrich, Weber, & Friederici, 2004; Ribeiro & Carvallo, 2008). Les résultats de la deuxième étude de cette thèse appuient néanmoins ceux d'études électrophysiologiques antérieures ayant montré des PEAs ou une MMN atypiques auprès d'enfants, adolescents et adultes nés prématurément (Fellman et al., 2004; Gomot et al., 2007; Jansson-Verkasalo et al., 2010; Kilpelainen et al., 1999; Maitre et al., 2013; Mikkola et al., 2007). Toutefois, dans ces études, la distinction entre la MMN et les PEAs en réponse à des stimuli verbaux et non verbaux, de même que leur utilisation respective comme marqueurs électrophysiologiques du développement langagier et attentionnel, n’ont pas été clairement établies.

Une conclusion importante de l’étude 2 vient des corrélations significatives observées entre les latences de la MMN, de la P150 et de la N250 aux stimuli verbaux et des scores plus faibles à l’échelle évaluant le langage expressif du Bayley-III. Le Bayley-III est un instrument normé et standardisé, largement utilisé pour évaluer le développement de l’enfant âgé de 1 à 42 mois (Albers & Grieve, 2007; Bayley, 2006; Lennon, Gardner, Karmel, & Flory, 2009). Les items constituant l'échelle langagière évaluent les compétences de communication réceptive et expressive telles que réagir à des noms ou mots familiers, suivre des instructions, comprendre des concepts temporels, la production de babillage, la combinaison de voyelles ou syllabes, l’approximation de mots, nommer des objets et des images, et raconter des histoires. L'échelle cognitive évalue des compétences telles que les précurseurs de l'attention et des comportements d'anticipation, l'exploration de l'environnement, la résolution de problèmes simples, la numération, et le jeu symbolique et imaginaire (Bayley, 2006). Les outils constituant le Bayley ont été utilisés entre autres dans les études évaluant le développement normal de l’enfant ou celui d’enfants nés prématurément ou présentant divers troubles ou retards développementaux (Greene, Patra, Nelson, & Silvestri, 2012; Gucayener et al., 2006; Huang et al., 2012; Samantha Johnson, Moore, & Marlow, 2014; Luttikhuizen dos Santos, de Kieviet, Königs, van Elburg, & Oosterlaan, 2013; Månsson & Stjernqvist, 2014; Milne, Mcdonald, & Comino, 2012; Spencer-Smith, Spittle, Lee, Doyle, & Anderson, 2015; Velikos et al., 2015; Vohr et al., 2012). Les corrélations significatives, mesurées entre des latences plus tardives à l’EEG en réponse aux stimulations verbales et un rendement langagier plus faible au

Bayley-III suggèrent donc que la MMN et les PEAs peuvent être utilisés dès l'âge de 3 mois afin d'appuyer les résultats comportementaux et aider à caractériser plus objectivement le risque de retard langagier en bas âge.

En revanche, la MMN observée en réponse aux stimuli non verbaux chez les enfants nés prématurément ne différait pas de celle observée chez les enfants nés à terme. De même, aucune corrélation significative n'a été observée entre les latences ou l'amplitude de la MMN et des PEAs aux stimuli non verbaux et le rendement des enfants à l'échelle cognitive du Bayley-III. Ces résultats suggèrent que les processus de discrimination préattentionnels auditifs sont préservés dans notre échantillon d'enfants nés avant terme. Les délais observés dans la MMN sont donc spécifiques à la discrimination des sons du langage et sont associés au rendement langagier plus faible au Bayley-III.

Hypothèse des lésions de la matière blanche

L'hypothèse la plus probable pour les réponses MMN et P150 de latences plus tardives chez les enfants nés prématurément est l'impact d'une naissance avant terme sur le développement de la substance blanche et les processus de myélinisation des axones. Comme nous l'avons abordé dans la première étude auprès des enfants ayant un développement typique (Paquette et al., 2013), des diminutions de latence de la MMN et des PEAs ont été souvent associées à une augmentation de la myélinisation axonale et de la densité synaptique au sein du cortex auditif, coïncidant avec les capacités croissantes de l'enfant à traiter et discriminer les stimuli auditifs complexes (Eggermont & Ponton, 2003; Eggermont, 1985; Lippé et al., 2009a; Lippé et al., 2009b; Moore & Linthicum, 2007; Ponton et al., 2002;

Ponton et al., 2000). Il est donc possible que la latence tardive de la MMN et de la P150 soit associée à des lésions locales ou diffuses de la substance blanche, qui sont très fréquentes chez le bébé né prématurément (Counsell et al., 2003; Liu et al., 2013; Volpe, 2009b). Des études en imagerie de diffusion ont en effet montré des altérations de la substance blanche en lien avec divers déficits sensoriels, moteurs ou cognitifs chez des enfants nés avant 37 semaines de gestation (Ball et al., 2013; Counsell et al., 2008; Peterson et al., 2000; S. Rose et al., 2008; Skranes et al., 2007; Stewart et al., 1999). Par exemple, dans une étude longitudinale effectuée auprès de nourrissons nés très prématurément, mais sans anomalies congénitales majeures, des corrélations significatives ont été observées entre un volume atypique de fibres axonales dans la région périventriculaire et un rendement plus faible aux échelles de langage et de cognition du Bayley-III à l'âge de 2 ans (He & Parikh, 2013). Ainsi, le risque de développement cognitif et langagier atypique chez les enfants prématurés pourrait être en partie expliqué par des altérations de la myéline et du développement axonal qui culmine généralement au cours des dernières semaines de gestation et des premières semaines de vie (Moore & Linthicum Jr, 2007). Ces processus développementaux sont particulièrement sensibles aux impacts d'une naissance prématurée, de même qu'aux bruits environnementaux des unités néonatales et de soins intensifs (Mcmahon, Wintermark, & Lahav, 2012).

Hypothèse de la connectivité fonctionnelle

Une autre hypothèse possible en lien avec les résultats électrophysiologiques atypiques observés chez les enfants prématurés est celle d'altérations de la connectivité cérébrale fonctionnelle. La connectivité fonctionnelle réfère à la synchronisation de l'activation cérébrale au sein de régions corticales distinctes durant l'accomplissement d'une tâche cognitive ou lors de l'activité spontanée au repos (Dennis & Thompson, 2013; Fair et al., 2010; Raichle & Snyder, 2007). Des patrons atypiques de connectivité fonctionnelle ont déjà été observés chez des nourrissons, des enfants et des adolescents nés prématurément (Cohen et al., 2008; Fox & Raichle, 2007; Fransson, Åden, Blennow, & Lagercrantz, 2011; Meijer et al., 2014; Omidvarnia, Metsäranta, Lano, & Vanhatalo, 2015; Schumacher, Stiris, & Larsson, 2015; Smith et al., 2009). Par exemple, dans une étude examinant la connectivité cérébrale fonctionnelle pendant le sommeil chez des nouveau-nés, les bébés nés à terme ont montré une connectivité plus importante que les bébés nés prématurément, mais d'âge corrigé équivalent entre les régions pariétales et temporales gauches. En revanche, les enfants prématurés ont montré une connectivité plus importante entre les régions temporales et pariétales bilatérales (Fuchino et al., 2013). Ces résultats suggèrent que le développement des réseaux neuronaux chez les bébés nés à terme et nés prématurément suit des trajectoires différentes durant la période périnatale. Par ailleurs, une autre étude investiguant la connectivité fonctionnelle auprès d'une cohorte d'adolescents nés extrêmement prématurément et d'adolescents nés à terme a montré l'implication différente des réseaux langagiers durant l'exécution d'une tâche lexico-sémantique (Schafer et al., 2009). Les deux groupes ont démontré l'activation conjointe des régions classiquement impliquées dans les processus sémantiques, tels que les gyrus temporaux supérieur et médian gauches et le gyrus frontal inférieur gauche. Toutefois, chez les adolescents nés prématurément, la région sensori-motrice gauche était également activée et davantage corrélée avec l'exactitude de leur réponse durant la tâche, alors que chez les adolescents nés à terme cette corrélation était retrouvée avec le gyrus frontal inférieur gauche. De plus, chez les adolescents nés prématurément les résultats ont également montré une connectivité moindre que chez les adolescents nés à terme entre les régions temporales et frontales gauches (Schafer et al., 2009). Ces résultats suggèrent un patron de réorganisation cérébrale des réseaux langagiers chez les enfants prématurés. Bien que l'hypothèse de la connectivité fonctionnelle du cerveau puisse expliquer certaines différences au niveau des réponses électrophysiologiques corticales chez les enfants nés prématurément, celle-ci n'a toutefois pas été étudiée directement dans cette thèse. Davantage d’études sont nécessaires pour mieux comprendre les liens entre la connectivité cérébrale fonctionnelle chez l’enfant et les différences d’amplitude et de latence des PEAs observables en lien avec l’âge. De plus, ces études permettraient de mieux comprendre l’impact d’une naissance prématurée sur les changements dans la connectivité des régions responsables du langage et de l’attention chez l’enfant né avant terme.

Limite des études et directions futures

Les résultats des études constituant cette thèse contribuent à la compréhension du développement des réseaux neuronaux engagés dans le traitement préattentionnel auditif et la discrimination langagière de l’enfant né à terme et de l’enfant né prématurément. Toutefois, leur interprétation doit se faire à la lumière de certaines limites inhérentes à chacune des études.

Dans la **première étude** de cette thèse, les conclusions portant sur les différences développementales sont basées sur un devis d’étude transversal et une taille d’échantillon relativement petite pour chaque groupe d’âge. Des études longitudinales du développement des réponses cérébrales de l’enfant et de l’adolescent aux sons verbaux et non verbaux permettraient de fournir des informations plus fiables sur le développement des processus préattentionnels auditifs et de discrimination langagière. Par ailleurs, la résolution spatiale des analyses traditionnelles de l'EEG ne permet pas une localisation anatomique précise des réseaux neuronaux impliqués dans le traitement des sons verbaux et non verbaux. La combinaison de l'EEG avec des méthodes d'imageries telles que l'imagerie par résonance magnétique (IRM), la spectroscopie proche de l'infrarouge (SPIR ou imagerie optique) [voir les études en Annexe 2 et Annexe 3, relatives à l'investigation des processus langagiers en imagerie optique auprès des enfants et adultes en bonne santé] ou encore des analyses de localisation des sources génératrices des composantes PEAs et MMNs permettraient une meilleure compréhension du développement anatomique et fonctionnel des réponses de l'enfant aux stimulations langagières et auditives.

De même, dans la **deuxième étude**, les conclusions issues des différences entre les groupes et l'âge des participants sont également basées sur un plan d'étude transversal et une taille d'échantillon relativement petite. Tout comme pour la première étude, l'utilisation d'un plan longitudinal auprès de cohortes d'enfants plus grandes permettrait d'obtenir davantage d'information sur la valeur prédictive de la MMN et des PEAs dans le développement cognitif et langagier de l'enfant né prématurément. De plus, dans cette étude, nous avons observé des rendements plus faibles à l'échelle de langage réceptif du Bayley-III chez les enfants de 12 mois, comparativement aux enfants de 3 et de 36 mois. Cette différence pourrait être expliquée par le contexte de l'évaluation neurodéveloppementale. En effet, il demeure difficile de mesurer objectivement le développement cognitif et du langage réceptif à l'aide d'observations comportementales en bas âge, particulièrement auprès des enfants de 3 et 12 mois. Par ailleurs, certaines études ont suggéré que les scores du Bayley-III pouvaient surévaluer légèrement le neurodéveloppement de l'enfant (Milne et al., 2012; Spencer-Smith et al., 2015; Vohr et al., 2012). Bien que nos résultats soient prometteurs pour une prise en charge précoce de l'enfant né prématurément, ceux-ci doivent tout de même être interprétés avec précaution. Davantage d'études longitudinales utilisant une combinaison d'outils neurodéveloppementaux en bas âge et neuropsychologiques à un âge plus avancé permettraient de se prononcer avec plus de certitude sur la valeur prédictive du Bayley-III dans l'étude du développement cognitif et langagier du nourrisson. De plus, des analyses longitudinales permettant d'évaluer le développement anatomique des sources génératrices des PEAs et de la MMN plus tardive chez l'enfant prématuré, de même que des analyses de connectivité cérébrale fonctionnelle des réponses de l'enfant, permettraient de mieux caractériser les différences observées entre les deux groupes lors de la discrimination de sons verbaux.

Les résultats issus de nos études mettent néanmoins en lumière plusieurs avenues potentielles dans l'étude du développement langagier et cognitif de l'enfant né prématurément et né à terme. D'une part, il est connu que les enfants naissant avant 37 semaines de gestation sont plus à risque que les enfants nés à terme de développer des troubles du langage. Or, peu d'études se sont penchées sur les sous-domaines linguistiques qui pourraient être plus spécifiquement affectés par une naissance prématurée. Des études futures pourraient donc évaluer de façon plus approfondie l'impact d'une naissance avant terme sur les constituants du langage tels que la conscience phonologique, l'acquisition du vocabulaire, de la morphosyntaxe, de la grammaire, ainsi que la compréhension pragmatique.

D'autre part, certains programmes d'intervention précoce se sont montrés efficaces, du moins à court terme, dans l'amélioration du rendement cognitif des enfants nés prématurément (Kiechl-Kohlendorfer et al., 2015; Kynø et al., 2012; Spencer-Smith et al., 2012). Toutefois, les données issues de la littérature sur les effets à long terme des programmes d'intervention précoce sont peu nombreuses, bien que certaines études longitudinales aient noté la persistance d'effets bénéfiques à l'âge scolaire (vers 7 et 8 ans) et à l'âge adulte (18 ans) (McCormick et al., 2006; Pascoe et al., 2013). Des études supplémentaires devraient être effectuées afin d'évaluer en profondeur l'efficacité à long terme des interventions précoces, par exemple sur le rendement académique, et professionnel, de même que sur l'ajustement social à l'adolescence et à l'âge adulte. Des interventions efficaces individualisées et adéquatement ciblées peuvent non seulement avoir des impacts bénéfiques sur les sphères cognitives, académiques et sociales de l'enfant, mais également sur l'adaptation des membres de la famille face aux besoins de l'enfant (Maupin & Fine, 2014; McCormick et al., 2006; Spencer-Smith et al., 2012). À plus long terme, ces programmes de dépistage et d'intervention précoces pourraient également être appliqués auprès d'autres populations à risque de développer des troubles du langage tel que les enfants vivant avec un trouble déficitaire de l'attention (avec ou sans hyperactivité; TDA/H), un syndrome d'alcoolisme fœtal ou les enfants ayant une histoire familiale de dyslexie ou de trouble spécifique du langage.

Enfin, il importe de parvenir à une approche plus fiable et uniforme de l'évaluation et du rendement cognitif de l'enfant en bas âge. Celle-ci doit tenir compte de l'âge à l'évaluation, des outils de mesure et normes employés ainsi que de l'utilisation des indices servant à interpréter les résultats. Les outils de mesure du développement cognitif et langagier de l’enfant doivent également couvrir un large éventail de sphères cognitives, langagières, motrices et adaptatives, et inclure la qualité de vie familiale et l’adaptation parentale face aux exigences de soins parfois accrus chez les enfants nés prématurément.

Conclusions générales

Dans l'ensemble, les résultats de cette thèse contribuent à la littérature scientifique en examinant les marqueurs électrophysiologiques du développement langagier et préattentionnel chez les enfants nés à terme ou prématurément. Dans la première étude, les différences d'âge en lien avec la discrimination des stimuli non verbaux surviennent plus tôt dans l'enfance que celles en lien avec les processus de discrimination verbale. Ceci suggère que les réseaux impliqués dans les processus langagiers sont encore immatures à l’âge scolaire, du moins jusqu'à 13 ans. De même, dans la deuxième étude, la latence des PEAs en réponse aux stimuli non verbaux a montré une maturation plus rapide, reflétée par une diminution plus rapide de la latence entre 3 et 36 mois, que celle des PEAs en réponse aux stimuli verbaux. Par ailleurs, des réponses MMN et P150 significativement plus tardives ont été observées dès l’âge de trois mois en réponse aux stimuli verbaux chez les enfants nés prématurément en comparaison aux enfants nés à terme, suggérant des capacités de discrimination langagière sous-optimales chez les enfants prématurés. Les résultats des corrélations montrent également que la réponse EEG aux stimuli verbaux est plus sensible que la réponse aux stimuli non verbaux dans le dépistage des retards langagiers éventuels chez les enfants prématurés. Dans l’ensemble, les résultats de cette thèse indiquent que les réseaux neuronaux impliqués dans la discrimination verbale sont plus vulnérables aux impacts physiologiques développementaux et/ou liés à la prématurité que ceux en lien avec les processus préattentionnels auditifs. Étant donnée l'ampleur des conséquences potentielles de la prématurité sur le développement de ces enfants, un dépistage précoce et une prise en charge rapide des enfants à risque sont essentiels. À plus long terme, ceux-ci pourraient permettre de mieux orienter les enfants à risque vers les programmes d'interventions appropriés et individualisés dans le but de limiter, voire même prévenir, les impacts négatifs de la prématurité sur le fonctionnement cognitif et langagier de l'enfant.

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6. ANNEXES

Annexe 1 : Voice Perception in Newborns and Infants

Book Chapter to appear in: *The Oxford Handbook of Voice Perception / PART II - Ontogenetic Development of Voice Perception (Eds: Pascal Belin & Sascha Fruehholz) (Submitted)*

Voice perception in newborn and infants

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Abstract

Human voice perception plays a significant role in our day-to-day interactions. However, little is known about how newborns and infants perceive and process this information. Yet the ability to perceive vocal cues is crucial, not only for speech and language learning, but also for the development of key social skills such as perceiving other people's emotions. It is therefore important to understand how typically developing infants perceive and process this information in the first few months of life. The aim of this chapter is to provide a better understanding of the early development of these abilities as well as an overview of the key recent behavioural and neuroimaging studies in foetuses, newborns, and infants. We describe and discuss 1) how newborns and infants perceive human voices, 2) how they extract and learn social cues from vocalizations, and 3) how they use this information to learn language.

Key words: Infants, voice perception, prosodic processing, social learning, speech, vocalization

Introduction

Like a fingerprint, our voice carries important signature information about our identity, gender, approximate age range, and affective state. In early infancy, children develop the ability to perceive sounds and voices. These abilities are prerequisites for speech and language processing later in life. Interestingly, evidence of an evolutionary basis for voice processing have led to the identification of brain regions that show a sensitive response to species-specific vocalization in the macaque brain, located along the superior-temporal plane (Petkov et al., 2008; Petkov, Logothetis, & Obleser, 2009). Similarly, in adult humans, voice perception is associated with activity in specific brain regions: bilaterally along the superior temporal sulcus (STS), with stronger activity in the right hemisphere (Belin et al., 2000; 2004). This region, called the temporal voice area (TVA), has been found to elicit greater neural activity in response to voice—both speech and nonspeech—compared to nonvocal environmental sound or scrambled speech (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000). In human infants, however, little is known about how voice perception abilities are developed or which brain regions are recruited in the early voice processing stages. Nevertheless, recent studies have highlighted the joint influence of the genetic expression underlying structural auditory development and early in-utero perceptual experience on the development of voice processing ability in newborns and preverbal infants.

1) How do newborns and preverbal infants perceive the human voice?

1.1 The anatomical basis of auditory and voice perception

Human auditory development begins very early in foetal life and follows a rapid sequence of events that are crucial for the structural maturation of the cochlea (the organ that receives acoustic information) and the auditory cortex. The first trimester of pregnancy extends from the day of conception to the third month of gestation. During this time, the initial formation of the organ of Corti occurs, along with the inner and outer hair cells of the cochlea (Moore & Linthicum Jr, 2007). These hair cells convert the physical movements produced by sound vibrations into neural signals, which are transmitted from the cochlea to the auditory cortex via the cochlear nerve (Graven & Browne, 2008; Hall, 2000; Moore & Linthicum Jr, 2007). The organ of Corti, the cochlea, and the cochlear nerve continue developing during the second trimester of pregnancy (4th to 6th month). At around 25 to 29 weeks, the main components of the auditory pathways can be identified. By the end of the sixth month, the cochlea has established axonal connections between the inner ear, the brainstem, and the temporal auditory cortex. At this stage the auditory system becomes functional, and the first evidence of foetal auditory perception can be observed using ultrasound imaging and foetal heart rate monitoring (Graven & Browne, 2008). During the last trimester, from the seventh month of gestation to birth, the myelination process of the axonal connections initiates, allowing prompt transmission of auditory information, including the voice.

1.2 Behavioural evidence of foetal voice perception

It is thought that foetuses perceive external sounds through bone vibrations and fluids that are conducted from the skull to the inner ear (Sohmer, Perez, Sichel, Priner, & Freeman, 2001). The earliest evidence of foetal auditory perception can be observed at around 25 to 26 gestational weeks by measuring behavioural changes such as variations in heart rate or body movements in response to loud sounds (Kisilevsky, Pang, & Hains, 2000; Morris, Philbin, & Bose, 2000). Unborn infants are therefore exposed to in-utero auditory stimulation. Even though the initial development of the basic structures responsible for auditory perception is governed by genetic expression, it is generally accepted that this early exposure allows the foetus to fine-tune the abilities to learn and to respond preferentially to certain auditory stimuli. This is known as an *epigenetic* process, or a process that alters gene activity without changing the DNA sequence, and leads to modifications that can be transmitted to daughter cells (Weinhold, 2006). In this case, the process is the impact of experience and exposure to certain stimuli (such as the mother's voice) on genetic expression and structural development (Graven & Browne, 2008; Werker & Tees, 1999).

Supporting the epigenetic model, several studies have reported evidence of a voice-sensitive response in foetuses, newborns, and very young infants. The first indications came from ultrasound imaging studies that investigated heart rate variations and body movement patterns. Heart rate changes, also called the cardiac orienting reflex, have been associated with stimulus-processing ability in foetuses, often elicited by low-intensity stimuli such as the average human voice (Groome et al., 2000; Groome et al., 1999; Lecanuet, Granier-Deferre, & Busnel, 1988). Among the first to investigate the foetal response to voice stimuli, Groome et al. (1999) found that from 36 to 40 weeks of gestation, foetal heart rate decelerates in response to speech sounds. More recently, Kisilevsky and Hains (2011) monitored foetal cardiac responses in 143 foetuses in four age groups (29–31, 32–34, 35–37, and more than 37 gestational weeks) while exposed to an audiotape of their mother reading a story segment. They found that the cardiac orienting reflex following the mother's voice onset could be reliably recorded starting at 32 gestation weeks. This heart rate variability in response to sensory stimuli has been associated with attentional orientation response in infants and foetuses. For instance, Richards and Casey (1991) developed a model of heart rate variability as an attentional response in infants. According to their model, the influence of attentional mechanisms on heart rate could be observed in distinct phases: 1) initial stimulus detection; 2) heart rate variability in response to stimulus orientation and 3) sustained attention, characterized by a new, stable heart rate; and 4) declining attention, associated with a return to baseline heart rate.

Variations in foetal heart rate have also been observed in studies of the discriminative foetal response to the mother's voice and an unfamiliar or the father's voice, suggesting that the mother's voice is learned through repeated in-utero exposure. For instance, Kisilevsky et al. (2003) measured increased heart rate in term foetuses when their mothers read a story segment. In contrast, when a stranger read the same segment, the foetal heart rate decreased. In a subsequent study, they compared foetal cardiac response to the recorded voices of the mother, the father, and a stranger (Kisilevsky et al., 2009). Results showed a stable foetal heart rate increase in response to the mother's voice but not the father's or stranger's voice. Instead, foetuses responded at the outset of the father's and stranger's voice with a brief heart rate increase before returning to baseline. Nevertheless, this suggests that the foetuses heard the voices, although they may not have recognized their father's voice. It was proposed that if foetuses have less exposure to the father's voice, they might need more time to process it compared to the mother's voice. In a replicated study, foetuses were systematically exposed to the father's voice 7 days prior to testing to ensure voice familiarity (Lee & Kisilevsky, 2014). Interestingly, results showed that foetuses responded similarly to both voices (father's and mother's) with a stable heart rate increase followed by sustained responses throughout the audio recording period. Thus, near-term foetuses can learn and recognize familiar voices to which they are repeatedly exposed. Overall, findings from studies that investigated heart rate variations and behavioural changes in foetuses suggest the presence of basic voice processing recognition such as attentional orientation, learning, and discrimination between familiar and unfamiliar voices.

1.3 Birth and developmental changes in the first months of life

1.3.1 Behavioural studies

Most of the pioneering studies of voice perception ability at birth or in the first few months of life have used the high-amplitude-sucking procedure to measure infants' behavioural responses to a variety of auditory stimuli. This method involves presenting the infant with a frequent auditory stimulus while measuring the infant's sucking rate with a specifically designed pacifier (DeCasper & Fifer, 1980). Once the infant demonstrates familiarity, or habituation, with the stimulus by a sucking rate that declines to a preset level, a new set of stimuli is presented. If the infant can discriminate between the two stimuli, a significant change in the sucking rate should be observed (DeCasper & Prescott, 2009; Floccia, Nazzi, & Bertoncini, 2000; Shi, Werker, & Morgan, 1999). This procedure has allowed researchers to examine the basic cognitive processes as well as the neural networks involved in voice perception. For instance, Floccia, Nazzi, and Bertoncini (2000) used this procedure with 40 newborns while they were presented with a single disyllabic word, spoken by either a single speaker (an unfamiliar male or female) or by the two speakers (male and female) alternately. Their results showed significantly slower sucking rate in newborns presented with the same voice compared to alternated voices. Interestingly, studies using this procedure have also shown that newborns can use prosodic and rhythmic information to discriminate between languages belonging to separate rhythmic classes, such as English and Japanese (Nazzi, Bertoncini, & Mehler, 1998), or between two languages they have never heard before, such as French and Russian for American newborns, or English and Italian for French newborns (Mehler et al., 1988). In addition, according to this paradigm, Shi et al. (1999) found that 1-to 3-day-old newborns could use perceptual acoustic cues in voices as well as phonological and rhythmic indices to discriminate between lists of either grammatical or lexical English words. The ability to discriminate between voices and rhythmic information in perceived vocalization very early in life is particularly relevant for the understanding of language acquisition later on. Thus, voice processing is the initial step in learning increasingly complex phonemic and linguistic information in the first months of life.

1.3.2 Neuroimaging and electroencephalography (EEG)

In recent years, the development of neuroimaging techniques such as functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), and electrophysiological (EEG) recording have made it possible to noninvasively assess brain activity associated with voice and speech processing in infants, without requiring sustained attention or a specific response. Accordingly, Beauchemin et al. (2010) used EEG and distributed source analyses to investigate newborns' cortical responses to a voice that was familiar (the mother's), less familiar (the attending nurse's), or unfamiliar. To evoke voice-specific responses, newborns were presented with a short auditory stimulus: the vowel /a/ as in the French word "*allô*" spoken by the mother, the nurse, or a female stranger. Results revealed a greater overall discriminative response for the mother's voice than for the two other voices, indicating a significant preferential response to the mother's voice. More interestingly, cerebral source analysis revealed that the newborn's response to the mother's and the unfamiliar voices were processed in spatially distinct brain areas. Thus, the mother's voice elicited a strong initial activation in the left temporal region, known to be related to language processing later in life, whereas unfamiliar voices were preferentially processed in the right temporal region, known to be the voice sensitive area in adults (Belin et al., 2000; Belin, Zatorre, & Ahad, 2002). This study was the first to show that newborns process their mother's voice and unfamiliar voices in distinct cortical areas. The activation recorded in the language-related area in response to the mother's voice within the first 24 hours of life supports the hypothesis that the acoustic processing of a familiar voice might benefit the development of language abilities later in life. These results also concur with findings from behavioural studies indicating that infants are better at discriminating phonemes or words spoken by their mothers over an unfamiliar speaker (Barker & Newman, 2004; Liu, Kuhl, & Tsao, 2003). Other recent infant neuroimaging studies also supported the hypothesis that the speaker's characteristics and voice familiarity could impact speech processing development in infants. Dehaene-Lambertz et al. (2010) found significant hemispheric asymmetry in 2-month-old infants when listening to speech segments spoken by their mother and a stranger, in favour of the left *planum temporale* for both conditions. However, when compared to the stranger's voice, the mother's voice elicited stronger activation of the bilateral anterior prefrontal cortex and the left posterior temporal region. Contrary to Beauchemin et al. (2010), the difference between the mother's and the stranger's voice was not significant in the right temporal sulcus. These results are most likely due to the processing of full speech segments as opposed to a single vowel. In addition, the two studies used very different neuroimaging techniques (fMRI and

EEG). Nevertheless, the results suggest that phonetic and speech processing in very young infants is sensitive to the speaker's characteristics as well as voice familiarity.

Grossmann, Oberecker, Koch, and Friederici (2010) used fNIRS to determine the emergence of the voice-sensitive area in 4- and 7-month-olds who were presented with vocal (words and nonwords) and nonvocal sounds (nature, animal, musical, and environmental). They found a significantly higher haemodynamic oxyhaemoglobin response in bilateral posterior areas of the temporal cortex in response to the human voice compared to nonvocal sounds. However, this activation pattern was not observed in 4-month-olds, who showed a greater haemodynamic response to nonvocal sounds in the anterior right temporal region. The authors suggested that the voice-sensitive response could still be immature in 4-month-olds, whereas 7-month-olds showed a more adult-like response to voice. It should be noted that the voice stimuli included both speech (words and nonwords) and nonspeech human vocalizations, whereas the nonvoice stimuli included both familiar and unfamiliar sounds. It is possible that the familiarity of certain nonvocal stimuli, as well as the combination of words and nonwords as vocal stimuli, could have generated unspecific activations in the youngest group. To examine this possibility, Lloyd-Fox, Blasi, Mercure, Elwell, and Johnson (2012) also investigated 4- and 7-month-old infants' responses to voice and nonvoice stimuli, but using more specific nonspeech voice stimuli (e.g., crying, laughing, coughing, yawning) and familiar nonvoice stimuli (e.g., rattling toys and running water). Their results revealed that for children of all ages taken together, the posterior portion of the temporal sulcus showed greater bilateral activation in response to familiar nonvoice stimuli, whereas voice stimuli elicited greater activation in the anterior portion of the left temporal sulcus only. Furthermore, a significant correlation was found between the strength of the voice-selective response in the right temporal sulcus and the infant's age, suggesting that the cerebral specialization for voice processing becomes more robust in the right hemisphere as the infant's brain develops and the cortical response to different stimulation becomes more specialized. Similarly, Minagawa-Kawai et al. (2011) analysed native and nonnative speech responses in 4-month-olds along with their responses to three nonspeech conditions (emotional human vocalizations, primate vocalizations, and scrambled sounds of all conditions). Results revealed a strong response to human emotional vocalization in the right superior temporal gyrus, with a left lateralized response in the superior temporal gyrus and the supramarginal gyrus for the native speech condition. Hence, as in adult humans, structural and functional hemispheric asymmetry has often been reported in infant voice perception.

In sum, the debate continues as to whether right cerebral specialization for voice processing is already present in newborns and very young infants. Methodological differences between studies could partially account for the inconsistent results. Differences include familiar and unfamiliar nonvocal sounds as control stimuli, speech and nonspeech vocalizations, as well as disparities in the temporal and spatial resolution of the brain imaging techniques used. That said, the reviewed literature has highlighted the impact of familiarity and emotional information (or prosodic content) on the infant's behavioural and cerebral responses to voice. Infants' perceptions of emotional prosody therefore play a crucial role in social and language development. The next section of this chapter focuses more specifically on how infants process emotional prosody in speech and vocalizations.

2) How do infants learn to extract social meaning from perceived vocalizations?

Emotional prosody refers to nonverbal cues in vocal expression that communicate information about the speaker's affective state. Prosodic information includes voice intonation (pitch), loudness, pauses, and rhythms (Cutler, Dahan, & van Donselaar, 1997). The processing of this information has been frequently associated with activation in the right hemisphere in adults, whereas the processing of spectrotemporal changes in pitch and speech sound has been associated with the left hemisphere (Schönwiesner, Krumbholz, Rübsamen, Fink, & von Cramon, 2007; Zatorre, Belin, & Penhune, 2002; Zatorre, Evans, Meyer, & Gjedde, 1992). Interestingly, neuroimaging studies in adults have shown that the right temporal voice area (TVA; Belin et al., 2002) is also associated with the processing of strong intensity emotional prosody (Beaucousin et al., 2007; Ethofer et al., 2006; Grandjean et al., 2005).

Prosodic processing has been examined in infants using normally spoken speech contrasted with speech with flattened pitch contour, which modifies the sentences' prosodic properties. For instance, in an fNIRS study, full-term newborns were presented with normally pitched and flat-pitched story segments (Saito et al., 2007). Significant increase in the haemodynamic oxyhaemoglobin concentration was observed over the left and right frontal regions at the beginning of the normal pitch condition, but not for the monotonous flat-pitch condition. Moreover, greater activation of the right temporo-parietal regions was also found in quietly sleeping 3-month-olds in response to unaltered sentences compared to flattened speech, suggesting that this region might already be responsive to prosodic processing (Homae, Watanabe, Nakano, Asakawa, & Taga, 2006). Conversely, in a subsequent study, they found significantly higher activation of the right temporo-parietal and bilateral prefrontal regions in 10-month-olds in response to flattened speech compared to the unaltered speech condition (Homae, Watanabe, Nakano, & Taga, 2007). To explain these contrasting results, the authors suggested that the unfamiliarity of the flattened speech induced an additional demand in these cortical regions in older infants. Specifically, speech processing in the infant brain would progress from analysing basic acoustic and pitch information in 3-month-olds to the attentional mechanism modulation involved in comparing and integrating prosodic structures in 10-month-olds. Nevertheless, the cerebral mechanisms responsible for prosodic processing appear to differ or undergo developmental changes between 3 and 10 months of age. Taken together, these studies demonstrated that infants can discriminate prosodic patterns very early in life, and that they respond differentially to pitch variability compared with monotonous speech. However, further investigation is needed to clarify the developmental patterns of speech variability over monotonous flattened speech in the first year of life.

In an EEG experiment, Grossmann, Striano, and Friederici, (2005) presented words with an angry, happy, or neutral prosody to 7-month-olds to investigate the effect of emotional prosody on voice and speech processing. Results showed that words spoken with an angry voice elicited responses of higher amplitude than words spoken with a happy or neutral tone, suggesting that infants are liable to react more strongly to negative than positive or neutral voice stimuli. The greater response to negative stimuli might be indicative of an evolutionary “negative bias”, as suggested by Vaish, Grossmann, and Woodward (2008). Specifically, as in animals and human adults, infants’ propensity to pay attention to and process negative information is fundamental for social and adaptive development. It allows them to learn and to respond quickly to potential danger (Ohman, Lundqvist, & Esteves, 2001). In 2010, the same group used fNIRS to further investigate the cerebral network underlying this response in 7-month-olds (Grossmann et al., 2010). They found that happy and angry prosody elicited a significant haemodynamic oxyhaemoglobin increase over the right temporal region, albeit spatially distinct. Whereas angry prosody elicited higher activation over the posterior portion of the right temporal region, happy prosody elicited higher activation over the right inferior frontal region. The activation recorded in the right temporal cortex was larger in response to angry compared to happy prosody. These findings support the notion that the temporal voice area specializes in processing emotional prosody very early in infancy. They also showed that negative and positive prosody differentially impact voice processing within the right hemisphere, supporting the emerging body of evidence for the ontogenetic evolution of a negativity bias in infants (Vaish et al., 2008). Also supporting this negative bias, Blasi et al. (2011) presented 3- to 7-month-olds with positive, negative, and neutral nonspeech vocalizations as well as nonvocal environmental sounds during fMRI recording. Initially they found that, compared to environmental sounds, neutral and emotional vocalizations elicited higher activation in the right frontal and temporal gyri. Sad vocalizations also elicited activation in the left orbitofrontal and insular cortex, known to be involved in emotional processing of speech. In contrast, activation elicited by happy vocalizations did not differ from that elicited by neutral vocalizations. In another recent study, Cheng, Lee, Chen, Wang, and Decety (2012) measured EEG mismatch responses (corresponding to changes detected in the auditory environment) elicited by the syllables “dada” spoken with a fearful, happy, or neutral tone and by synthesized nonvocal stimuli in full-term newborns aged 1 to 5 days. In a first experiment, happily uttered syllables elicited a stronger mismatch response than nonvocal sounds, and this response was lateralized to the right hemisphere. In a second experiment, fearful compared to neutral syllables elicited a stronger response in the right hemisphere. In addition, fearful syllables elicited a stronger response than happy syllables, but this difference was found bilaterally over the frontal regions.

Taken together, these findings confirm that even a few days after birth, the infant's brain shows a preference for the human voice and emotional prosody processing. However, although most studies support early specialization for voice and prosody processing in the right hemisphere, the debate continues as to whether or not these abilities are due to early specialization of the neural networks in the infant's brain. Furthermore, little is known to date on how infants use the social and prosodic information transmitted by voice and speech stimuli to learn about their social environment and adjust to it. Nevertheless, developmental studies have clarified the influence of social stimuli and context on learning. For instance, it has been suggested that infants between 9 and 10 months of age can learn and discriminate phonetics in a foreign language as long as the learning sessions are supported by interpersonal interaction, as opposed to exposure to recorded audiotapes only (Kuhl, Tsao, & Liu, 2003). Additionally, Reeb-Sutherland et al. (2011) recently showed that 1-month-olds who performed an associative learning task showed improved performance when they were exposed to social (a female voice) versus nonsocial (tone or backward voice) auditory stimuli in a modified eye blink paradigm. Although more evidence is needed to fully understand how the developing child uses this information in the first few years of life, these results suggest that infants can learn more easily in socially and ecologically meaningful settings.

3) From voice perception to language acquisition: what are the major developmental steps?

We have reviewed the literature on the early perception and processing of vocal inputs in foetuses, newborns, and infants. Cognitive and linguistic development is grounded on early sensory experience. The nature of this experience is therefore likely to have long-lasting effects on cognition and language acquisition. Although questions remain as to whether the neural networks underlying these abilities are already specialized in the first few months of life, it is well recognized that these basic auditory skills are a prerequisite for subsequent speech processing and further language development. Specifically, when young infants start learning word forms, they encode not only the word, but also the properties of the speaker's voice, such as the prosody, pitch, and affect that are transmitted (Houston & Jusczyk, 2000). During the first months of life, this process becomes rapidly language-specific as infants start paying attention to phonemes and words that are relevant to their own language. With exposure and experience, they learn that the phonetic information (such as voice onset time and phonemic category boundary) indicates the word's semantic and lexical identity better than the voice characteristics do (Werker & Curtin, 2005). Hence, in this section of the chapter, we briefly describe how infants use these vocal cues to learn language, as well as the major steps in this acquisition process.

3.1 Early phoneme discrimination and perceptual narrowing

From birth, infants have a propensity to attend to vocal and speech sounds over nonspeech, and they continue to show this preference over the next several months (Vouloumanos & Werker, 2004, 2007). During the first months of life, infants can also discriminate speech-sound differences between rhythmically different languages (Werker & Tees, 2002). Furthermore, recent neuroimaging studies indicate that young infants and newborns show a preference for their native language over rhythmically different non-native languages (Minagawa-Kawai et al., 2011; Peña, Pittaluga, & Mehler, 2010; Sato et al., 2012; Vannasing et al., submitted). This discriminative sensitivity is probably due to the different rhythmic properties of speech, and it is preserved even when phonological cues other than rhythm are removed from the stimuli (Ramus, Hauser, Miller, Morris, & Mehler, 2000; Ramus, Pallier, Dupoux, & Dehaene, 2002). Moreover, studies of speech perception in monolingual infants have shown that the ability to differentiate between native and foreign speech sounds improves with exposure and experience (Bosch & Sebastián-Gallés, 2001; Kuhl et al., 2006; Sundara, Polka, & Genesee, 2006; Tsao, Liu, & Kuhl, 2006). The infant's ability to distinguish between sounds in a foreign language declines in the second half of the first year (Best & McRoberts, 2003; Kuhl et al., 2006; Kuhl & Rivera-Gaxiola, 2008; Werker & Curtin, 2005). For instance, in a high-amplitude sucking and head turning paradigm, 4-month-old Japanese babies distinguished between the /r/ and /l/ sounds as reliably as 4-month-olds raised in English-speaking households (Purves et al., 2001). At around age 10 to 12 months, infants living in English-speaking households, who are consistently exposed to English, become better at detecting the difference between the /r/ and /l/ sounds, which are prevalent in the English language. In contrast, at the same age, Japanese and Hindu babies, with less exposure to these sounds, decline in their ability to detect them (for a review, see Kuhl, 2004; Werker & Tees, 2002).

This dynamic could be explained by the perceptual narrowing that infants show around the end of the first year of life. Throughout this learning process, the sensitivity to vocal cues and phonetic information that are not featured in the child's linguistic and social environment gradually declines. Early experience with different languages therefore has lasting effects on speech perception. For instance, compared to monolingual infants, bilingual-learning infants take longer to establish phonetic categorical boundaries for their native language (Bosch & Sebastián-Gallés, 2001; Kuhl & Rivera-Gaxiola, 2008). Nevertheless, recent studies have also shown that although phonetic discrimination is less mature in bilingual infants aged 6 to 9 months than in same-aged monolingual infants, bilingual infants show increasing ability to discriminate between phonetic units in both languages with increasing age (Garcia-Sierra et al., 2011; Petitto et al., 2012; Rivera-Gaxiola, Silva-Pereyra, & Kuhl, 2005). Infants raised in a multilingual environment therefore appear to benefit from an extended period of sensitivity to learn different languages.

Conclusion

Whereas most previous developmental studies have investigated speech and language processing, very few have focused the anatomical and functional specificity of voice processing in infants. However, it is now well recognized that language acquisition as well as social development require adequate perceptual skills, and more particularly, voice perception and processing abilities in early infancy. In order to understand how infants learn social cues from perceived vocalization, the initial perceptual abilities that emerge in the late stages of foetal life and early infancy need to be considered, along with the age-related changes associated with speech processing within the first year of life. This chapter was motivated by three critical questions. 1) What are the underlying mechanisms of human voice perception in newborns and young infants? 2) How can infants extract and learn or process socially relevant information from perceived vocalizations? 3) What are the major developmental phases of these learning processes, particularly for language acquisition?

One conclusion that can be drawn from this review is that late prenatal and early postnatal auditory experience helps tune and shape the initial stages of voice perception and speech acquisition. Thus, foetuses and newborns show heightened interest toward social stimuli such as their mother's voice or emotionally charged speech stimuli compared to familiar nonvocal stimuli such as environmental sounds. However, investigations in infants of the cerebral basis for voice perception and the neural networks involved have yielded mixed results, and the developmental mechanisms underlying the functional and structural cerebral specialization for voice processing in infants remain controversial. Although voice-selective specialization may vary considerably across young infants, many researchers have hypothesized that this response becomes more robust by the second half of the first year, especially within the right hemisphere (Lloyd-Fox et al., 2012). Additionally, methodological differences across studies such as stimulus type and familiarity (e.g., speech versus nonspeech vocal stimuli), control conditions, paradigms, and imaging techniques as well as the infant's age could have produced conflicting results on the lateralization and specialization of a cerebral voice area in infants. Further investigations, particularly with cross-sectional or preferably longitudinal designs, could help clarify the comparative contribution of these factors.

Another significant conclusion that we may draw from this review is that infants show an early preference for social and familiar stimuli. It has been hypothesized that this preference might be the result of an evolutionary process, such that humans are more liable to treat social and familiar stimuli more favourably. Early exposure to human voices and the infant's abilities to process prosodic, phonetic, and familiar information in vocalization help establish the neural basis for language development. Nevertheless, despite recent findings, relatively little is known about the cerebral processing of voice sounds in infancy. Understanding how the infant's brain processes vocal and linguistic information requires an integrative approach that combines evidence from genetic, behavioural, structural, and functional brain imaging.

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Annexe 2: Developmental patterns of expressive language hemispheric lateralization in children, adolescents and adults using functional near-infrared spectroscopy

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Developmental patterns of expressive language hemispheric lateralization in children, adolescents and adults using functional near-infrared spectroscopy

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Abstract

The development of language hemispheric specialization is not well understood in young children, especially regarding expressive language functions. In this study, we investigated age-related changes in expressive language lateralization patterns in a population of children (3 to 6 and 7 to 10 years old), adolescents (11 to 16 years old), and young adults (19 to 30 years old). During functional Near-Infrared Spectroscopy recordings, all participants performed a verbal fluency task, which consisted in naming as many words as possible belonging to a given semantic category. Hemoglobin concentration changes were measured in bilateral frontal and temporal cortical areas. During the language task, results showed a strong left hemisphere response along with weaker right hemisphere activation in all groups. Age-related increases in hemodynamic responses were found bilaterally, with younger children showing smaller hemodynamic responses than adolescents and adults in both hemispheres. Overall, these findings confirm that a left hemisphere specialization is already established in young children and persists through adulthood. Early left hemisphere specialization for expressive language suggests that language development hinges on structural and functional properties of the human brain with little reorganization occurring with development.

Keywords: Near-Infrared Spectroscopy (NIRS), optical imaging, expressive language development, children, verbal fluency, hemispheric lateralization patterns

1. Introduction

It is now well recognized that language functions are associated with structural and functional hemispheric differences in adults (Cai, Van der Haegen, & Brysbaert, 2013; Hugdahl & Westerhausen, 2009; Knecht et al., 2000; Mazoyer et al., 1993). Geschwind & Levitsky (1968) were among the first to suggest a left structural asymmetry and reported a longer left *planum temporale* in a majority of the post-mortem brains they studied compared to the homologous area in the right hemisphere. Their findings supported the works of Pierre Broca in 1861 who observed left fronto-temporal lesions in aphasic patients, suggesting a left hemisphere functional dominance for language (Broca, 1861). Since then, anatomical asymmetries have been documented in infant and fetus brains, suggesting that hemispheric differentiation is already present at birth (Chi, Dooling, & Gilles, 1977; Glasel et al., 2011; Wada, Clarke, & Hamm, 1975).

Several neuroimaging and neuropsychological studies have also associated language processing with functional asymmetries within left frontal and temporal regions in healthy individuals and in various clinical populations (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000; Belin, Zatorre, & Ahad, 2002; Binder, Frost, Hammeke, Rao, & Cox, 1996; Dorsaint-Pierre et al., 2006; Gallagher, Bastien, et al., 2008; Gallagher, Béland, & Lassonde, 2012; Knecht et al., 2000; Springer et al., 1999; Szaflarski et al., 2002; Szaflarski, Holland, Schmithorst, & Byars, 2006; Vannest, Karunanayaka, Schmithorst, Szaflarski, & Holland, 2009; Zatorre, 1989). However, little is known about the development of language hemispheric specialization throughout childhood and adolescence, especially regarding expressive language functions. Indeed, research in this domain remains sparse and it is still unclear whether language maturation relies on inborn functional properties within the left hemisphere or if functional hemispheric specialization matures with experience and exposure to a given language (Dehaene-Lambertz, Hertz-Pannier, & Dubois, 2006).

Regarding receptive language function, studies using various brain imaging techniques in typically developing individuals have supported a left lateralization for speech-sounds processing already present at birth (Beauchemin et al., 2010; Peña et al., 2003) or in the first months of life (Bortfeld, Fava, & Boas, 2009; Bortfeld, Wruck, & Boas, 2007; Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Dehaene-Lambertz, 1997; Kuhl et al., 2006). Other evidence from electroencephalography recordings suggested that the temporal lobe contains specific neural circuits for phoneme discrimination (Marie Cheour et al., 1998). More recently, it has been found that newborns discriminate between the vowel /a/ spoken by the mother's voice and spoken by a female stranger's voice: a left temporal activation was found for the mother's voice and a right temporal activation for the stranger's (Beauchemin et al., 2010). These results were interpreted as indicative of a phonemic discrimination in the mother's voice only, supporting functional left lateralization at a very young age for receptive language abilities.

In contrast, studies investigating expressive language functions in children have produced controversial results. Some suggest that left hemispheric specialization is probably not well established in young children and continues to increase with age, possibly into early adulthood (Berl et al., 2012; Everts et al., 2009; Gaillard et al., 2000; Holland et al., 2001, 2007; Lidzba, Schwilling, Grodd, Krägeloh-Mann, & Wilke, 2011; Ressel, Wilke, Lidzba, Lutzenberger, & Krägeloh-Mann, 2008; Szaflarski, Holland, Schmithorst, & Byars, 2006). For instance, Holland et al. (2001) found a significant relationship between hemispheric specialization of language functions and age in children aged 7 to 18 years who completed a verbal fluency task during an fMRI recording. These authors showed increasing degrees of left hemisphere dominance with age. In another study, they also found correlations between degrees of left hemisphere lateralization for language functions and age, but also showed that the lateralization pattern varies depending on the task (Holland et al., 2007). Specifically, the authors presented their subjects, aged between 5 and 18 years, with four language tasks involving different cognitive processes (verb generation, story processing, syntactic prosody and word-picture matching tasks) to evaluate age-related changes in lateralization according to each paradigm. Results showed that age-related changes in lateralization patterns in healthy children were stronger and cerebral activations were more left lateralized during a verb generation task than during the other three tasks. In addition, the greatest changes were observed in the inferior frontal gyrus and dorsolateral prefrontal regions. These results support earlier work by Wood et al. (2004) showing that the degree of lateralization changes with age might be task-dependent. The authors examined children, adolescents and adults while they performed a verb generation task and a verbal fluency task (lexical retrieval) during an fMRI scan. Most children showed left-lateralized activation patterns, but the strength of hemispheric dominance increased with age only in the case of the verb generation task.

Others, however, have documented similar language representations in children aged between 7 and 14 years and adults using a verbal fluency task, suggesting that language lateralization patterns related to expressive language are already established by age 7 (Gaillard et al., 2003). Likewise, using a picture naming task in a MEG study, Sowman, Crain, Harrison & Jonhson (2014) found significant left lateralization in 24 preschool-aged children aged 3 to 6 years, suggesting that cerebral regions responsible for language production are already left lateralized at this young age. Moreover, in a recent study by Cai and colleagues (2013), the authors examined a group of left-handed participants with atypical right hemispheric speech dominance and found that they were all also atypically left hemispheric dominant for spatial attention. This result (Cai et al., 2013) supports the innate origin hypothesis of language lateralization since there is little probability that the opposite asymmetry of both functions in all their participants could be due to independent lateralization rather than to a common origin.

Overall, controversy still exists for expressive language lateralization representation in children, adolescents and adults. Divergent conclusions regarding the maturation of expressive language dominance may stem from methodological differences regarding sample age ranges and language tasks in these studies. To our knowledge, there is no study investigating expressive language development covering both an extensive age range and an early stage of expressive language development using the same task across ages. In addition, another major limitation stems from difficulties in assessing expressive language functions in young children, mainly because of movement restrictions and difficulty in assessing task performance during data acquisition. For instance, various neuroimaging techniques, including fMRI (Gaillard et al., 2000; Holland et al., 2001, 2007; Szaflarski et al., 2006) and magnetoencephalography (MEG) (Kadis et al., 2011; Ressel et al., 2008; Sowman, Crain, Harrison, & Johnson, 2014), have been employed to examine the developmental dynamics of expressive language. Alternately, functional near-infrared spectroscopy (fNIRS) is a non-invasive, functional imaging technique that has no major restrictions on movements or verbalization during recording, which renders the technique suitable for investigations in young children (Wilcox, Bortfeld, Woods, Wruck, & Boas, 2005). This technique is based on the light absorption properties of oxyhemoglobin (HbO), deoxyhemoglobin (HbR) and total hemoglobin (HbT) concentrations within the near-infrared spectrum, allowing for measurement of hemodynamic changes related to cerebral activity (Boas, Dale, & Franceschini, 2004; Gratton, Fantini, Franceschini, Gratton, & Fabiani, 1997; Gratton, & Fabiani, 2007; Strangman, Boas, & Sutton, 2002; Watanabe et al., 1998). In the past few years, our research group has successfully used fNIRS for the assessment of expressive and receptive language abilities in healthy adults (Paquette et al., 2010) and children (Gallagher et al., 2007), epileptic patients (Gallagher, Bastien, et al., 2008; Gallagher, Lassonde, et al., 2008), and healthy adults performing a reading aloud task (Safi et al., 2012). However, NIRS studies investigating left and right hemispheric specialization in young children have mainly used receptive language paradigms in contrast with expressive language development (for recent reviews, see Homae, 2014; Rossi, Telkemeyer, Wartenburger, & Obrig, 2012).

Given the methodological differences between previous studies and the limitations regarding the assessment of children performance in a scanner, the present study aimed to characterize the maturation patterns of hemispheric specialization for expressive language functions in a sample covering different developmental stages of development (3 years old to adulthood), using the same expressive language task (verbal fluency) across ages. In order to accurately evaluate expressive language development across all ages, we used fNIRS, which allows subjects to speak overtly due to its relatively good tolerance to movement and thus allows monitoring of the child's performance. This task was used by our team in several previous studies (Gallagher et al., 2007; Gallagher, Bastien, et al., 2008; Gallagher, Lassonde, et al., 2008) and was shown to reflect vocabulary knowledge that starts to develop in preschool years and continues to grow through adulthood. It was chosen based on studies by Holland and colleagues (2001; 2007) and Woods and colleagues (2004), who showed that age related-changes in lateralization varies depending on the task, with the greatest age changes identified using this task. Thus, it was hypothesized that if language specialization establishes itself early in childhood, left brain areas devoted to expressive language processing (Broca's area) should be activated in young children and little reorganization should occur with development. In contrast, if cerebral language dominance is developed with experience and exposure to language, a more bilateral activation pattern should be observed early in development with a gradual left hemisphere specialization with age.

2. Methods

2.2 Participants

Thirty-two French-speaking children (3 to 16 years old, 16 males / 16 females) performed a verbal task during fNIRS recording. Based on previous developmental studies (Bishop 2011; Paquette et al., 2013), and in order to reflect their developmental cognitive stage (Piaget & Inhelder, 1969; Piaget, 1972), children were grouped into three age ranges covering different developmental stages: early childhood or preschool age (3 to 6 years old, n=10), late childhood or school age (7 to 10 years old, n=10) and adolescence (11 to 16 years old, n=12). In order to identify the age range in which lateralization patterns of expressive language functions adopt the adult pattern, 11 French-speaking young adults (19 to 30 years old, five males / six females) were also recruited. In addition, in order to support our age range division, we looked at homogeneity of individual data among groups using dispersion graphs of HbO values in left and right anterior and posterior ROIs. We performed Z-score analyses on each subject's individual data according to his/her respective group average. All results were less than 2.5 standard deviations from the respective group average, except for one adolescent who has been excluded (mean HbO concentration more than 3.5 standard deviations from the group average).. Data from two adult participants (deactivation recorded in all channels or no hemodynamic changes observed) were also withdrawn from the original sample. Other exclusion criteria included history of hearing, speech, language, and neurological or developmental disorders. Subsequent analyses and results included a total of 40 participants. The demographic data of the participants is presented in Table 1.

Insert Table 1 here.

2.3 Procedure

Each of the participants or their parents had to carefully read and sign a consent form providing detailed information about the experimental procedure approved by the Ethics Committees of Sainte-Justine University Hospital Center. Prior to the fNIRS recording, handedness was assessed using the Edinburgh Inventory (Oldfield, 1971). To assess handedness in participants younger than 10 years old, a child-friendly homemade version of the Edinburgh Inventory was used.

fNIRS sessions took place in a dark, soundproof room. All participants completed a verbal fluency task requiring the naming of as many words as possible belonging to a given category (e.g. animals, toys or fruits). Each participant was seated in a comfortable chair, placed approximately 45 inches from a 20-inch computer screen. Using the *Presentation* software (Neurobehavioral Systems Inc., Albany, CA, USA), semantic categories were successively and visually presented on a monitor in a block-design paradigm. The youngest children received auditory assistance in reading the category nouns. Each block had a 90-second duration which was divided as follows: a 30-second baseline period, followed by 30 seconds of verbal fluency and a 30-second resting period. All participants completed a practice session, followed by 11 blocks, each associated with a different semantic category meaningful to young children.

2.4 Functional near-infrared spectroscopy recording

fNIRS recordings were performed using a multi-channel Imagent Tissue Oxymeter (ISS Inc., Champaign, IL, USA) with 32 sources operating at 690 nm, 32 sources operating at 830 nm, and 8 detectors (photomultiplier tubes connected to the head by 3 mm fiber bundles). The Oxymeter used a frequency domain, time-resolved method that provides a precise quantification of HbO and HbR concentrations. The cerebral activity was recorded over bilateral frontal, temporal and temporo-parietal areas, thus covering the anterior (Broca's area) and posterior (Wernicke's area) language networks and their right counterparts. The source-detector distance was held constant between three and five centimeters and the optical fibers were maintained on the surface of the head using a rigid helmet. Several helmets of different sizes were available to ensure that an appropriate helmet size was used for each participant. A standard montage was created and adapted for each helmet according to the 10-20 system and the corresponding Brodmann Areas (BA). The regions of interest (ROIs) covered the F3/4 (BA 6, 8 and 9), F7/8 (BA 44, 45, 46 and 47), T3/4 (BA 21 and 42), and T5/6 areas (BA 37 and 39). Figure 1 shows the regions covered by the montage over left and right hemispheres.

Insert Figure 1 here

Optical intensity (DC), modulation amplitude (AC) and phase data were obtained at an acquisition rate of 19.5312 Hz. For each participant, the exact localization of each source and detector, as well as four fiducial points (nasion, left and right pre-auricular, and tip of the nose), were digitized and recorded using the stereotaxic system *BrainsightTM Frameless 39* (Rogue research Inc., Montreal, QC, Canada) allowing for individual registration and reconstitution of the montage on a MRI template (*Colin27*, see Evans, Collins, & Milner, 1992). Total duration of the fNIRS session, including consent, positioning of sources and detectors, and recording, was approximately 90 minutes.

2.5 Data analysis

The optical intensity was selected for subsequent analysis to estimate changes in HbO and HbR concentrations. Optical intensity was first normalized according to the baseline. Automatic artifact detection was then applied to the normalized data and visual examination of each time-series was performed by two experimenters (N.P., J.T.) in order to detect abrupt changes in light intensity (inter-rater agreement of 0.95 was obtained). As young children often show movement artifacts, abrupt variations of intensity were corrected and short duration movement artifacts were removed and interpolated before filtering. Individual blocks were excluded from the analysis if they comprised more than 15 % of movement artifact. Data was filtered using a band-pass filter of 0.1 Hz and Modified Beer Lambert Law with differential path length factor (DPF) corrections was applied according to the age of the participant (Duncan et al., 1996; Strangman, 2003). Variations in HbO and HbR concentrations were then averaged for each channel across the 11 blocks. The averaged data was co-registered and projected on the MRI template from the Montreal Neurological Institute in order to visualize the activated brain regions (Holmes et al., 1998). Data analyses were performed using Matlab version 7.9 (The Mathworks, USA) and HomER^{TM} (PMI Laboratory, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA).

For each participant, a visual inspection of HbO and HbR concentration data was performed for baseline, verbal task and resting periods. Because language production is a main function of Broca's area, channels with the highest amplitude changes in ROI covering Broca's area (BA 44, 45, 46 and 47) were selected for further analyses. In order to assess the reliability and the specificity of the hemodynamic response recorded in Broca's area with regard to expressive language function, the activity recorded over the posterior region (Wernicke's area and homologous right regions) (BA 21, 42, 37, 39) was also included in the analyses.

Statistical analyses were carried out using the SPSS statistics program, version 21.0 (SPSS Inc., Chicago, IL, USA). A three-way ANOVA (group (4) x hemisphere (2) x region (2)) was used to quantify age-related differences in amplitude of the hemodynamic responses using mean HbO concentration in a 5-second time-window centered on the HbO peak, for each participant. Hemisphere (left; right) and region (Broca; Wernicke) were the within-subject factors, and group was the between-subjects factor (3 to 6 years old; 7 to 10 years old; adolescents; adults). Bonferroni correction for multiple comparisons and Greenhouse-Geisser adjustments for violation of sphericity were performed (corrected p values are reported), and post-hoc pairwise comparisons were performed using Tukey's Honest Significant Difference (HSD) test. In addition, to ensure that the hemodynamic changes between groups were related to maturational changes, rather than to task performance, correlational analysis between the number of words named during the task and HbO concentration changes recorded over left and right Broca's and Wernicke's areas were performed using Pearson correlational analysis. For all analyses, alpha levels of $p < 0.05$ was considered significant.

3. Results

3.1 Behavioral results

All participants produced words aloud in the verbal fluency task. The total number of words pronounced by each participant is presented in Table 1. A one-way ANOVA revealed that the amount of words named differed significantly across groups (F (3, 37) = 12.01, $p < 0.001$). Tukey HSD multiple comparisons showed that the younger children's group produced significantly fewer words (mean = 79.70, SD = 15.63 words) than adolescents (mean = 124.27, SD = 37 words) ($p = 0.004$) and adults (mean = 154.78, SD = 31 words) ($p < 0.001$). Older children also pronounced significantly fewer words (mean = 112.88, SD = 18.29 words) than adults ($p = 0.018$). Similar comparisons between younger and older children, older children and adolescents, and adolescents and adults were not significant ($p > 0.05$).

3.2 fNIRS results

The minimum number of trials included in the analyses was of 6 blocks per participant. The total number of trials included in the analyses did not differ significantly between groups ($F_{(3,39)}$: 2.56, $p = 0.07$). However, the adult group tended to have more blocks included in their analyses than did the 3- to 6-year-old children ($p = 0.077$) due to less movement artifacts while performing the verbal fluency task (number of trials; 3 to 6 years old: mean = 8.7 trials, SD 1.34; 7 to 10 years old: mean = 9 trials, SD 1.56; adolescents: mean = 9.27 trials, SD 1.56; adults: mean = 10.33 trials, SD 0.71).

Figure 2 shows mean hemodynamic responses (HbO, HbR and HbT concentrations) recorded during the verbal fluency task over the left (blue lines) and the right (red lines) Broca's and Wernicke's areas (BA 44, 45, 46, 47; BA 21, 42, 37, 39) for each of the four groups. Topographic representations at 25-second latencies after language task onset are represented next to their corresponding waveforms. In all groups, strong initial activations (i.e. increase in HbO concentration) are seen in Broca's area during the language task along with weaker activations in the mirror area of the right hemisphere. In contrast, little activation could be observed in Wernicke's area and its right counterpart, especially in younger and older children. Table 2, Figure 3 and Figure 4 show the averaged concentration of HbO and HbR for each hemisphere in each group.

Insert Figure 2 here.

3.2.1 *Group, region and hemisphere effects on HbO concentration.*

ANOVA calculated on the mean HbO concentration over Broca's and Wernicke’s areas and their right homologous counterparts revealed significant main effects for group (F (3, 36) = 5.03, $p = 0.005$), region (F (1, 36) = 127.24, $p = 0.001$) and hemisphere (F (1, 36) = 7.05, $p = 0.012$), along with a significant hemisphere by region interaction (F (1, 36) = 32.16, $p = 0.001$). Tukey HSD post-hoc analyses and pairwise comparisons showed higher HbO concentrations in the left hemisphere (mean 12.31, ± 0.996 µmol/L) than in the right hemisphere (mean 9.808, ± 0.943 µmol/L) in all groups. Significantly higher HbO concentrations were also found in the left Broca’s areas compared to left Wernicke’s areas (Broca left: 19.206, ± 1.197; Wernicke left: 5.42, ± 1.114) ($p = 0.001$). However, no significant differences could be observed between those regions in the right hemisphere (Broca right: 13.54, ± 1.136; Wernicke right: 6.079, ± 0.999) ($p = 0.530$). In addition, when all regions were taken together, younger children showed significantly smaller amplitude responses than adolescents ($p = 0.015$) and adults ($p = 0.013$) (younger children: 6.244, ± 1.691; adolescents: 13.841, ± 1.613; adults 14.368, ± 1.783 µmol/L). Similar comparisons between younger and older children (9.789, ± 1.691 µmol/L) and between adolescents and adults or older children were not significant ($p > 0.05$). No other interactions were significant.

Correlation analyses between the number of words produced by participants and the brain activation amplitude recorded over the 4 ROIs were not significant (Broca left: $r = 0.303$, $p = 0.064$; Broca right: $r = 0.289$, $p = 0.078$; Wernicke left: $r = 0.109$, $p = 0.516$; Wernicke right: $r = 0.127$, $p = 0.446$).

Insert Figure 3 here

Insert Table 2 here

3.2.2 Group, region and hemisphere effects on HbR concentration.

An ANOVA calculated on the mean HbR concentration over Broca's and Wernicke's areas and their right homologous counterparts revealed a significant main effect for region (F (1, 36) = 8.979, p = 0.005). Pairwise comparisons revealed that for all groups, in both hemispheres, HbR concentration was significantly lower in Broca's areas (mean = -3.119, ± 0.554 μmol/L) than in Wernicke areas (mean = -1. 454, ± 0.422 μmol/L). Main effects for group, hemisphere, and group by region or by hemisphere interactions were not significant.

Insert Figure 4 here

Insert Table 3 here

4. Discussion

Previous studies report conflicting results regarding left hemispheric specialization for language: is it established in early childhood or does it develop with age and exposure to linguistic stimuli? Some authors have reported that hemispheric lateralization for speech processing observed in children is not as strong as in adults (Holland et al., 2001, 2007), suggesting that consolidation might occur during language acquisition. In contrast, Gaillard. and colleagues (2003) found no association between age and language asymmetry representation within a group of children between 7 and 14 years old. Furthermore, they found similar proportions of left language lateralization in children and adults, suggesting an already well-established left expressive language specialization at 7 years of age. Controversial conclusions from previous studies may stem from methodological issues regarding imaging techniques or language paradigms. In the present study, we aimed to investigate the maturation of expressive language lateralization patterns through childhood and adolescence using fNIRS and the same language paradigm in all age groups. However, as reported in the Results section, analyses on HbR concentration were not significant, either for hemispheres or for groups. In fact, most fNIRS studies reported HbO, or HbT, rather than HbR, mainly because HbO and HbT tend to show larger responses than HbR, due to physiology (for a review, see Ferrari & Quaresima, 2012). Therefore the following discussion will focus mainly on HbO results.

Our results showed that left hemisphere dominance found during a verbal fluency task was already present in the youngest group of children. At this age range (3 to 6 years), hemodynamic responses were significantly stronger in the left hemisphere than in the right one, and this left-lateralized language pattern persisted through adulthood. This finding suggests a cerebral specialization of Broca’s area in the very early stage of expressive language development, supporting earlier work by Sowman and colleagues (2014) who showed a left cerebral specialization in 3- to 6-year-old children performing a picture-naming task. In addition, in our study, activity recorded over the posterior control regions (Wernicke's area) did not differ between hemispheres, supporting the hypothesis for a specialization of the left Broca's area for expressive language functions in children and adolescents.

Our findings also revealed that mean amplitudes in HbO concentration of hemodynamic responses in the adolescents and adults were greater than those recorded in the younger children’s group, showing greater involvement of both hemispheres in older participants. Furthermore, correlational analyses suggested that this increasing involvement of both hemispheres was most likely due to maturational changes rather than task performance changes over age. The increasing involvement of left and right hemispheres with age in Broca's area might reflect gradual maturation of the white matter in this region, which allows for more efficient inter- and intra-hemispheric task-specific information exchanges (Luders, Thompson, & Toga, 2010). Indeed, white matter maturation is an important part of brain development from childhood through adulthood, allowing a faster and more effective communication within specific brain regions and between hemispheres (Nagy et al., 2004; Paus, 2005). For instance, it has been shown that the corpus callosum undergoes maturation in children from 5 to 18 years old, characterized by a gradual increase in callosal thickness following an anterior-to-posterior growth pattern (Thompson et al., 2000). Our results thus contribute to the understanding of cerebral development through childhood and adolescence in regions specifically devoted to language production.

A growing number of studies have reported distinct patterns of brain activation in children, adolescents, and adults, notably regarding the development of language function (Gogtay et al., 2004; Luna et al., 2001; Moore & Linthicum Jr, 2007; Paquette et al., 2013; Porter, Collins, Muetzel, Lim, & Luciana, 2011). In a study assessing the relationship between language abilities and cortical thickness across development, Porter et al. (2011) found a significant relationship between increasing speech fluency skills and decreasing cortical thickness in regions involved in the language network, such as Wernicke's and Broca's areas and the perisylvian regions. Conversely, others have described a positive association between cortical thickness in most multimodal associative areas and the overall IQ measured in samples of healthy children, adolescents (Karama et al., 2009; Shaw et al., 2006) and young adults (Narr et al., 2007). Although there is an agreement across studies that cortical grey and white matter changes follow a non-linear pattern throughout childhood and adolescence, further research is needed to fully understand the impact of the ongoing structural and functional changes in the developing brain and specific cognitive functions such as languages processes.

4.1 Methodological considerations

As stated above, controversial results from previous studies on language developmental patterns may stem from differences in methodology, including the use of different imaging techniques (fMRI, MEG, ultrasound Doppler, etc.) and the use of different language paradigms. In addition, several imaging techniques, including fMRI, do not always allow the participant to perform an expressive language task overtly into the scanner, and thus does not permit the measurement of task performance. Therefore, the experimenter cannot ensure that the child understood and performed the task adequately. Furthermore, most techniques require the participant to remain still during data acquisition, which might be a great challenge for young children. fNIRS tolerates body movements and allows the child to speak out loud during data acquisition, which enables the examiner to measure his performance. In our previous work, we showed that the verbal fluency task used in the present study was appropriate to elicit a clear activation in the Broca's area in healthy and epileptic adults and children (Gallagher et al., 2007; Gallagher, Lassonde, et al., 2008; Gallagher, Bastien, et al., 2008). We also found a good concordance between fNIRS, fMRI and the intracarotid amobarbital test (IAT or Wada Test) for expressive language brain localization in patients with epilepsy (Gallagher et al., 2007; Gallagher, Lassonde, et al., 2008). Indeed, this language protocol is now used as a non-invasive alternative to IAT and fMRI in children with epilepsy who cannot tolerate IAT or fMRI (Gallagher, Bastien, et al., 2008).

4.2 Study limitations and further directions

In the present study, we used a cross-sectional design to investigate the developmental patterns of language. However, it is well recognized that childhood is often characterized by high inter-individual variability, especially regarding functional and structural brain maturation (Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002; Paus, 2005; C. Ponton et al., 2002). Because of the small sample size of this study, inference about infant and children language development is limited. A longitudinal design and a larger number of participants in each age group may clarify some results and define the trajectory of language development more precisely. In addition, it would be interesting in further studies to investigate the qualitative aspects of speech production such as motor ability, lexical access, or prosody and their respective influence on hemispheric lateralization of language functions.

5. Conclusions

In summary, our results suggest that left hemispheric lateralization for expressive language is present early in development, as has previously been documented for receptive language functions (Beauchemin et al., 2010; Bortfeld et al., 2009, 2007; Dehaene-Lambertz et al., 2002; Kuhl et al., 2006; Peña et al., 2003). However, the involvement of cortical language brain areas becomes greater with increasing age, probably due to maturation and myelination processes gradually taking place during brain development. Likewise, gradual maturation and myelination of the corpus callosum throughout childhood and adolescence may allow for the increasing involvement of the right hemisphere. To our knowledge, this is the first study that attempted to characterize the maturation of expressive language patterns with fNIRS from such an early stage, during childhood and adolescence, and to assess the emergence of the adult pattern. Similar to receptive language function, expressive language left lateralization seems to be established at an early developmental stage and both hemispheres appear to become functionally more involved in language function during adolescence and adulthood.

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Tables and Figures

Table 1. Demographic data of the participants

Participant	Gender	Age	Handedness	Number of words named during the task
FVL113	F	3	R	54
FVE04	M	4	R	81
FVE30	F	4	R	63
FVE17	M	5	R	85
FVE34	M	5	R	75
FVE23	F	5	B	83
FVE28	M	6	B	67
FVE06	F	6	R	91
FVE14	F	6	R	108
FVE03	F	6	R	90
FVE01	F	7	R	–[a]
FVE24	M	7	R	108
FVE02	F	8	R	–[a]
FVE33	F	8	R	100
FVE26	M	8	R	120
FVE07	M	9	B	107
FVE35	F	9	R	97
FVE05	M	10	R	154
FVE32	M	10	R	102
FVE36	F	10	R	115
FVE22	M	11	R	138
FVE15	F	11	R	124
FVE16	M	13	R	137
FVE13	F	13	R	199
FVE31	M	14	R	72
FVE18	F	14	R	176
FVE09	M	15	R	105
FVE11	M	15	B	93
FVE12	M	15	R	114
FVE08	F	15	R	97
FVE27	M	16	R	112
FVE10	F	16	R	198[b]
FVE19	F	23	R	135
FVE25	M	23	R	129
FVE21	M	20	B	130
FVE20	F	23	R	186
FVE29	F	19	R	188
FVL310	M	28	R	110
FVL311	M	25	R	–[a,b]
FVL312	F	26	B	163
FVL301	M	28	R	–[a,b]
FVE01	M	30	R	198
FVE02	F	24	R	154

M=Male; F=Female; R=Right; B=Bilateral

[a] Missing values due to technical issues.

[b] Excluded from analyzes due to extreme hemodynamic values.

Table 2. Mean amplitudes (micromolar/L) in HbO2 and HbR concentration in Broca's area and right counterpart

Groups (*n*)	Left hemisphere (SD)		Right hemisphere (SD)	
	HbO_2	HbR	HbO_2	HbR
3–6 years (*n*=10)	13.9 (5,61)	−2.93 (3,66)	6.14 (6,33)	−1.17 (3,82)
7–10 years (*n*=10)	18.15 (9,2)	−1.86 (3,68)	11.84 (7,24)	−1.76 (5,03)
11–16 years (*n*=11)	20.65 (4,71)	−2.69 (4,61)	17.12 (5,37)	−3.91 (3,96)
Adults (*n*=9)	24.12 (9,93)	−6.29 (3,87)	19.06 (9,54)	−4.32 (3,74)

Table 3. Mean amplitudes (micromolar/L) in HbO2 and HbR concentration in Wernicke's area and right counterpart

Groups (*n*)	Left hemisphere (SD)		Right hemisphere (SD)	
	HbO_2	HbR	HbO_2	HbR
3–6 years (*n*=10)	2.86 (5,43)	−0.93 (4,06)	2.08 (3,43)	−2.08 (3,79)
7–10 years (*n*=10)	3.45 (6,75)	−0.62 (3,68)	5.73 (6,16)	−0.65 (3,10)
11–16 years (*n*=11)	6.89 (3,06)	−1.05 (1,89)	10.71 (5,08)	−2.11 (2,67)
Adults (*n*=9)	8.48 (11,24)	−2.95 (2,56)	5.81 (9,53)	−1.23 (2,99)

Figure legends

Figure 1. Schematic view of the regions covered by the montage. Optical channels covered BA 6, 8, 9, 44, 45, 46 and 47 in the frontal cortex; BA 21, 42, 37 and 39 in the temporal cortex and homologous right regions. Big dots represent the detectors and small dots represent the sources (combined 690 and 830 nm).

Figure 2. Time course (X-axis) of the mean hemodynamic responses measured over left (blue lines) and right (red lines) ROIs during the verbal fluency task (horizontal green line) and rest period in children 3 to 6 years old, 7 to 10 years old, adolescents 11 to 16 years old, and adults, respectively. The Y-axis indicates relative changes in concentration (micromolar) for HbO (solid lines), HbR (dotted lines) and HbT (shadowed lines). Cerebral language activation in Broca's area is characterized by a large increase in HbO, accompanied by a small decrease in HbR. Topographic representations of the cerebral activation at 25 seconds are represented next to their corresponding hemodynamic curves, the color scale indicating mean HbO concentration (μmol/L).

Figure 3. Histograms of averaged hemodynamic responses in HbO (A) and HbR concentration (B) recorded over Broca's area for each group during the language task. Blue bars represent the response recorded in the left hemisphere and purple bars represent the responses recorded in the right hemisphere. The Y-axis indicates the averaged mean changes in concentration (in micromoles) for each group. Error bars indicate the standard errors. Significant effects for Group and Hemisphere factors on mean HbO concentration are also represented.

Figure 4. Histograms of averaged hemodynamic responses in HbO (A) and HbR concentrations (B) recorded over Wernicke's area for each group during the language task. See Figure 3 for the legend description. The Y-axis indicates the averaged mean changes in concentration (in micromoles) for each group. Error bars indicate the standard errors. Significant effects for Group and Hemisphere factors on mean HbO concentration are also represented.

Figure 1. Schematic view of the regions covered by the montage

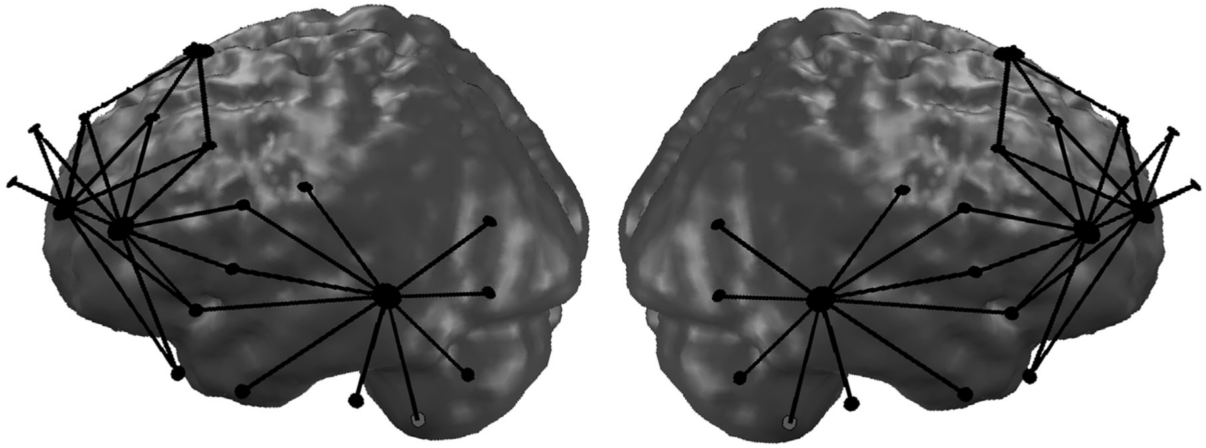


Figure 2. Time course of the mean hemodynamic responses measured over left and right ROIs

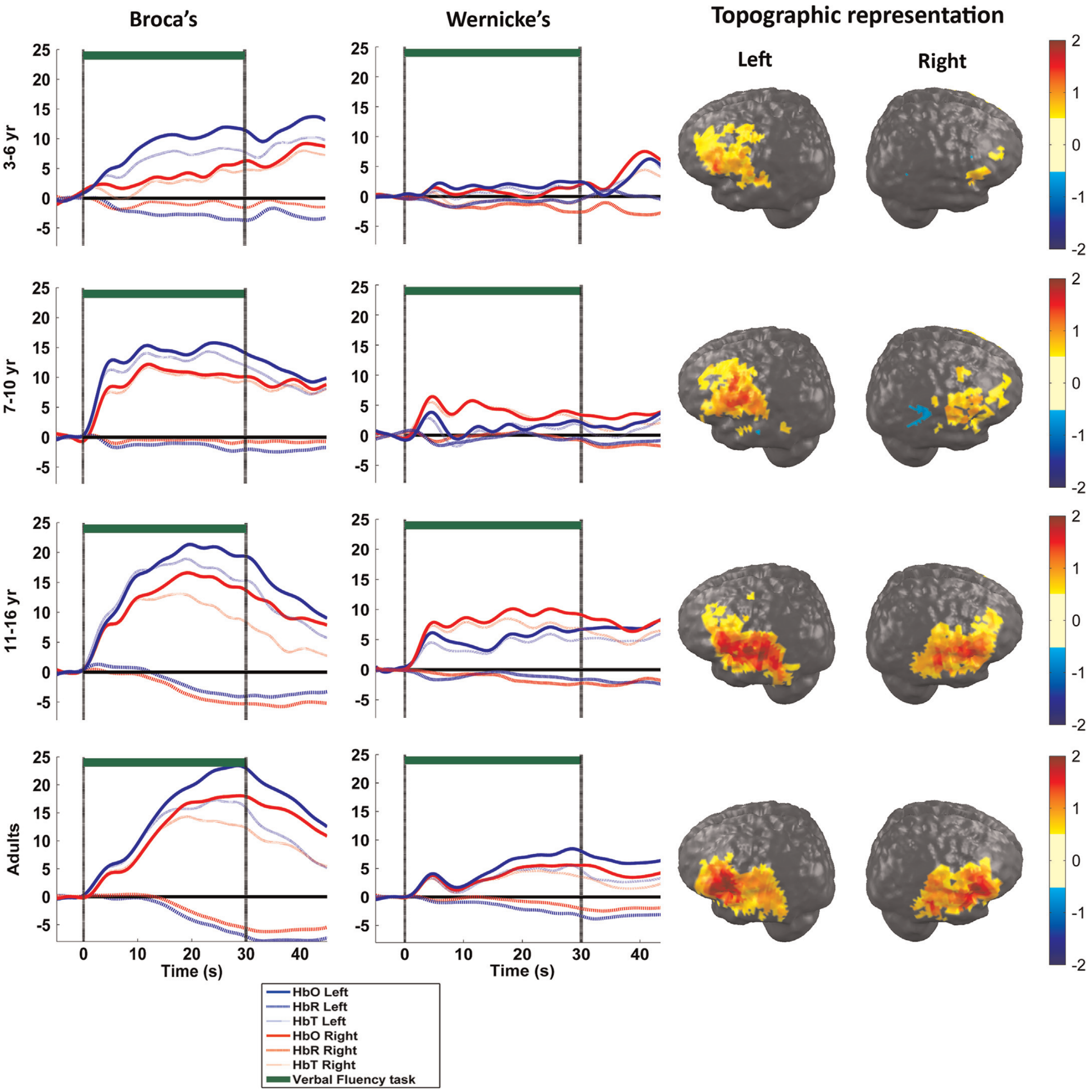


Figure 3. Histograms of averaged hemodynamic responses in HbO and HbR concentration recorded over Broca's area

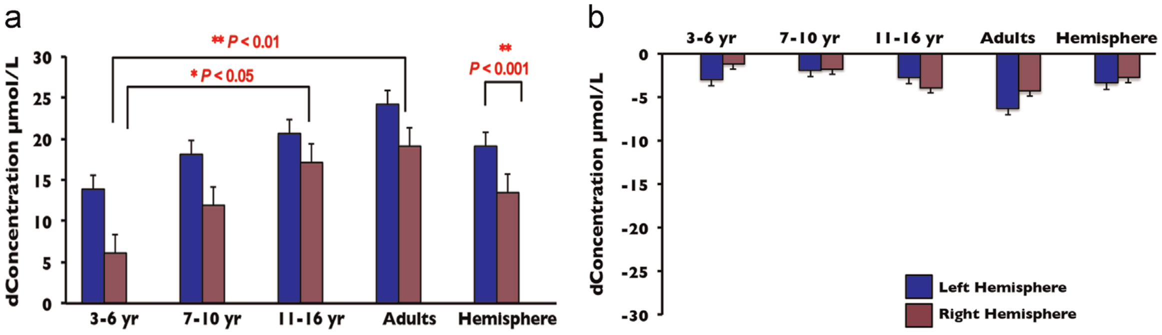
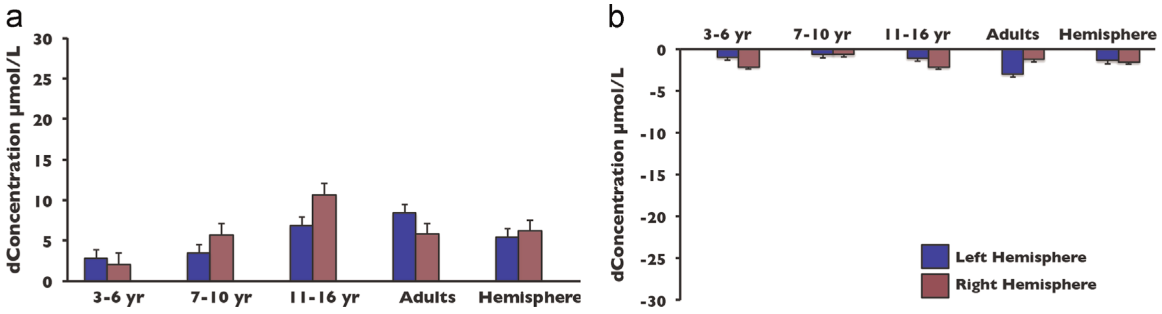


Figure 4. Histograms of averaged hemodynamic responses in HbO and HbR concentration recorded over Wernicke's area



Annexe 3 : Lateralization of receptive language using near infrared spectroscopy

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Lateralization of receptive language function using near infrared spectroscopy

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Running title : NIRS in receptive language brain mapping

Abstract

In recent decades, functional magnetic resonance imaging (fMRI) has proven to be more effective than the Wada test in the evaluation of language lateralization in special populations such as epileptic patients and children. However, fMRI requires that subjects remain motionless during data acquisition, making the assessment of receptive and expressive language difficult in young children and population with special needs. Near-Infrared spectroscopy (NIRS) is a non-invasive technique that has proven to be more tolerant to motion artifacts. The aim of the present study was to investigate the use of NIRS to assess receptive language patterns using a story listening paradigm. Four native French-speakers listened to stories read aloud by a bilingual speaker in both French and Arabic. To determine if the signal recorded was affected by episodic memory processes, a familiar story and an unknown story were presented. Results showed that listening to stories in French elicited a significantly higher left lateralized response than listening to stories in Arabic, independently of the familiarity of the story. These results confirm that NIRS is a useful non-invasive technique to assess receptive language in adults and can be used to investigate language lateralization among children and epileptic patients slated for epilepsy surgery.

Key words: Language lateralization, Near infrared Spectroscopy (NIRS), Optical Imaging, Brain mapping, Epilepsy.

Pre-surgical examination of epileptic patients traditionally includes language lateralization assessment [1]. However, language is a complex entity involving multiple levels of processing. Expressive language tasks (e.g. verbal fluency) are the most frequently used paradigms to investigate language lateralization [2, 3]. Receptive language paradigms, however, may be more suitable when working with young children or patients with mental retardation as they do not require active participation of the subject [4]. A number of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies suggest a left temporo-frontal stream specifically involved during syntactic and semantic processing, both necessary to comprehension [5, 6, 7]. For instance, the processing of sentence with canonical Subject-Verb-Object structure involves a pathway that includes the frontal inferior gyrus, the supplementary motor area and the temporal inferior gyrus [8]. These authors further suggest that the left temporal inferior gyrus would play a role in the integration of the Subject, the Verb and the Object into a semantically coherent sentence.

Thus, it appears that the integration of acoustic, semantic and syntactic processes is necessary for language comprehension [9]. Therefore, studies aiming to localize receptive language must rely on language tasks requiring integration of information processed in theses modules, such as coherent sentences or story comprehension tasks. Using fMRI, Schlosser, Aoyagi, Fulbright, Gore & McCarthy (1998) observed a stronger activation of the left superior temporal sulcus compared to the right homologous region when English-speaking participants listened to English sentences [10]. In contrast, Turkish sentence presentation (control task) did not induce similar cerebral activations in any of the participants. Reporting similar results, Mazoyer et al. (1993) used fMRI and PET while participants were listening to Tamil (participants' unknown language) and French (participants' mother tongue) spoken stories. After subtraction, they found a stronger activation for French stories in the left superior and left medial temporal gyri [5].

Although these studies confirm a left hemisphere specialization for receptive language processing [5, 10], the specific involvement of different brain regions in each level of processing is still controversial [11]. Some authors suggest that other processes such as mental imagery and episodic memory retrieval may be implicated when subjects listen to stories [12]. For instance, activation that has been observed in the parieto-temporal junction and in the prefrontal medial cortex may be due to the latter processes [11, 13]. Because mental imagery and episodic memory retrieval might be associated with story comprehension, their relation with receptive language processing must be further investigated. To our knowledge, no previous studies have investigated the impact of episodic memory and mental imagery processes on the brain activation patterns observed in receptive language processing. The use of a paradigm involving the presentation of a known story versus an unknown one might shed light on this matter.

The brain activation patterns of receptive language processing have been mainly studied with fMRI and PET. However, the invasive and restrictive nature of these techniques often make them inappropriate for young children, epileptic patients or patients with mental retardation [2, 14]. To date, few studies have been conducted with near-infrared spectroscopy, a non-invasive technique that allows the measurement of blood oxygenation changes related to cerebral activation [15, 16]. Also known as optical imaging, this technique is based on the light absorption properties of oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) [17]. Good agreements have been observed between NIRS and fMRI, MEG and PET [9, 18, 19]. However, NIRS has a better temporal resolution than fMRI and its mobile and cheaper nature confers it with important advantages over the other techniques. Moreover, its configuration does not require subject containment, thus allowing the participant to move and speak. This makes it ideal while evaluating cognitive and linguistic functions or for research with young children and special populations [2, 4, 9, 20].

The present study aims to investigate the use of NIRS to assess brain lateralization patterns for receptive language functions in healthy adults while further controlling for episodic memory retrieval and mental imagery processes. Using a story listening task, we hypothesized that (1) French-speaking participants would show a greater left lateralized activation pattern in response to a French story compared to an Arabic one and, (2) if episodic memory retrieval affects the processing of the information, a different activation pattern should be observed in response to an unknown story (Martine and the Witch) compared to a known story (Snow White).

Methodology

Participants

Six healthy volunteers (3 men; mean age = 22 years (16-28 years), *SD* = 3.85) without neurological impairments were tested. The handedness of each subject was assessed using the *Edinburgh Inventory* [21]: four were right-handed and two were ambidextrous with a right predominance. All were native from the Quebec province, French-speaking and without knowledge of the Arabic language. Two subjects (1 man, 1 woman) were withdrawn from the analyses due to technical artifacts. This study has been approved by the Ethics Committee of the Ste-Justine University Hospital Center and informed consent was obtained from all participants.

Optical imaging recording

The data were gathered using a multi-channel spectrometer *Imagent Tissue Oxymeter* (ISS Inc., Champaign, III, USA) made of 50 sources emitting a 690 nm wavelength, 50 sources emitting a 830 nm wavelength and 16 detectors. The sources were placed on the subject's scalp using a rigid helmet adapted to the subject's head. Due to the anatomical variability of the subjects' head, two different helmet sizes were used (57 cm and 59 cm), and a standard montage was created for each of these helmets. Both montages were created using the software *Brainsight^{TM} Frameless 39* (Rogue Research, Canada) from a standardized MRI template, the Colin27 [22]. A total of 144 channels, using a source-detector distance from 2.9 cm to 6 cm, were symmetrically laid out to cover the left cerebral regions known to be related to language functions (Broca's area and Wernicke's area), as well as the right homologous regions. Figure 1 shows the regions covered by the montage.

Insert Figure 1 here

For each subject, the exact localization of each source and detector, as well as four fiducial points (nasion, left and right pre-auricular, and tip of the nose), were digitized and recorded using the stereotaxic system *Brainsight* to allow the individual reconstitution of the montage on the MRI template. Finally, a simultaneous EEG recording with four electrodes placed on the scalp (Fz, Cz, Pz and Oz according to the 10/20 international system) was carried out in order to control for the subjects' alert state during the task.

Stimuli and Procedure

Two stories were used: Snow-White (known story) and Martine and the Witch (unknown story). Stories were recorded using *Cool Edict Pro*^{Tm} in French and Arabic by the same speaker to control for acoustic and voice factors. The amplitude (between 64 dB and 76 dB) and the duration of the stimuli (20s each) were adjusted and standardized with the same software. All the stimuli were presented to the participants using *MatLab 7.0.4* and transmitted by two loudspeakers located at an equal distance (approximately 155cm) from the subject, at ear level.

Testing took place in a dark, sound-proof room. Subjects came twice to the laboratory. The experimental procedure and the language sequence were the same from one visit to the other. Participants were seated, with eyes closed. They were asked to relax in order to avoid abrupt movements and to listen carefully to the stories. They listened first to the story of *Snow-White* in both languages and, in a second testing session, to the story of *Martine and the Witch* in both languages. The time interval between both sessions was approximately two months to control for repeated measure reactivity. At each visit, participants listened to short extracts of the story read in French and the same story extracts read in Arabic. Each condition comprised 18 blocks with an interstimulus interval of 40s. Stories were presented in a continuous order to make it possible for the participant to follow the story. The order of the language was counterbalanced from one subject to the other (all the stimuli in French followed by all the stimuli in Arabic or all the stimuli in Arabic followed by all the stimuli in French). The total duration of each recording session was approximately 80 min, including the set-up of the helmet, optodes, detectors and electrodes. At the end of each session, participants had to answer some questions related to the stories to further control for comprehension and attention levels as well as for the familiarity of the stories.

Data processing

The data acquisition rate was 19.5312 Hz downsampled by a factor of 5 to lighten the data processing. The raw hemodynamic signal was normalized with a 10s pre-stimulus time. Artefact rejection took place by withdrawing segments with light intensity amplitudes smaller than 100 DC or a normalized standard deviation higher than 50 %. The optical intensity of the raw data (DC) was filtered using a low frequency zero-phase digital filtering with a cut off frequency at 0.1 Hz. A Modified Beer Lambert Law with a differential path length factor (DPF) correction according to the age of each subject was applied [23, 24]. Finally, the variation in the HbO and HbR concentrations were averaged for each channel and each condition. Averages were co-registered and projected on the Colin27 standard MRI template [22] to visualize the activated brain regions. Subsequent analysis was conducted only on the HbO signal.

Results

Preliminary analysis - All participants answered correctly the questions regarding the content of each of the two stories. None reported having ever heard the “unknown” story

Martine and the Witch and all of them were quite familiar with the “known” story Snow White. Finally, EEG monitoring revealed no signs of drowsiness in any condition. Using the international 10-20 system [25], six regions were delimited for all subjects: left frontal-temporal (F7 and T3), left medial-temporal (T3 and T5) left temporal-parietal (T5 and P3), as well as the right homologous areas (see figure 1a). For each of these regions, oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) changes during task periods were examined and the region of interest (ROI) was selected using the maximal amplitude and duration of HbO changes. Each subject’s ROIs were then fitted on a segmented Atlas 116 template [26]. In response to French, the regions of activation found in all subjects included the superior temporal gyrus, the middle temporal gyrus and the angular gyrus (see figure 1b for a representation of the activated areas). Subsequent analyses were conducted on these individual ROIs.

Insert Figure 2 here

Figures 3 and 4 show the hemodynamic changes recorded in response to the known and the unknown stories respectively in both languages for subject GT whose results are representative of the group. For the French condition, HbO concentration increased at the beginning of the story segment in the left hemisphere (blue lines), while in the right hemisphere only a small increase was observed (red lines). A maximal peak was recorded around 6s after the beginning of the stimulus in both hemispheres and for both stories. However, the amplitude of the change in the signal induced by the story in French was higher and lasted longer in the left hemisphere (until 16 s after the beginning of the stimulus compared to 10 s in the right hemisphere). This effect was observed for both stories (known and unknown stories). In contrast, the change in the hemodynamic signal recorded in response to the story in Arabic showed a decrease starting at 9 s after the beginning of the stimulus in both hemispheres and for both stories.

Insert Figure 3 and Figure 4 here

In order to assess the hemispheric lateralization pattern, a comparison by subtraction was performed. For each of the four conditions, the hemodynamic signal induced in the right hemisphere was subtracted from the hemodynamic signal observed in the left hemisphere. The area under the curve (AUC) of the subtraction for HbO concentration (between 0 and 25 seconds) was then used as a measure of lateralization. According to this calculation, a positive HbO AUC would suggest left hemisphere dominance while a negative HbO AUC would suggest right hemisphere dominance. Figures 3e, 3f and 4e, 4f display the results of the subtraction for subject GT. The group mean (four subjects) and standard error of AUC for each condition are plotted in figure 5.

Insert Figure 5 here

Effects of language and story familiarity were further assessed using a two-way repeated measure ANOVA (French/Arabic language for known/unknown story), in which the dependent measure was the AUC resulting from the subtraction (left AUC minus right AUC). As expected, results revealed a significant main effect for language [F (1, 3) = 10.33, $p < 0.05$] with a large effect size (eta square = 0.78). The story familiarity (known vs. unknown) was not significant [F (1, 3) = 0.12, *p* = 0.75, eta square = 0.04] neither was the interaction language by familiarity effect [F (1, 3) = 0.51, *p* = 0.84, eta square = 0.02].

Discussion

Our findings indicate that the hemodynamic signal changes associated to French stories are greater in the left than the right temporal regions, suggesting a left hemisphere dominance for receptive language in French-speaking participants. In contrast, Arabic stories (i.e. unknown language) did not induce specific hemispheric patterns. Consistent with previous reports [5, 10] using similar listening tasks in fMRI or PET, the left superior temporal gyrus and left middle temporal gyrus, were particularly activated. Despite the limited sample size of our study, a very large effect size for language was found, further supporting the efficacy of optical imaging in assessing receptive language lateralization processes.

The findings of the present study also provide a new approach to calculate language hemispheric lateralization. Previous studies have mainly used the Laterality Index (LI) formula (L + R / L –R) where L is the maximal peak found in the left hemisphere and R is the maximal peak found in the right hemisphere. The usual LI value goes from -1 (right hemisphere dominance) to +1 (left hemisphere dominance). However, the interpretation of the laterality index depends on the use of subjective parameters such as number of voxels used in fMRI, the maximal peak, or the selected timing [27]. Moreover, its computation is only possible with positive or absolute values, which limits its use with blood-oxygen level dependent measures (BOLD) as in optical imaging and fMRI. In the present study, we suggest that subtracting the hemodynamic signal of the hemispheric regions (Area Under the Curve

HBO Left - AUC HBO right) provides a more objective measure of hemispheric lateralization. This new method may be more suitable for optical imaging as it takes into account the decrease in HbO concentration. The use of the subtracted AUC values as a measure of lateralization may thus provide a more confident index because it better reflects the variation of HbO concentration all along the story segments. Nevertheless, further validation of this method is needed in assessing language lateralization. This study also aimed to determine whether the presentation of a well-known story would affect the activation patterns observed in specific brain regions involved in memory of imagery processes. Our results suggest that participants responded similarly to the known and unknown stories, regardless of the episodic memory retrieval expected while listening to the known story. This result confirms the robustness of our paradigm in assessing language rather than memory processes.

In sum, our findings confirm the use of optical imaging as a reliable and simple tool to study receptive language lateralization patterns in adults using story comprehension paradigms. Taking into account the numerous advantages of NIRS, these results are encouraging for further investigation of language development in children as well as for receptive language lateralization patterns in special populations such as patients with mental retardation and/or epileptic patients. This is of special importance, considering the fact that these populations often show restricted capabilities making other imaging methods inappropriate to study language lateralization which, in cases of intractable epilepsy, constitute a necessary part of the pre-surgical investigation.

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Figure Legend

Figure 1. Cerebral regions covered by the standard montage (a) and cortical representation of the activated regions observed in all subjects (b).

Figure 2. Hemodynamic responses to the known story for subject GT. The y-axis indicates relative changes in concentration (micromolar) for HbO (continuous line) and HbR (dotted line) during presentation of the story segments (20 s). Hemodynamic changes during stories in French in the left and right hemispheres are represented respectively in (a) and (c). Hemodynamic changes during stories in Arabic in the left and right hemispheres are represented in (b) and (d). Hemispheric subtractions of the hemodynamic signal (left minus right) are illustrated for the story told in French (e) and in Arabic (f).

Figure 3. Hemodynamic responses to the unknown story for the same participant (GT). The y-axis indicates relative changes in concentration (micromolar) for HbO (continuous line) and HbR (dotted line) during the presentation of the story segments (20 s). Hemodynamic changes during the story in French in the left and right hemispheres are represented respectively in (a) and (c). Hemodynamic changes during the story in Arabic in the left and right hemisphere are represented in (b) and (d). Subtractions of the hemodynamic signal (left minus right) are illustrated for the story told in French (e) and in Arabic (f).

Figure 4. Average ($n = 4$) of the hemispheric lateralization (Area Under the Curve HbO Left - AUC HbO right) in response to the known story (black bars), and the unknown story (gray bars), in both languages. The y-axis indicates average changes in concentration (micromolar)

for HbO Error bars indicate the standard errors. Positive HbO AUC indicates left hemisphere specialization while negative HbO AUC suggests right hemisphere specialization.

Figure 1. Cerebral regions covered by the standard montage and cortical representation of the activated regions

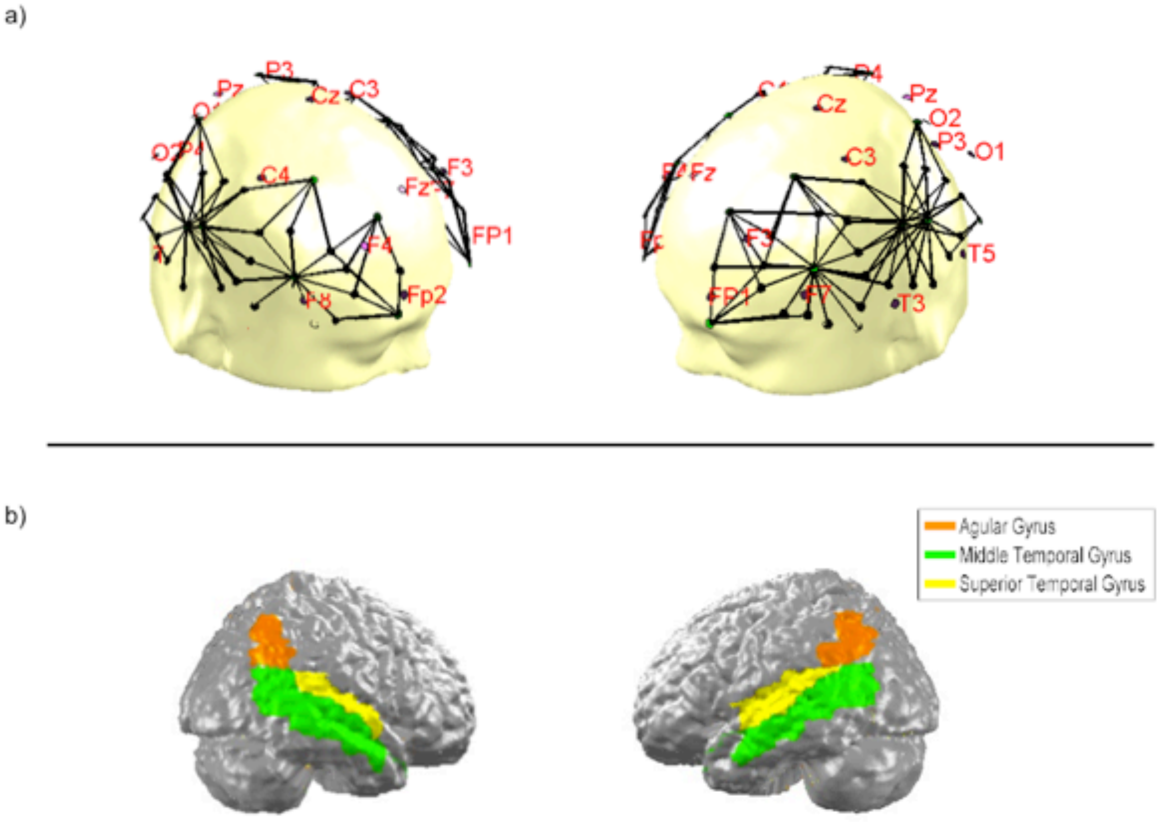

Figure 2. Hemodynamic responses to the known story for subject GT

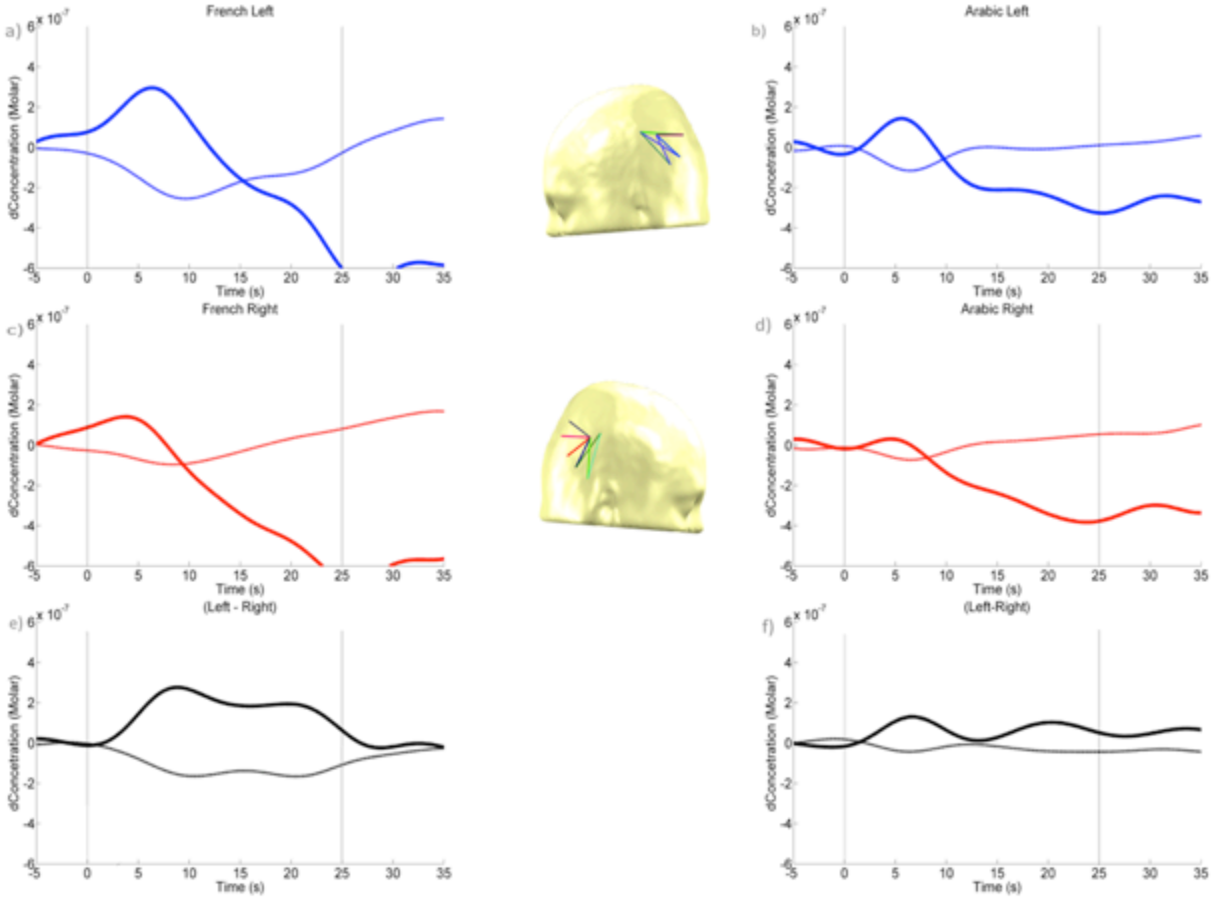

Figure 3. Hemodynamic responses to the unknown story for the same participant (GT)

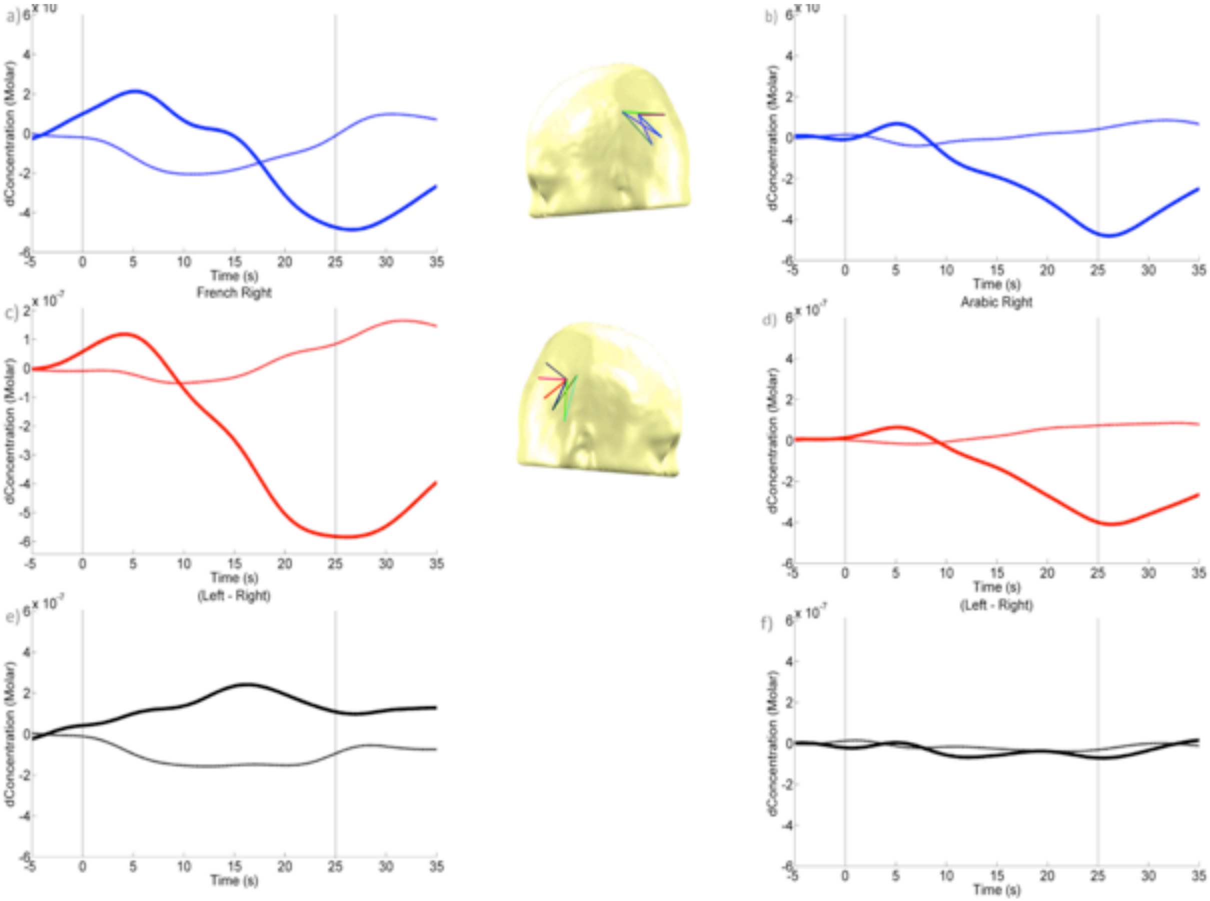

Figure 4. Average of the hemispheric lateralization to the known and the unknown story, in both languages