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Utilisation de l'électrophysiologie dans l'étude du développement des capacités d'intégration audiovisuelle du nourrisson à l'âge adulte

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Résumé

Une littérature abondante documente les bénéfices de l'intégration multisensorielle chez les adultes ainsi que les mécanismes cérébraux sous-jacents à ces habiletés. Toutefois, de nombreuses questions sur le développement de l'intégration multisensorielle chez l'enfant demeurent sans réponse et les travaux chez les animaux ainsi que les données comportementales, électrophysiologiques et en neuroimagerie chez l'homme ne forment pas de consensus quant à son caractère inné ou acquis.

Le premier objectif de la présente thèse vise donc à recenser les écrits de la littérature sur le développement des capacités d'intégration multisensorielle. Cette revue de la littérature, qui constituera l'article 1 de la thèse, présente les études comportementales et neuronales en faveur du caractère inné ou acquis des processus d'intégration multisensorielle. L'article 1 suggère que certaines habiletés de traitement multisensoriel sont présentes chez le nourrisson et le jeune enfant, mais que la capacité à intégrer les informations multisensorielles de façon optimale demeure un long processus qui se développe tardivement au cours de l'enfance et de l'adolescence. Cette revue nous a également permis de mieux cibler les lacunes de la littérature relatives au développement neuronal des capacités d'intégration, avec une attention particulière sur l'intégration d'informations audiovisuelles non linguistiques.

Ainsi, aucune étude en électrophysiologie ne s'est encore penchée sur la progression développementale des capacités d'intégration audiovisuelle chez les nourrissons et les enfants d'âge préscolaire. Ce constat a justifié la tenue de l'étude expérimentale présentée à l'article 2 dont l'objectif vise à caractériser la progression développementale neurotypique des mécanismes d'intégration d'informations audiovisuelles non linguistiques dès l'âge de 3 mois jusqu'à l'âge adulte. Cette recherche vise également à confirmer l'âge où les mécanismes d’intégration audiovisuelle, d’une part, commencent à fonctionner de façon similaire aux adultes et, d’autre part, atteignent leur pleine maturité. Pour ce faire, nous avons mené une étude expérimentale transversale sur un vaste échantillon composé de 121 participants neurotypiques en utilisant l’électrophysiologie à haute densité, plus sécifiquement par le biais d’analyses temps-fréquence. Notre étude démontre la présence de précurseurs de l’intégration audiovisuelle dès l’âge de 2 ans. De plus, nous observons que les jeunes de 11-14 ans commencent à intégrer ces informations de façon similaire aux adultes, mais que les mécanismes d’intégration audiovisuelle atteignent leur pleine maturité tardivement au cours de l’adolescence soit entre les âges de 15 et 17 ans. Cette étude appuie la littérature quant à l’émergence progressive des capacités à intégrer les informations audiovisuelles, permet de documenter la progression développementale de ces capacités et répond à l’absence de littérature sur les processus neuronaux de l’intégration audiovisuelle chez le nourrisson et l’enfant d’âge préscolaire.

Dans l’ensemble, cette thèse offre une meilleure compréhension du développement neurotypique des mécanismes d’intégration audiovisuelle et fournit un point de comparaison pour étudier ces processus auprès d’enfants présentant des troubles neurodéveloppementaux souvent accompagnés de déficits sensoriels.

Mots clés : intégration multisensorielle, intégration audiovisuelle, audition, vision, électrophysiologie, ondelettes, développement neurotypique, troubles neurodéveloppementaux

Abstract

An abundant litterature documents the benefits associated to multisensory integration in adults as well as brain mechanisms underlying these skills. However, numerous questions regarding the development of multisensory integration during childhood remain unanswered and there is no consensus among animal data in addition to behavioral, electrophysiological and neuroimaging studies conducted in humans wether these skills are innate or acquired.

The first objective of this thesis is to review the literature on the development of multisensory integration capacities. This review, which will constitute the first article of this thesis, presents neuronal and behavioral studies in favour of the nature or nurture character of multisensory integration mechanisms. This review suggests that the capacity to detect and form multisensory associations begins very early in development, but that the ability to integrate multisensory information in an optimal manner is a progressive process that continues to develop over childhood and adolescence. This work has also allowed us to better target the gaps in the existing literature related to the neuronal development of integration capacities, with special emphasis on the integration of non linguistic audiovisual information.

Thus, to date no electrophysiological study has yet address the developmental progression of audiovisual integration capacities in infants and preschool children. This ascertainment has justified the conduct of the experimental study presented in the second article with the aim of characterizing the neurotypical developmental progression of non linguistic audiovisual information integration mecanisms as early as 3 months of age to adulthood. This research is also aimed at confirming the age when audiovisual integration mechanisms, on the one hand, begin to operate in a similar fashion than adults and, on the other hand, reach their full maturity. For these purposes, we have conducted an experimental study. Here, we undertook a cross-sectional experimental investigation on a large cohort of 121 neurotypical individuals using high-density electrophysiology more specifically through time-frequency analysis. Our study revealed the presence of precursors of audiovisual integration in children as young as two years of age. Moreover, our results indicate that 11- to 14-year-old adolescents start to integrate this information in an adult-like manner, but that audiovisual integration mechanisms reach their full maturity late throughout adolescence between the age of 15 and 17 years. This study supports the literature regarding the progressive emergence of the capacities to integrate audiovisual information, documents the developmental progression of these capacities and answers the absence of literature on the neuronal processes of audiovisual integration in infants and preschool children.

Overall, this thesis provides a better understanding of the development of audiovisual integration mechanisms and provides a benchmark to investigate these processes in children with neurodevelopmental disorders often accompanied with sensory impairments.

Key words: multisensory integration, audiovisual integration, audition, vision, electrophysiology, wavelets, neurotypical development, neurodevelopmental disorders

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Section méthodologie et résultats

Article 2

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Liste des sigles et des abréviations

A	Auditif
ADD/ADHD	Attention deficit disorder with or without hyperactivity
ADHD-C	Attention deficit disorder combined type
ADHD-I	Attention deficit disorder inattentive type
ANOVA	Analyse de variance / Analysis of variance
ASTP	Aire supérieure temporale polysensorielle
AV	Audiovisuel / Audiovisual
A+V	Somme des réponses unisensorielles auditives et visuelles / Sum of the unisensory auditory and visual responses
CN	Caudate nucleus
CS	Colliculus supérieur
CGL	Corps genouillé latéral
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition / Manuel diagnostique et statistique des troubles mentaux, 5e édition
EEG	Électrophysiologie / Electrophysiology
ERP	Event-related potential
fMRI	Functional Magnetic Resonance Imaging
IRMf	Imagerie par résonance magnétique fonctionnelle
IMS	Intégration multisensorielle
IUGR	Intrauterine growth retardation
MEG	Magnétoencéphalographie /Magnetoencephalography
Ms	Milliseconde / Millisecond

MSI	Multisensory integration
N	Négativité
NIRS	Spectroscopie proche infrarouge
PÉ	Potentiel évoqué
PÉA	Potentiel évoqué auditif
PÉV	Potentiel évoqué visuel
P	Positivité
SIP	Sillon intrapariétal
SC	Superior colliculus
SMD	Sensory Modulation Disorder
SN	Substantia nigra
SPD	Sensory Processing Disorder
STS	Sillon temporal supérieur
TDA/H	Trouble déficitaire de l'attention avec ou sans hyperactivité
TSA	Trouble du spectre de l'autisme
µV	Amplitude (microvolt)
μV^2	Puissance (microvolt au carré)
V	Visuel

Il n’est « rien dans notre intelligence
qui ne soit passé par nos sens ».

Aristote

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Cette thèse de doctorat représente un travail de longue durée, et pour cette raison, constitue une tranche de vie qui m'a permis de faire des rencontres fortuites, de vivre des collaborations stimulantes, de susciter des réflexions personnelles et scientifiques et de créer de nouvelles amitiés. Derrière cette thèse se trouve la contribution de plusieurs personnes que je désire remercier car celles-ci retrouveront dans ce travail, l'aboutissement de leurs efforts pour lesquels j'exprime ma plus affectueuse gratitude.

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1. INTRODUCTION

1.1 Introduction générale

Les objets et les évènements perçus à travers nos différents organes sensoriels ne confèrent pas une impression d'un monde morcelé fait de sensations indépendantes, mais bien au contraire, procurent une perception unifiée et cohérente de l'environnement qui nous entoure. En effet, dans la vie quotidienne les décisions et les actions que nous croyons effectuées à partir d'informations provenant d'un seul sens, tel que la vision, sont fortement influencées par des renseignements provenant d'autres sens tels que l'audition ou le toucher et qui, malgré leur apparence superflue, sont informatifs. Par exemple, à la lecture de la présente thèse, vous interprétez des stimuli visuels (les mots que vous lisez), auditifs (les bruits de fond que vous essayez d'ignorer en lisant), tactiles (l'effleurement du papier entre vos doigts), olfactifs (l'odeur du dîner qui est en train de cuire), gustatifs (la gomme à la menthe que vous mâchez) et proprioceptifs (la sensation que vous donne le fait d'appuyer votre tête sur votre main). Puisque chaque sens obtient et transmet de façon indépendante un rapport unique de l'évènement, la synthèse des différents signaux sensoriels permet une évaluation plus juste et complète de la perception de l'évènement influençant ainsi notre perception du monde et la prise de décisions dans des situations les requérant (Ernst & Banks, 2002). Ce phénomène qu'est l'intégration multisensorielle (IMS) a une énorme valeur adaptative et joue indubitablement un rôle fondamental dans l'histoire évolutive des espèces vivantes. Les gains et bénéfices comportementaux découlant de la capacité sous-jacente du cerveau à intégrer différentes entrées sensorielles liées à un seul évènement ont été documentés et corroborés par une littérature scientifique abondante à ce sujet (Diederich & Colonius, 2004; Lovelace, Stein, & Wallace, 2003). Depuis les trois derniers siècles, les chercheurs tentent de nous éclairer sur les mécanismes de base de l'IMS et sur leur ontogenèse. Grâce à l'avènement des techniques de neuroimagerie, les données chez l’animal et l’homme adulte ont apporté des concepts fondamentaux sur les bases cérébrales des processus d’IMS et ont corroboré leurs avantages comportementaux. De même, plusieurs études comportementales ont porté sur l'influence des processus d’IMS dans la perception des évènements chez le nourrisson et l’enfant. D’ailleurs, l’étude de ce phénomène a soulevé un débat sur la part respective de l’inné et de l’acquis dans le développement de l’IMS. Tandis que certains chercheurs stipulent que le système nerveux serait multisensoriel dès la naissance, d’autres font valoir le rôle significatif que joue l’expérience dans le développement de notre capacité à intégrer les diverses informations sensorielles. Cette question, débattue dans la communauté scientifique, sera d’ailleurs abordée dans la revue de la littérature qui constitue l’article 1 de la présente thèse. Celle-ci fait également état des connaissances actuelles sur les capacités et processus cérébraux sous-jacents au développement de l’IMS chez les nourrissons et les enfants neurotypiques. Bien que certains résultats comportementaux suggèrent la présence d’IMS dès les premières semaines de vie, aucune étude en électrophysiologie ou en neuroimagerie n’a encore examiné le développement de ces capacités avant l’âge de 7 ans. Ainsi, le deuxième article de la présente thèse vise à étudier la progression développementale des mécanismes d’intégration audiovisuelle (AV) et à exposer l’âge auquel ceux-ci atteignent leur maturité. Ces objectifs seront étudiés à l’aide d’une approche électrophysiologique et plus spécifiquement, par le biais d’analyses temps-fréquence. Une meilleure compréhension du développement des mécanismes d’IMS chez les individus neurotypiques fournit un point de comparaison pour étudier ces processus chez certaines populations cliniques à risque de présenter des problèmes sensoriels, notamment les individus présentant un trouble du spectre de l’autisme (TSA) (Bao, Doobay, Mottron, Collignon, & Bertone, 2017; Charbonneau et al., 2013; Collignon et al., 2013; Stevenson et al., 2014), une dyslexie (Francisco, Jesse, Groen, & McQueen, 2017; Hahn, Foxe, & Molholm, 2014; Laarhoven, Keetels, Schakel, & Vroomen, 2016; Ye, Rüsseler, Gerth, & Münte, 2017), un trouble du langage oral (Kaganovich, Schumaker, Leonard, Gustafson, & Macias, 2014; Knowland, Evans, Snell, & Rosen, 2016; Meronen, Tiippana, Westerholm, & Ahonen, 2013), un trouble déficitaire de l'attention avec ou sans hyperactivité (TDA/H) (Benn, 2017; Cheung & Siu, 2009; Ghanizadeh, 2011). Des relations neurophysiologiques possibles entre les problèmes d'IMS et certains troubles neurodéveloppementaux sont d'ailleurs abordées dans l'article 1 de cette thèse.

Ainsi, l'introduction de cette thèse est divisée en plusieurs sections. La première vise à définir l'IMS et présenter les bases cérébrales sous-jacentes aux capacités d'intégration. Par la suite, un survol du développement respectif des systèmes sensoriels, auditif et visuel, sera effectué suivi par une présentation des gains comportementaux et des données neuronales sur l'intégration AV chez l'adulte. L'état actuel des études comportementales et électrophysiologiques sur le développement de l'intégration AV chez les nourrissons et les enfants sera exposé suivi d'une présentation des limites associées à ces études. Il est à noter que certains de ces sujets seront abordés relativement brièvement, puisqu'ils ont été par la suite largement détaillés dans l'article 1. La dernière partie de l'introduction présente l'électrophysiologie (EEG) cérébrale et les analyses associées ainsi que leur apport dans l'étude des mécanismes d'intégration AV.

À la suite de cette introduction, les objectifs principaux seront abordés suivi du corps de la thèse qui comporte deux articles. Le premier consiste en une revue de la littérature et le second présente une étude électrophysiologique. Les résultats issus de ce deuxième article seront détaillés et intégrés sous forme de discussion générale à la lumière de la littérature.

Cette discussion fera également l'objet des limites de notre recherche ainsi que des impacts cliniques et des perspectives d'études futures. Enfin, une conclusion générale sera présentée. Un manuscrit additionnel sur le développement de la perception de la voix et du langage chez le nouveau-né auquel j'ai activement participé (deuxième auteure) a récemment été accepté comme chapitre de livre et est également disponible en annexe.

1.2 Intégration multisensorielle

1.2.1. Définition et opérationnalisation

Les informations sensorielles peuvent être traitées de manière séparée : nous parlerons alors d'information unisensorielle par opposition à une information multisensorielle, contenant deux canaux sensoriels ou plus. Lorsque nous parlons d'information multisensorielle, nous décrivons un objet contenant au moins deux types d'informations sensorielles. Dès la naissance, nous interagissons avec le monde à travers nos sens, ce qui nous procure des informations complémentaires sur l'environnement. Pour percevoir et interagir dans un monde cohérent, notre cerveau doit fusionner le plus efficacement possible les informations des différents sens. L'IMS correspond au mécanisme perceptif consistant à associer les informations en provenance de différentes modalités sensorielles dans un percept unique multidimensionnel optimal (Stein, 2012). Les informations sensorielles issues d'un même objet ou évènement sont mieux et plus rapidement traitées que le même objet défini par l'information provenant d'une seule modalité sensorielle. Cette efficacité supérieure d'une présentation bisensorielle ou multisensorielle est reliée à la capacité du cerveau à intégrer les signaux redondants (Ernst & Bülthoff, 2004; Giard & Peronnet, 1999; Harrington & Peck, 1998; Miller, 1982; Molholm et al., 2002). Pour être intégrées, les estimations sensorielles doivent avoir la même unité, les mêmes coordonnées et doivent concerner les mêmes propriétés environnementales (Ernst & Bülthoff, 2004). Plus spécifiquement, la synchronie temporelle, la coïncidence spatiale ainsi que la détection des propriétés dites amodales (c.-à-d., propriétés d'un objet ou d'un évènement perçu qui ne sont pas liées à une modalité sensorielle particulière telles la taille, la forme, le rythme, le tempo, l'intensité) renforcent la probabilité que les deux informations recueillies proviennent d'un même objet et constituent donc un prérequis à leur intégration. Par exemple, la taille de l'objet que l'on touche et voit à la fois et la parole que l'on entend et lit sur les lèvres du locuteur fournissent des perceptions d'évènements uniques tirés d'informations redondantes véhiculées par deux modalités.

L'IMS peut s'opérationnaliser par une différence statistiquement significative entre la réponse évoquée par une stimulation multisensorielle et celle évoquée par sa composante unisensorielle. Cela s'applique aussi bien au niveau comportemental que neuronal (Ghazanfar, Maier, Hoffman, & Logothetis, 2005). Sur le plan comportemental, le gain associé à la combinaison des informations multisensorielles se traduit par une diminution des temps de réaction ainsi qu'une meilleure performance dans les tâches de précision et de détection d'une cible en comparaison à la présence d'informations provenant d'une seule modalité (Diederich & Colonius, 2004). Au niveau neuronal, l'IMS se manifeste par une augmentation de la fréquence de décharge des neurones multisensoriels. Ainsi, généralement, le taux d'influx nerveux des neurones multisensoriels évoqué par une stimulation bisensorielle est significativement plus élevé que la réponse neuronale générée lors de la stimulation unisensorielle la plus efficace (Binns & Salt, 1996; Stein & Meredith, 1993; Stein, Stanford, Ramachandran, Perrault, & Rowland, 2009).

1.3 Bases cérébrales de l’IMS

Avant de se pencher sur les données comportementales et électrophysiologiques de l’IMS, une synthèse des connaissances sur les structures et régions cérébrales impliquées dans cette capacité sera présentée.

1.3.1 Colliculus supérieur : premier modèle d’étude

La structure cérébrale la plus étudiée dans le domaine de l’IMS est sans aucun doute le colliculus supérieur (CS) qui joue un rôle important dans les comportements d'attention et d'orientation. L’existence des neurones multisensoriels fut mis en évidence pour la première fois au niveau de cette structure dans des travaux sur le mammifère (Stein & Meredith, 1993; Wallace & Stein, 1997). Le CS reçoit des afférences visuelles, auditives et somesthésiques provenant des voies sensorielles ascendantes ainsi que des projections descendantes du cortex qui convergent en différentes combinaisons sur les neurones multisensoriels (Champoux, Bacon, Lepore, & Guillemot, 2008; King, 2004; Stein, Stanford & Rowland, 2014; Wallace, Wilkinson, & Stein, 1996). Chaque neurone multisensoriel détient plusieurs champs récepteurs spécifiques aux diverses modalités sensorielles auxquelles il est sensible. L’organisation spatiale topographique du CS démontre que ce qui est important pour les neurones de cette structure est l’endroit où survient un évènement et non la modalité sensorielle de cet évènement. Le chevauchement des champs récepteurs unisensoriels dans le neurone multisensoriel conditionne la façon dont celui-ci répond aux stimuli issus de la même région de l’espace. Ainsi, les stimuli provenant de la même source spatiale activeront différents champs récepteurs, quelle que soit leur modalité, des neurones logés dans la même région du CS (Stein et al., 2014). Des neurones multisensoriels et des réponses bisensorielles à des stimuli AV sont également présents au niveau du thalamus (Benedek, Perenyi, Kovacs, Fischer-Szatmari, & Katoh, 1997; Matsumoto, Minamimoto, Graybiel, & Kimura, 2001), de l'amygdale (Nishijo, Ono, & Nishino, 1988), du striatum (Chudler, Sugiyama, & Dong, 1995; Graziano & Gross, 1993; Nagy, Eördegh, Paróczy, Márkus, & Benedek, 2006; Nagy, Paróczy, Norita, & Benedek, 2005), de la substance noire (Nagy et al., 2005; 2006) et de l'insula (Bushara, Grafman, & Hallett, 2001). De plus, des connexions entre le CS et plusieurs structures sous-corticales et corticales sont également mises en évidence dans plusieurs études chez l'homme et l'animal (Harting, Huerta, Hashikawa, & van Lieshout, 1991; Huerta & Harting, 1984; Sommer & Wurtz, 2001).

1.3.2 Aires associatives : modèle anatomique classique

Le premier modèle ayant tenté d'expliquer l'IMS, le modèle hiérarchique classique, suggérait un traitement hiérarchique des informations sensorielles où les informations en provenance des différentes aires sensorielles primaires et secondaires seraient acheminées vers les aires associatives multisensorielles pour que l'intégration des différents stimuli se produise (Bushara et al., 2003; Calvert & Thesen, 2004). Par la suite, des connexions descendantes pourraient influencer l'activité des neurones retrouvés dans les cortex de niveaux hiérarchiques inférieurs. Le transfert d'information entre les niveaux serait assuré par des connexions cortico-corticales réciproques (Felleman & Van Essen, 1991; Rockland & Pandya, 1979). Malgré la grande variabilité des protocoles et des analyses proposés par les techniques de potentiels évoqués (PÉs) et de neuroimagerie, les études sur l'IMS ont révélé un certain nombre d'aires corticales impliquées de manière récurrente dans l'intégration des informations AV. Parmi ces aires, nous retrouvons les aires associatives qui peuvent recevoir des entrées en provenance de plusieurs modalités sensorielles ou des entrées convergentes provenant de plusieurs modalités.

1.3.2.1 Lobe temporal

Chez le primate, l'aire supérieure temporale polysensorielle (ASTP), localisée au niveau du sillon temporal supérieur (STS), est connue pour détenir des neurones multisensoriels (Barraclough, Xiao, Baker, Oram, & Perrett, 2005; Beauchamp, 2005; Schroeder & Foxe, 2002) et avoir des connexions bidirectionnelles avec les cortex unisensoriels auditif, visuel et somatosensoriel (Cusick, 1997; Padberg, Seltzer, & Cusick, 2003; Schmahmann & Pandya, 1991). Bien que le rôle de l'ASTP semble assez bien établi dans l'IMS du langage (Beauchamp, Lee, Argall, & Martin, 2004; Calvert, Campbell, & Brammer, 2000; Kang et al., 2006), des études en neuroimagerie chez l'homme ont également démontré l'existence d'intégration de stimuli AV non linguistiques. En effet, une plus grande activation fut démontrée dans les portions postérieures du STS en réponse à des stimuli AV non linguistiques, tels que des objets et des animaux, en comparaison à leur présentation unisensorielle auditive et visuelle respective (Beauchamp et al., 2004; Hein et al., 2007; Sestieri et al., 2006; Taylor, Moss, Stamatakis, & Tyler, 2006). Les connexions de l'ASTP comprennent des afférences visuelles provenant des aires visuelles postérieures pariétales (Cusick, Seltzer, Cola, & Griggs, 1995; Seltzer & Pandya, 1994), d'aires du lobe temporal (Boussaoud, Ungerleider, & Desimone, 1990; Kaas & Morel, 1993; Saleem, Suzuki, Tanaka, & Hashikawa, 2000) et du cortex visuel primaire (Falchier, Clavagnier, Barone, & Kennedy, 2002). Des afférences provenant de la partie visuelle du noyau pulvinar du thalamus peuvent aussi fournir une partie de l'activation visuelle (Bruce, Desimone, & Gross, 1986).

1.3.2.2 Lobe pariétal postérieur

Le cortex pariétal postérieur des primates contient des aires qui semblent encoder la localisation des objets (Colby & Goldberg, 1999). Bien que les afférences visuelles fournissent la principale source d'information sensorielle vers les aires du sillon intrapariétal (SIP) du cortex pariétal postérieur, des études anatomiques (Lewis & Van Essen, 2000a, 2000b) et physiologiques (Grunewald, Linden, & Andersen, 1999; Linden et al., 1999) chez le primate, ont révélé des évidences de convergence multisensorielle dans le SIP. En effet, des neurones multisensoriels répondant à des stimuli visuels, auditifs, somatosensoriels et vestibulaires (Avillac, Deneve, Olivier, Pouget, & Duhamel, 2005; Schlack, Sterbing-D'Angelo, Hartung, Hoffmann, & Bremmer, 2005) ont été mis en évidence dans les aires du SIP. Cette structure reçoit également des afférences visuelles, auditives et somesthésiques provenant de plusieurs aires corticales (Hackett, Stepniewska, & Kaas, 1998; Lewis & Van Essen, 2000a; Nakamura et al., 2001). Chez l'homme, le cortex pariétal postérieur a aussi été montré en neuroimagerie et en EEG comme jouant un rôle dans l'IMS (Blanke & Arzy, 2005; Kitada et al., 2006; Molholm et al., 2006; Sereno & Huang, 2006). Ensemble, les aires du SIP ne semblent pas impliquées directement dans l'intégration AV, mais jouent un rôle important dans les activités sensorimotrices, telles que les tâches de préhension, et ce, principalement à travers les modalités visuelles et somesthésiques (Cohen & Andersen, 2002).

1.3.2.3 Lobe frontal

Les études neuroanatomiques chez les primates ont démontré une convergence des afférences sensorielles de diverses modalités au niveau des neurones multisensoriels des cortex prémoteur, préfrontal et cingulaire antérieur (Chavis & Pandya, 1976; Fuster, Bodner, & Kroger, 2000; Graziano & Gandhi, 2000; Graziano, Reiss, & Gross, 1999; Jones & Powell, 1970). De plus, des connexions réciproques ont été rapportées récemment entre des cortex sensoriels primaires et certaines régions des cortex préfrontal et prémoteur (Barbas et al., 2005; Budinger, Laszcz, Lison, Scheich, & Ohl, 2008; Liu et al., 2013; Romanski, Bates, & Goldman-Rakic, 1999; Sugihara, Diltz, Averbeck, & Romanski, 2006). Par ailleurs, de récentes études en neuroimagerie ont révélé la présence d'une intégration d'informations AV non linguistiques dans le cortex préfrontal (Bushara et al., 2001; Paraskevopoulos, Kuchenbuch, Herholz, & Pantev, 2012) et le cortex cingulaire antérieur (Benoit, Raij, Lin, Jääskeläinen, & Stufflebeam, 2010; Laurienti et al., 2003).

1.3.3 Aires sensorielles primaires : modèle anatomique moderne

Jusqu'à la fin des années 1990, il était admis que les cortex primaires ne pouvaient être sensibles à d'autres stimuli que ceux correspondant à la modalité à laquelle ils étaient dévolus. Le dogme selon lequel l'IMS n'était possible qu'à un plus haut niveau de traitement cognitif fut renversé par des études sur les animaux et les humains qui ont permis de découvrir la présence de convergence multisensorielle dans les aires cérébrales traditionnellement considérées unisensorielles (Kayser, Petkov, Augath, & Logothetis, 2007; Martuzzi et al., 2006; Romei, Murray, Merabet, & Thut, 2007; Wang, Celebrini, Trotter, & Barone, 2008;

Watkins, Shams, Tanaka, Haynes, & Rees, 2006; Figure 1). Les travaux anatomiques chez les animaux (Clavagnier, Falchier, & Kennedy, 2004; Falchier et al., 2002; Rockland & Ojima, 2003) ont révélé l'existence de connexions directes entre les cortex primaires, visuel et auditif, durant le traitement de stimuli AV. Il a été démontré qu'une information provenant d'une modalité sensorielle peut moduler l'activité neuronale dans le cortex sensoriel d'une autre modalité. En effet, des études en IRMf ont démontré une activation du cortex auditif suite à des stimulations visuelles et une modification de l'activité du cortex visuel par des sons (Laurienti et al., 2002; Mishra, Martinez, Sejnowski, & Hillyard, 2007). De plus, la présence de connexions entre les aires sensorielles primaires favoriserait également des interactions multisensorielles rapides. En effet, des études en PÉs ont démontré la présence d'intégration AV précoce au niveau des cortex sensoriels spécifiques auditif et visuel (Giard & Peronnet, 1999; Molholm et al., 2002; Senkowski, Talsma, Grigutsch, Herrmann, & Woldorff, 2007). La précocité de ces interactions multisensorielles suggère que celles-ci ne dépendent pas uniquement de connexions en retour des aires associatives vers les aires unisensorielles et que les aires associatives ne constituent pas le dernier échelon du traitement sensoriel, mais fonctionnent plutôt en parallèle aux réseaux unisensoriels (Bushara et al., 2003; Calvert & Thesen, 2004).

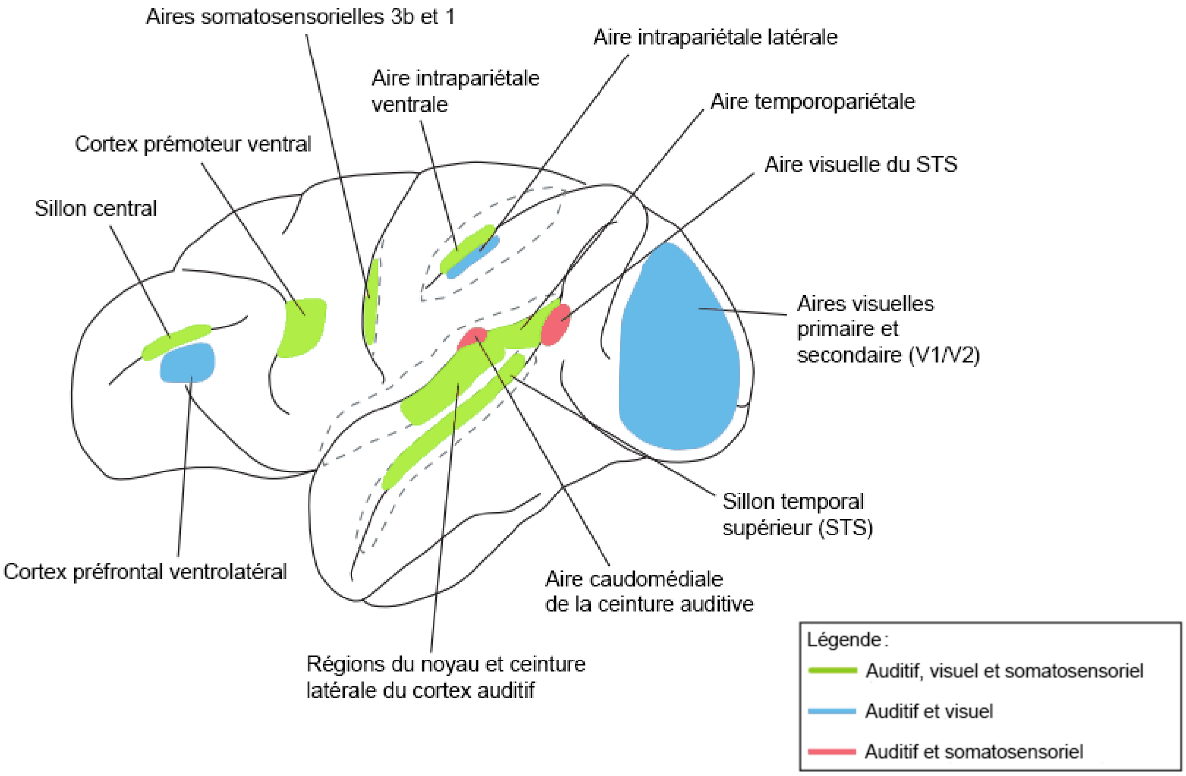

Figure 1. Modèle anatomique moderne des régions corticales multisensorielles chez le primate. Les zones colorées représentent les régions dans lesquelles des évidences anatomiques et électrophysiologiques ont démontré de l'IMS (Inspiré de Ghazanfar & Schroeder, 2006).

1.4 Principes généraux de l'IMS

Les stimuli multisensoriels peuvent faciliter ou atténuer la réponse des neurones multisensoriels dans des conditions bien précises. Le caractère intégratif d'un neurone multisensoriel dépend de quatre principes distincts : les règles spatiale et temporelle, le principe de l'efficacité inverse ainsi que de la préservation des champs récepteurs (*voir* Stein & Meredith; 1993, *pour une revue à ce propos*; Stein et al., 2014).

1.4.1 Règle spatiale

La règle de coïncidence spatiale stipule que la réponse des neurones multisensoriels du CS est maximale lorsque les stimuli multisensoriels sont alignés spatialement (Meredith & Stein, 1986). Ceci serait la conséquence du chevauchement et de l'étendue suffisamment grande des champs récepteurs unisensoriels dans le neurone multisensoriel (Stein & Meredith, 1993; Wallace & Stein, 2007; Figure 2).

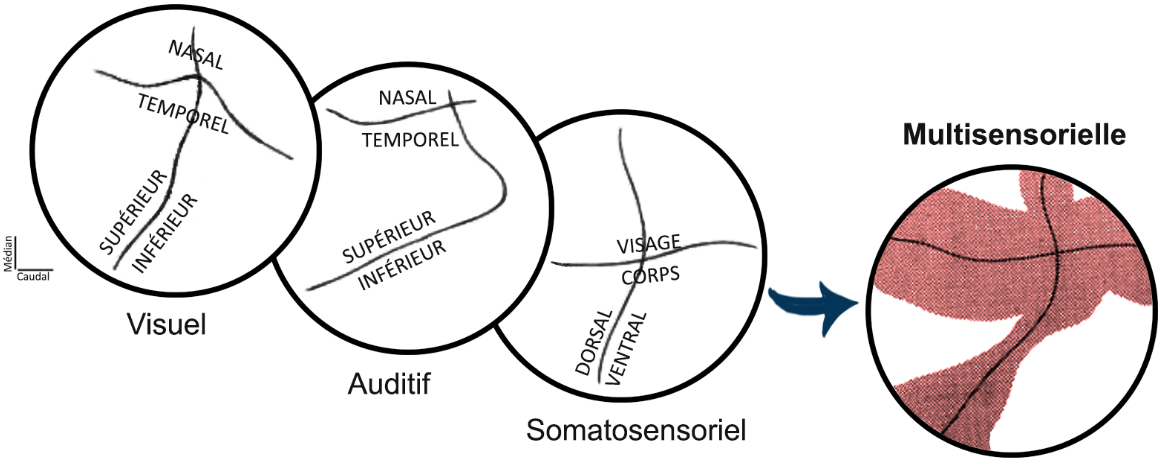

Figure 2. Superposition des cartes spatiales au niveau des colliculus supérieurs pour les modalités visuelle, auditive et somesthésique (Inspiré de Stein et Meredith, 1993).

Ainsi, l'information provenant de plusieurs modalités sensorielles d'une même zone spatiale suscite une réponse largement supérieure des neurones multisensoriels que la réponse unisensorielle la plus élevée, ou même que la somme arithmétique des réponses unisensorielles les plus importantes, phénomène de potentialisation connu sous le nom de sur-additivité (Wallace & Stein, 1997; Figure 3). En contrepartie, les stimuli de différentes modalités sensorielles ayant des origines spatiales discordantes peuvent réduire ou même supprimer la réponse neuronale multisensorielle (Kadunce, Vaughan, Wallace, Benedek, &

Stein, 1997), alors inférieure aux réponses unisensorielles, phénomène connu sous le nom de sous-additivité.

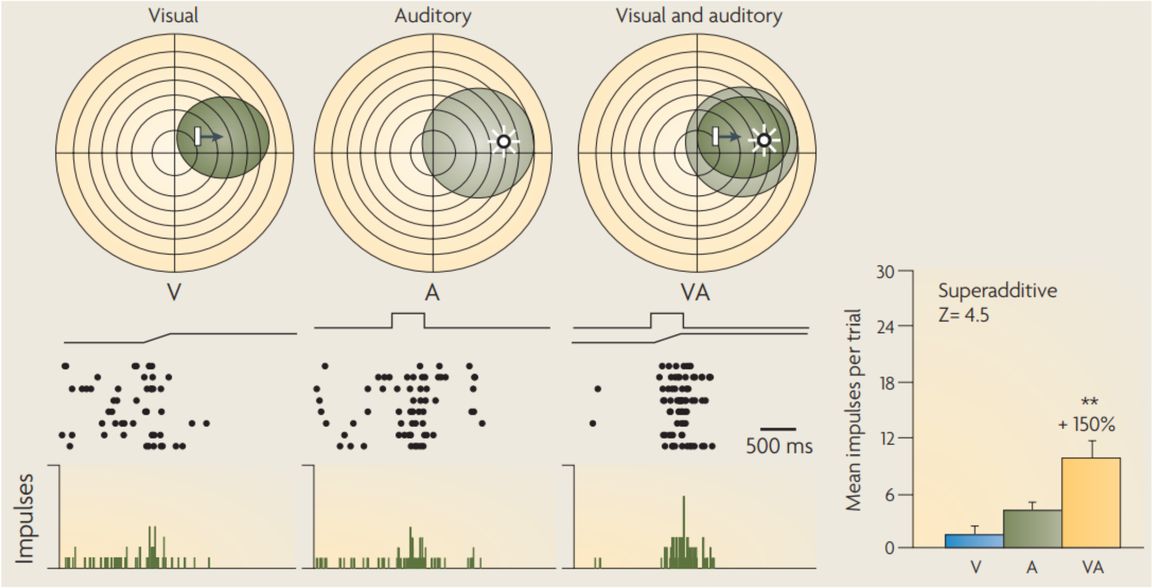

Figure 3. La figure suivante illustre l'IMS au sein d'un neurone multisensoriel du CS. Les champs récepteurs auditifs et visuels de ce neurone sont représentés par les cercles verts (visuel : vert foncé, auditif : vert pâle). Les stimuli auditifs (A) sont représentés par un cercle blanc entouré de traits et les stimuli visuels (V) par une barre blanche. De faibles stimuli A et V (représentés par les points noirs) sont intégrés afin de produire une augmentation de la réponse multisensorielle. L'augmentation de la combinaison des réponses excède la somme des réponses aux stimulations unisensorielles (voir histogramme) donnant lieu à une réponse sur-additive. Reproduit avec la permission de Macmillan Publishers Ltd: [*Nature Reviews Neuroscience*], Stein & Stanford, copyright (2008).

1.4.2 Règle temporelle

Selon Wallace et Stein (1997), les stimuli provenant de plusieurs modalités sensorielles doivent survenir au sein d'une même fenêtre temporelle afin d'être traités comme provenant d'un même évènement et ainsi susciter une réponse des neurones multisensoriels. En effet, il semble que ce soit le recouvrement des patrons d'activité neuronale plutôt qu'une parfaite synchronie qui déterminera la réponse maximale (Meredith, Nemitz, & Stein, 1987; Wallace et al., 1996). Ceci étant dit, en raison des propriétés physiques des stimuli (les ondes lumineuses se propagent plus rapidement que les ondes sonores) et de la vitesse de conduction axonale selon les modalités (les informations auditives activent le CS plus rapidement que les informations visuelles), les informations sensorielles issues d'un même évènement activent les neurones multisensoriels à différentes latences. Pour pallier ce décalage, la présence d'une fenêtre temporelle suffisamment large permet le chevauchement des activités neuronales induites par les différents stimuli sensoriels et assure ainsi leur intégration (Meredith et al., 1987; Stein et al., 2014; Stein & Wallace, 1996). Bien qu'elle dépende des combinaisons sensorielles, la durée de cette fenêtre permettant une augmentation des réponses neuronales aux stimulations multisensorielles est généralement de 100 millisecondes (ms) et peut atteindre 1500 ms (Alais, Newell, & Mamassian, 2010). Ainsi, la règle de coïncidence temporelle indique que l'ampleur de la réponse multisensorielle est d'autant plus forte que les composantes unisensorielles sont temporellement proches (sur-additivité). En revanche, en cas de disparité temporelle importante, la réponse neuronale sera inchangée ou même diminuée (sous-additivité; Stein et al., 2014). Les règles de sur- et de sous-additivité sont représentées à la Figure 4.

1.4.3 Préservation des champs récepteurs

Selon Stein et ses collègues (1993, 2014) des neurones multisensoriels conservent les mêmes propriétés pour les entrées multisensorielles et unisensorielles afin d'assurer la cohérence du monde sensoriel. Dans ce contexte, les stimuli ayant la même origine spatiale et temporelle permettent de détecter et de localiser plus rapidement une cible présente dans un monde perceptif changeant.

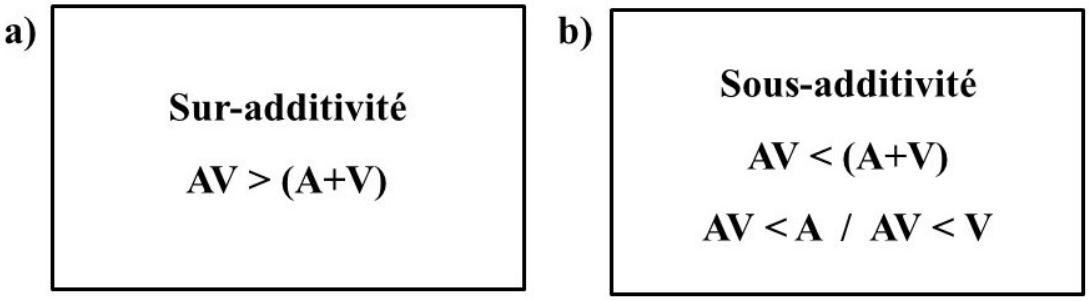

Figure 4. Résumé des deux principaux critères d'IMS (A : information auditive; V : information visuelle; AV : information audiovisuelle). a) Sur-additivité : l'effet de la combinaison du stimulus multisensoriel AV est plus grand que la somme des stimuli unisensoriels le composant. b) Sous-additivité : l'effet du stimulus AV est plus petit que la somme des stimuli unisensoriels ainsi que chaque stimulus unisensoriel seul.

1.4.4 Efficacité inverse

Toujours dans le CS, différents types de neurones montrant une réponse multisensorielle différente ont été décrits en fonction de l'efficacité, donc de l'intensité des stimuli présentés (Perrault, Vaughan, Stein, & Wallace, 2005). La mesure de l'efficacité de la combinaison multisensorielle a été proposée comme étant le pourcentage de gain apporté par la combinaison de stimuli par rapport à la réponse maximale de chacun des stimuli unisensoriels à eux seuls (Stein & Meredith, 1993). Il a été observé que plus les stimuli unisensoriels sont de faible intensité, plus leur combinaison produira un gain important : c'est la règle d'efficacité inverse (Stein & Meredith, 1993; Stanford, Quessy, & Stein, 2005). Plus précisément, cette règle stipule que la présentation combinée de stimuli unisensoriels de faible intensité, produira une réponse neuronale multisensorielle d'autant plus augmentée. Ainsi, un stimulus unisensoriel dont l’intensité est inférieure au seuil de détection peut être perçu par l’adjonction d’une autre composante sensorielle elle-même peu ou pas efficace (Meredith & Stein, 1986). Cette propriété est intéressante au niveau comportemental car elle permettrait d'augmenter la saillance (baisse du seuil de détection) de stimuli peu efficaces (Stein & Meredith, 1993; Stein & Stanford, 2008; Stein et al., 2014). À l’inverse, plus un stimulus unisensoriel est efficace par lui-même et moins il produira de réponse en combinaison avec un autre.

1.5 Intégration audiovisuelle

La vision et l'audition sont reconnues pour leur collaboration étroite dans la perception, comme en témoigne une littérature abondante. L’article 2 de la présente thèse s’intéresse spécifiquement au développement de l’intégration AV avec l’âge. Ainsi, les prochaines sections porteront sur ce type d’IMS.

1.5.1 Développement des systèmes auditif et visuel

Il est possible de supposer que l’expérience multisensorielle, sous l’effet de la maturation cérébrale, contribue à l’amélioration des capacités multisensorielles. Par ailleurs, cette amélioration peut également dépendre directement du développement de chacun des systèmes sensoriels et ainsi de leur capacité à mieux prélever et discriminer les informations sensorielles. Les études développementales portant sur les premiers mois de la vie démontrent que les sens de l’audition et de la vision apparaissent fonctionnels, mais demeurent immatures.

Ainsi, afin de mieux comprendre le développement des capacités d'intégration AV il importe de porter une attention particulière sur le développement respectif de chacun de ces sens.

1.5.1.1 Système visuel

L'organisation du système visuel se caractérise par deux voies distinctes permettant l'analyse de paramètres différents dans la perception visuelle et qui demeurent relativement séparées de la rétine au cortex (Daw & Daw, 2006). Le traitement initial de l'image prend place dans la rétine. L'information visuelle rejoint les axones des cellules ganglionnaires de la rétine, emprunte le nerf optique pour être ensuite relayée par le corps genouillé latéral (CGL) au niveau du thalamus avant de parvenir au cortex visuel primaire ou cortex strié (aire V1). L'impulsion électrique de V1 se propage ensuite vers les aires visuelles extra-striées (V2, V3, V4, V5/MT) où l'information visuelle sera traitée par deux voies distinctes impliquées dans des types de perception complémentaires. La voie magnocellulaire permet de déterminer la position spatiale d'un objet (voie dorsale, occipito-pariétale ou du « où ») et la voie parvocellulaire joue un rôle majeur dans la reconnaissance et l'identification visuelle (voie ventrale, occipito-temporale ou du « quoi ») (Snowden et al., 2012; Tovée, 1996).

Bien que le système visuel débute son développement anatomique au cours de la période gestationnelle, il demeure immature à la naissance tout en continuant de se spécialiser jusqu'à l'âge adulte (Brecelj, 2003). En effet, dès la 28$^{\text{ième}}$ semaine de gestation, le cortex visuel primaire connaît une expansion volumique fulgurante pour ensuite atteindre sa taille adulte vers l'âge de 4 mois suite à la naissance (Huttenlocher, 1990). Cette augmentation du volume paraît liée à l'augmentation de taille du corps du neurone et de la longueur des dendrites en lien avec une phase d'intense synaptogenèse. Il est estimé que seulement environ

10% du total du nombre de synapses qui existent dans le cortex visuel humain sont formés à la naissance. En effet, dans le cortex visuel primaire, la synaptogenèse est la plus rapide entre 2 et 4 mois, suivie d'une élimination progressive de 40% de la densité synaptique entre les âges de 8 mois et 11 ans (fonction visuelle mature) (Huttenlocher, de Courten, Garey, & Van der Loos, 1982). Quant à la myélinisation du système visuel, celle-ci débute entre le sixième et le huitème mois de vie fœtale, et se développe depuis le CGL vers le chiasma et le globe oculaire pour se poursuivre dans les nerfs optiques jusqu'à l'âge de 2 ans (Héran, Koskas, & Vignal, 2010; Magoon & Robb, 1981) et dans le cortex visuel primaire jusqu'à 5 ans (Huttenlocher & Dabholkar, 1997) pour ensuite se prolonger dans le cortex visuel extra-strié jusqu'à l'âge adulte (Paus et al., 2001). Sur le plan fonctionnel, plusieurs études animales ont démontré que le développement du traitement visuel s'effectue majoritairement après la naissance et dépend des stimulations visuelles environnementales (Crair, Gillespie, & Stryker, 1998; White & Fitzpatrick, 2007). D'ailleurs, la complexification et la spécialisation des réponses neuronales en réaction à des caractéristiques spécifiques d'un stimulus visuel s'accroîent avec l'âge. Au cours des premières années de vie, les PÉVs afffichent notamment des changements au niveau de la latence et de l'amplitude pour atteindre une morphologie adulte entre l'âge de 1 et 6 ans (Crognale, 2002; Kos-Pietro, Towle, Cakmur, & Spire, 1997; Madrid & Crognale, 2000).

1.5.1.2 Système auditif

Pour être analysée et décodée, l'onde sonore voyage à travers le système auditif qui est constitué de plusieurs relais fonctionnels accomplissant chacun une partie du traitement permettant de construire le percept auditif et, ultimement, de le lier avec nos connaissances et expériences. Au niveau périphérique, les ondes sonores sont transformées en signal nerveux par les cellules ciliées de la cochlée située dans l'oreille interne. Ensuite, ce signal progresse le long des noyaux du tronc cérébral, rejoint le cortex auditif primaire, responsable du décodage des composantes acoustiques élémentaires comme la fréquence et l'intensité (Bilecen, Seifritz, Scheffler, Henning, & Schulte, 2002; Formisano et al., 2003), pour ensuite atteindre les aires corticales auditives non primaires qui répondent aux composantes spectralement et temporellement complexes des sons (Hall et al., 2002; Hart, Palmer, & Hall, 2003).

Dès les toutes premières semaines de gestation, le processus de développement du système auditif se met en place et mènera à la formation des composantes de l'oreille ainsi que des voies auditives. D'un point de vue anatomique, les structures de l'oreille externe et moyenne s'édifient principalement durant le premier trimestre de la grossesse suivi par le développement de l'oreille interne qui prendrait fin dans le huitième mois de gestation (Lecanuet & Schaal, 1996). La majorité des études développementales suggèrent que l'audition fœtale débuterait et se développerait très progressivement entre la 20$^{\text{ième}}$ et la 28$^{\text{ième}}$ semaine de gestation (Aslin, Pisoni, & Jusczyk, 1983; Chelli & Chanoufi, 2008; Shahidullah & Hepper, 1993). Quant à lui, le développement anatomique des voies auditives centrales se fait parallèlement à celui du système périphérique. En effet, la maturation des différentes structures composant les premier (noyaux cochléaires), deuxième (complexe olivaire supérieur, thalamus), troisième (CS), et dernier relais (corps genouillé médian) des voies auditives primaires s'étend du quatrième au septième mois de gestation. La migration neuronale depuis les zones de prolifération périventriculaires débute vers la huitième semaine de vie au niveau du tronc cérébral, mais se prolonge après la naissance au niveau du cortex cérébral. De même, la myélinisation intervient après la croissance et la multiplication neuronale, et se développe progressivement de la périphérie vers le centre. Ainsi, les racines du nerf auditif sont complétement myélinisées vers 24-26 semaines de gestation, mais la maturation et la myélinisation des projections thalamo-corticales au sein du cortex auditif atteignent un stade adulte vers l'âge de 5 ans. De même, les connexions atteignent leur pleine efficacité entre les âges de 11 et 12 ans (Moore & Linthicum, 2007). Ainsi, le système auditif serait opérationnel dès le début du troisième trimestre de la gestation et continuerait de s'affiner lors de l'enfance et même l'adolescence (Hnath-Chisolm, Laipply, & Boothroyd, 1998; Ruben, 1995). Sur le plan fonctionnel, une réactivité fœtale à des stimulations acoustiques (Grimwade, Walker, Bartlett, Gordon, & Wood, 1971) a été enregistrée dans plusieurs études (Lecanuet, Granier-Deferre, Cohen, Le Houezec, & Busnel, 1986; Ruben, 1995; Trudinger & Boylan, 1980). Au moment où la cochlée commence à répondre aux sons, des réponses évoquées peuvent être enregistrées jusqu'au niveau du cortex auditif primaire entre la 24ième et la 37ième semaines de grossesse (Draganova et al., 2005; Starr, Amlie, Martin, & Sanders, 1977; Weitzman & Graziani, 1968). La maturation des potentiels d'action s'accroît pendant la période fœtale et se poursuit pendant la période post-natale (Uziel, Marot, & Germain, 1980). 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 leur amplitude augmente (Cheour, Leppänen, & Kraus, 2000; Lippé, Martinez-Montes, Arcand, & Lassonde, 2009; Moore & Linthicum, 2007; Wunderlich, Cone-Wesson, & Shepherd, 2006).

1.6 Intégration AV chez l’homme adulte

1.6.1 Gain comportemental

Tel que mentionné précédemment, la capacité du cerveau à intégrer différentes informations sensorielles d’un même évènement confère des gains comportementaux notables qui seront abordés dans la revue de littérature (article 1). L’article 2 portant spécifiquement sur l’intégration AV non linguistique, les études exposant les avantages comportementaux associés à ce type d’IMS seront exposées dans la présente section.

Chez les adultes, des effets de facilitation comportementale tels qu’une diminution des temps de réaction ont été rapportés lorsque les informations auditives et visuelles sont présentées de façon simultanée ou dans un temps rapproché et partagent la même source spatiale (Colonius, Diederich, & Steenken, 2009; Fendrich & Corballis, 2001; Slutsky & Recanzone, 2001; Spence, Baddeley, Zampini, James, & Shore, 2003; Teder-Sälejärvi, Di Russo, McDonald, & Hillyard, 2005; Yang et al., 2013; Zampini, Shore, & Spence, 2003). De même, plusieurs études comportementales récentes ont révélé que les adultes intègrent les informations AV redondantes de façon optimale (Alais & Burr, 2004; Battaglia, Jacobs, & Aslin, 2003; Heron, Whitaker, & McGraw, 2004). Les gains comportementaux peuvent également se traduire par des effets de facilitation multisensorielle (c.-à-d., influence d'un stimulus accessoire sur le stimulus principal) où la présentation simultanée ou proche dans le temps d’un son, pertinent ou non pour la réalisation d’une tâche, induit notamment une diminution des temps de réaction à une cible visuelle et augmente l’intensité perçue du stimulus visuel (Fiebelkorn, Foxe, Butler, & Molholm, 2011; Lippert, Logothetis, & Kayser, 2007; McDonald, Teder-Salejarvi, & Hillyard, 2000; Noesselt et al., 2007; Stein & Wallace, 1996). Par exemple, un flash lumineux est identifié beaucoup plus rapidement quand il est précédé d’un son (McDonald et al., 2000) et l’émission d’un son peut améliorer la perception de l’intensité d’une lumière (Stein, London, Wilkinson, & Price, 1996).

1.6.2 Corrélats électrophysiologiques de l’intégration AV

Sur le plan neuronal, une méthode fréquemment employée pour mesurer l’IMS consiste à comparer la réponse évoquée par les stimuli audiovisuels (AV) à la somme des réponses émanant de chacune des modalités sensorielles auditive (A) et visuelle (V).

$$\text{Intégration AV} = \text{réponses AV} - [(\text{réponses A}) + (\text{réponses V})]$$

D’ailleurs, plusieurs travaux en EEG et en magnétoencéphalographie (MEG) ont fait appel à ce modèle d’additivité pour étudier les processus d’intégration AV chez l’homme adulte par le biais de tâches passives ou requérant une réponse de la part du participant (Fort, Delpuech, Pernier, & Giard, 2002a, 2002b; Giard & Peronnet, 1999; Molholm, Ritter, Javitt, & Foxe, 2004; Molholm et al., 2002; Raij et al., 2010; Stekelenburg & Vroomen, 2007; Talsma & Woldorff, 2005; Teder-Sälejärvi, McDonald, Di Russo, & Hillyard, 2002; Vidal, Giard, Roux, Barthelemy, & Bruneau, 2008). Des effets de sur-additivité (Cappe, Thut, Romei, & Murray, 2010; Giard & Peronnet, 1999; Sakowitz, Quiroga, Schürmann, & Başar, 2005; Talsma, Doty, & Woldorff, 2006) et de sous-additivité (Molholm et al., 2002; Stekelenburg & Vroomen, 2007; Vroomen & Stekelenburg, 2010) ont été mesurés dans les études employant des PÉs. La mesure des PÉs repose sur l'enregistrement des modifications de l'activité cérébrale liées à une stimulation externe (p. ex., visuelle, auditive). Ces concepts seront abordés en detail dans une section subséquente. Par exemple, certaines études ont démontré que l'information AV peut moduler l'amplitude des composantes EEG N1 et P2 auditives ainsi que la N1 visuelle (Besle, Bertrand, & Giard, 2009; Giard & Besle, 2010; Molholm et al., 2002; Stekelenburg & Vroomen, 2007, 2012). De même, une augmentation de l'amplitude des réponses oscillatoires AV évoquées a été trouvée dans les bandes de fréquences thêta, alpha, bêta et gamma (Sakowitz et al., 2001, 2005; Sakowitz, Schürmann, & Başar, 2000; Senkowski, Molholm, Gomez-Ramirez, & Foxe, 2005; Yan et al., 2016).

Les récentes études ont mis en évidence deux stades d'intégration distincts suite à la présentation de stimuli AV. En effet, des effets d'intégration précoce (autour de 50 ms) ont été démontrés dans plusieurs études en PÉs (Fort et al., 2002; Foxe & Schroeder, 2005; Giard & Peronnet, 1999; Molholm et al., 2004; Molholm et al., 2002; Talsma & Woldorff, 2005; Vidal et al., 2008) ainsi que dans certaines bandes de fréquences (Senkowski, Molholm, et al., 2005; Senkowski et al., 2007; Senkowski, Talsma, Herrmann, & Woldorff, 2005) au niveau pariéto-occipital. De même, de l'intégration AV a été observée entre 100 et 200 ms notamment dans les régions fronto-centrales (Molholm et al., 2002; Sakowitz et al., 2000; Senkowski, Molholm, et al., 2005; Teder-Sälejärvi et al., 2002; Tucker, 1993; Yan et al., 2016) et pariéto-temporales (Giard & Peronnet, 1999; Gondan & Röder, 2006; Teder-Sälejärvi et al., 2002).

Bien qu'il existe des divergences quant au type de composantes EEG observé, à la bande de fréquences ainsi qu'à la localisation cérébrale dans lesquelles la réponse neuronale se manifeste, l'ensemble de ces études démontre la présence de processus d'intégration AV chez l'adulte.

1.7 Inné ou acquis ?

Une question importante est de savoir si cette capacité à intégrer les informations multisensorielles de façon optimale est ancrée en nous dès la naissance ou si elle se développe au cours de l'enfance en fonction de l'expérience. La revue de la littérature incluse dans la présente thèse (article 1) s'attardera, en partie, sur le développement des capacités d'intégration dans plusieurs modalités sensorielles. Ainsi, nous n'aborderons que de façon sommaire la dichotomie inné-acquis de l'intégration AV.

1.7.1 Études animales

De récents travaux neurophysiologiques réalisés chez les animaux corroborent l'idée que le développement de la capacité du cerveau à intégrer les informations AV s'échelonne au cours d'une période postnatale prolongée (Wallace & Stein, 1997, 2001; Yu, Rowland, & Stein, 2010). Bien que les neurones multisensoriels corticaux et sous-corticaux soient fonctionnels dès la naissance, les travaux chez le chat ont démontré qu'ils ne répondent qu'à un seul type d'information sensorielle et que l'émergence des propriétés intégratives de ces neurones ne survient qu'après plusieurs mois de vie (Wallace, Carriere, Perrault, Vaughan, & Stein, 2006; Wallace & Stein, 1997). De plus, la maturation des réponses multisensorielles dépend fortement de l'expérience environnementale et des afférences des aires corticales (Wallace & Stein, 2001, 2007). Par exemple, suite à une privation visuelle les neurones multisensoriels émettent des réponses atypiques et échouent à intégrer les informations des différentes modalités (Wallace, Perrault, Hairston, & Stein, 2004). De même, chez des chats élevés dans un environnement où les stimuli auditifs et visuels émanent de lieux différents, des neurones du CS développent une forme d'intégration où les stimuli spatialement disparates sont intégrés de la même façon que s'ils venaient d'un même endroit, suggérant que les principes gouvernant l'intégration des sens puissent être très plastiques et que ceux-ci s'établissent en fonction des propriétés de l'environnement (Wallace & Stein, 2007). De plus, la maturation des réponses multisensorielles dépend fortement des afférences des aires corticales. En effet, le retrait du sillon ectosylvien antérieur et du cortex latéral suprasylvien au cours des premiers stades développementaux chez le chat perturbe le développement des propriétés multisensorielles du CS (Jiang, Jiang, Rowland, & Stein, 2007; Wallace et al., 2006).

1.7.2 Sensibilité à la synchronie chez le nourrisson

Les résultats de plusieurs études comportementales contemporaines appuient deux conceptions sur le développement des habiletés multisensorielles. Le premier courant de pensée, celui de l'approche de différenciation développementale (Bower, 1974; Gibson 1969; Gibson 1966), suggère que le nouveau-né entre dans le monde avec des systèmes sensoriels fonctionnels et, conséquemment, est sensible aux propriétés amodales et peut percevoir des relations multisensorielles. D'une part, la capacité à lier les stimulations provenant de différents sens pourrait être antérieure à la naissance et remonter à la vie in-utéro. Différents travaux démontrent la présence d'une aptitude du fœtus à effectuer des mises en relation et des apprentissages multisensoriels (James, 2010). De plus, il a été démontré que les nouveau-nés détiennent des habiletés de perception multisensorielle de bas niveau et bénéficient des informations redondantes telles que la détection des relations de l'intensité et de la synchronie (Bahrick & Lickliter, 2000, 2004; Lewkowicz, 1996). Par exemple, des nouveau-nés peuvent détecter des relations AV sur la base de la cohérence spatiale et temporelle (Morrongiello, Fenwick, & Chance, 1998; Slater, Brown, & Badenoch, 1997) et l'exploration visuelle est influencée par la présence et l'orientation de la source d'un son dès l'âge de 3 semaines (Lewkowicz & Turkewitz, 1980). De plus, de nombreuses études comportementales ont révélé que les nourrissons, âgés entre 2 mois et 1 an, peuvent percevoir et discriminer des relations AV, faire des appariements entre un son et une image et même percevoir des illusions s'appuyant sur des interactions AV (Scheier, Lewkowicz, & Shimojo, 2003). Ces résultats comportementaux sont également appuyés par deux études en EEG démontrant que les nourrissons de 3 et 6 mois discriminent des stimuli AV non linguistiques synchrones et asynchrones (Hyde, Jones, Porter, & Flom, 2010; Kopp, 2014).

D'autre part, l'approche de l'intégration intersensorielle, s'inscrivant dans une tradition piagétienne, préconise, qu'à la naissance, les différents systèmes sensoriels ne communiquent pas entre eux et que des relations multisensorielles ne sont formées qu'après plusieurs mois, voire des années de vie à travers l'expérience de l'enfant et ses interactions avec l'environnement (Birch & Lefford, 1963, 1967; Piaget, 1952). Bien que la perception multisensorielle survienne précocement il apparaît qu'elle s'améliore et se diversifie rapidement au cours des premières années de vie (Lewkowicz, 2003; Lickliter & Bahrick, 2000; Neil, Chee-Ruiter, Scheier, Lewkowicz, & Shimojo, 2006; Spence & McDonald, 2004; Walker-Andrews, 1997). Quoique la capacité à détecter des relations simples de synchronie ou d'asynchronie entre des sons et des images (Bahrick, 1992; Lewkowicz, 1992) apparaisse au cours des premières semaines de vie, certains travaux ont démontré que les nourrissons âgés entre 2 et 8 mois requièrent quatre à cinq fois plus de temps que les adultes pour discriminer des stimuli multisensoriels synchrones et asynchrones (Lewkowicz, 1996). L'aptitude à percevoir des informations multisensorielles de bas niveau constituerait ainsi un pivot dans le développement progressif de compétences multisensorielles de plus haut niveau qui se complexifient avec l'âge (Lewkowicz & Ghazanfar, 2009; Lickliter & Bahrick, 2000). En effet, les nourrissons ne parviennent à apparier des objets en mouvement au son émis sur la base de leur structure (p. ex., hochet qui contient une grosse bille et un autre qui renferme plusieurs petites billes) (Bahrick, 1987) et de leur durée de présentation (Lewkowicz, 1986) qu'à partir de 6 mois, et en fonction du rythme d'action unissant l'image et le son d'un objet en mouvement pas avant l'âge de 10 mois (Lewkowicz, 2003).

1.7.3 Intégration AV chez l'enfant

Les travaux chez l'adulte ont démontré l'existence d'une fenêtre temporelle d'une centaine de millisecondes à l'intérieur de laquelle il est possible d'intégrer des informations auditives et visuelles décalées dans le temps comme appartenant à un évènement unique (Dixon & Spitz, 1980; Noesselt et al., 2007). La présence de toute autre information sensorielle survenant en dehors de cette fenêtre de temps sera perçue indépendamment et ne sera pas intégrée au percept multisensoriel (Colonius & Diederich, 2011; Pöppel, 1997). De récentes études comportementales ont révélé que la fenêtre temporelle pour combiner des stimuli AV serait nettement plus large à l'enfance en comparaison à l'âge adulte et n'atteindrait pas la maturité avant l'âge de 9 ans (Chen, Shore, Lewis, & Maurer, 2016; Hillock-Dunn & Wallace, 2012; Hillock, Powers, & Wallace, 2011; Lewkowicz, 1996), engendrant un biais à percevoir des informations auditives et visuelles asynchrones comme un même évènement. Ce manque de précision quant à la détection de l'asynchronie temporelle militerait en faveur d'un développement tardif des capacités d'intégration AV.

De plus, les bénéfices et gains comportementaux associés à l'IMS ne sont généralement observés que tardivement au cours du développement. En effet, les études comportementales comparant les temps de réaction (Miller, 1982; Raab, 1962) des enfants à des stimuli unisensoriels et multisensoriels reflètent une variabilité dans les résultats. En effet, ces études suggèrent que les capacités d'intégration AV demeurent sous-optimales durant l'enfance et même l'adolescence (Barutchu, Crewther, & Crewther, 2009; Barutchu et al., 2010; Downing, Barutchu, & Crewther, 2015; Gori, Sandini, & Burr, 2012; Nardini, Bales, & Mareschal, 2016) et que les adolescents parviennent à intégrer comme les adultes vers l'âge de 14 ans (Brandwein et al., 2011). D'ailleurs, l'étude en EEG de Brandwein et collaborateurs (2011) corrobore ces résultats comportementaux. Dans cette étude, les auteurs ont examiné la progression développementale des capacités d'intégration AV chez des enfants neurotypiques âgés de 7 à 16 ans et des adultes en employant des stimuli non linguistiques. Les résultats issus de cette recherche ont révélé que l'amplitude de la réponse AV était significativement plus grande que la sommation des réponses auditives et visuelles (A+V), et ce, uniquement chez les adultes et les enfants âgés entre 13 et 16 ans, suggérant une immaturité de l'intégration AV avant cette tranche d'âge. L'intégration AV observée a été enregistrée entre 100 et 120 ms au niveau des régions fronto-centrales ainsi qu'entre 100 et 150 ms au niveau pariétal.

En somme, bien qu'une sensibilité aux relations multisensorielles soit observée dès la naissance, les résultats neurophysiologiques chez l'animal et les études chez l'enfant militent en faveur d'un développement progressif des capacités d'intégration AV qui se perfectionnent significativement au cours du développement.

1.8 Limites de la littérature dans l'étude des capacités de l'IMS chez l'enfant

Jusqu'à présent, la grande majorité de la littérature multisensorielle chez le nouveau-né et le nourrisson repose sur l'étude de processus multisensoriels aussi divers et variés que l'imitation précoce, le transfert intermodal, les appariements AV et l'acquisition de la parole (Walker-Andrews, Lewkowicz, & Lickliter, 1994). De plus, les paradigmes comportementaux employés divergent selon le type d'habiletés multisensorielles étudié notamment l'utilisation de la technique du regard préférentiel (Spelke, 1976) et la procédure d'habituation-reconnaissance (Lewkowicz, 1992; Pons, Lewkowicz, Soto-Faraco, & Sebastián-Gallés, 2009). Malgré le caractère multisensoriel associé à ces tâches comportementales, celles-ci ne mesurent pas pour autant si les informations multisensorielles ont été effectivement intégrées (Stein et al., 2010). Par exemple, la technique du regard préférentiel permet d'enregistrer la direction du regard du nourrisson pour savoir s'il apparie une séquence de sons à la scène visuelle lui correspondant. Ainsi, les études multisensorielles chez le nourrisson sont davantage conçues pour étudier la détection des différences ou des équivalences entre des stimulations auditives et visuelles. Une grande partie des travaux en IMS réalisés chez l'enfant requièrent des réponses comportementales actives de la part des participants. Ces réponses comportementales permettent de mesurer des temps de réaction qui constituent certainement des indicateurs plus utiles et valables du gain comportemental découlant de processus d'IMS que les paradigmes comportementaux employés chez le nourrisson. Il est toutefois possible que les différences comportementales obtenues puissent résulter de différences dans l'interprétation des consignes de la tâche ou refléter des processus d'allocation des ressources attentionnelles plus matures chez les participants plus âgés. L'utilisation de l'EEG constituerait ainsi une métrique pertinente qui permettrait de pallier ces limites en mesurant effectivement la réponse neuronale reliée à l'IMS. Par le biais de tâches passives n'exigeant aucune réponse de la part des participants, l'EEG limiterait les demandes attentionnelles ainsi que la variabilité interindividuelle de compréhension de la tâche. Par la finesse de sa résolution temporelle, cette technique constitue également un moyen privilégié pour étudier de manière précise la progression développementale des capacités d'IMS. À ce titre, bien que les travaux sur les capacités d'IMS à l'âge scolaire soit nombreux, une infime quantité de travaux en EEG s'est penchée sur la progression développementale de l'IMS (Brett-Green, Miller, Gavin, & Davies, 2008; Kaganovich & Schumaker, 2014; Knowland, Mercure, Karmiloff-Smith, Dick, & Thomas, 2014), et ce, toute modalité sensorielle confondue. On constate également un manque de données notable sur le développement des capacités d'IMS à l'âge préscolaire (entre 3 et 5 ans). Ces constats contribuent à notre manque de connaissances sur la progression développementale de l'intégration AV.

1.9 Réponses électrophysiologiques

1.9.1 L'électrophysiologie de surface : principe général

L'EEG de surface est une technique non invasive permettant d'enregistrer l'activité électrique cérébrale sous la forme d'une différence de potentiel entre une paire d'électrodes situées sur la surface du scalp (Brannon, Roussel, Meck, & Woldorff, 2004). Grâce à son excellente résolution temporelle (Constant & Sabourdin, 2012), l'EEG permet de suivre dans le temps la réponse sensorielle à l'échelle de la milliseconde ainsi que sa localisation grâce aux informations spatiales apportées par les méthodes de topographie et d'analyses de sources.

L'activité électrique cérébrale recueillie est visualisable lors de l'état de vigilance basal du cerveau (EEG continu), mais aussi en réaction aux stimulations endogènes et exogènes. Cette réaction spécifique à une stimulation, communément appelée potentiel évoqué (PÉ), demeure une des principales mesures électrophysiologiques utilisée dans l'étude du développement de la vision, de l'audition et de l'IMS. Ces PÉs correspondent à la modification de l'activité électrique dans différentes populations de neurones en réponse à un évènement ou une stimulation sensorielle de nature visuelle, auditive ou autre (Luck, 2005). Les PÉs obtenus par *moyennage* permettent de dégager des ondes cérébrales spécifiques (Luck, 2005), appelées aussi composantes, qui apparaissent comme une série de déflections de polarité positive (P) ou négative (N) mesurées à différents temps d'apparition et diverses localisations sur le scalp. Plus précisément, les PÉs sont identifiés par les paramètres suivants : 1) l'amplitude qui permet d'observer la grandeur de l'onde et qui est mesurée en fonction du voltage (µV) maximal de la déflection, 2) la latence qui démontre l'intervalle de temps entre un stimulus et une réaction et qui se définit par le temps de culmination (ms) et 3) le nombre de déflections présentes dans le signal EEG moyenné suite à la présentation du stimulus.

1.9.2 Potentiels évoqués visuels et auditifs

Les potentiels évoqués visuels (PÉVs) et auditifs (PÉAs) représentent donc l'activité cérébrale moyennée en réponse à une stimulation visuelle et auditive respectivement. Chez l'adulte, les réponses typiquement obtenues au moyen des PÉVs consistent en trois déflections majeures : la N70 (onde négative entre 75-90 ms), la P100 (onde positive entre 90-120 ms) ainsi que la N100 (onde négative entre 130-200 ms) (Crognale, Kelly, Weiss, & Teller, 1998; Odom et al., 2010). Ces ondes transitoires reflètent l'activité de générateurs corticaux situés dans les aires visuelles corticales primaires (Vanni et al., 2004; Zhang & Hood, 2004) et sont enregistrées au moyens d'électrodes placées sur le lobe occipital, généralement aux sites centro-occipital (Oz) et de chaque côté de celui-ci, aux sites O1 et O2 (Odom et al., 2010). La morphologie des PÉVs varie en fonction du type de stimulus présenté. La stimulation visuelle la plus utilisée en recherche est probablement le damier noir et blanc à contraste élevé par inversement ou apparition-disparition couramment utilisé en clinique. Celle-ci représente la stimulation idéale afin d'évoquer une réponse globale du système visuel en développement (Roy, Barsoum-Homsy, Orquin, & Benoit, 1995; Taylor & McCulloch, 1992) puisque le nouveau-né possède les compétences visuelles pour traiter ce stimulus. Dans la recherche que nous allons présenter (article 2), la stimulation visuelle était constituée par l'apparition et la disparition d'un damier noir et blanc (2 degrés) dont le PÉV élicité était composé des ondes P100 et N100 (Figure 5).

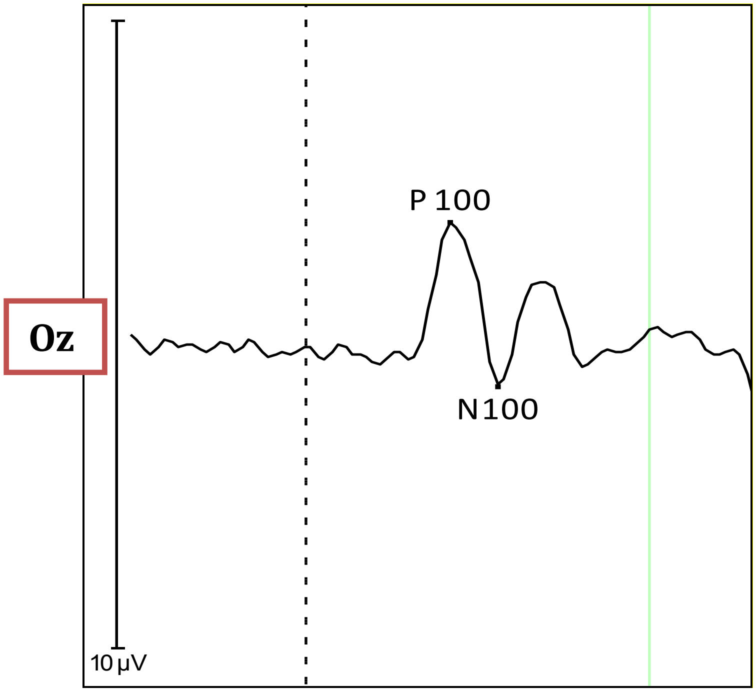

Figure 5. Exemple d’enregistrement d’un PÉV chez nos participants adultes dans la région centro-occipitale (Oz) suite à la présentation d’un damier noir et blanc.

Chez l’adulte, le PÉA cortical observé dans les conditions expérimentales très simples d'écoute passive de tonalités ou de clicks répétitifs se caractérise par les composantes suivantes : la P100 (onde positive entre 60-80 ms), suivie par un large complexe N100 (onde négative autour de 120 ms) et P200 (onde positive entre 180-200 ms) (Naatanen, 1992). Ces ondes sont générées en grande partie dans le plan temporal du cortex auditif primaire (Tremblay, Kraus, McGee, Ponton, & Otis, 2001) et sont enregistrées sur les régions centrales (Cz) et fronto-centrales (FCz) (Vaughan & Ritter, 1970). Dans la recherche que nous allons présenter, la stimulation auditive était constituée par la présentation d’un ton de 1000 Hz (article 2). Le ton de 1000 Hz est un stimulus employé dans d’autres études examinant les processus d’intégration AV (Brandwein et al., 2011, 2012; Molholm et al., 2002) et notre étude pilote auprès d'un groupe d'adultes est venu confirmer la présence des composantes de PÉAs N100 et P200 typiquement observées (Figure 6).

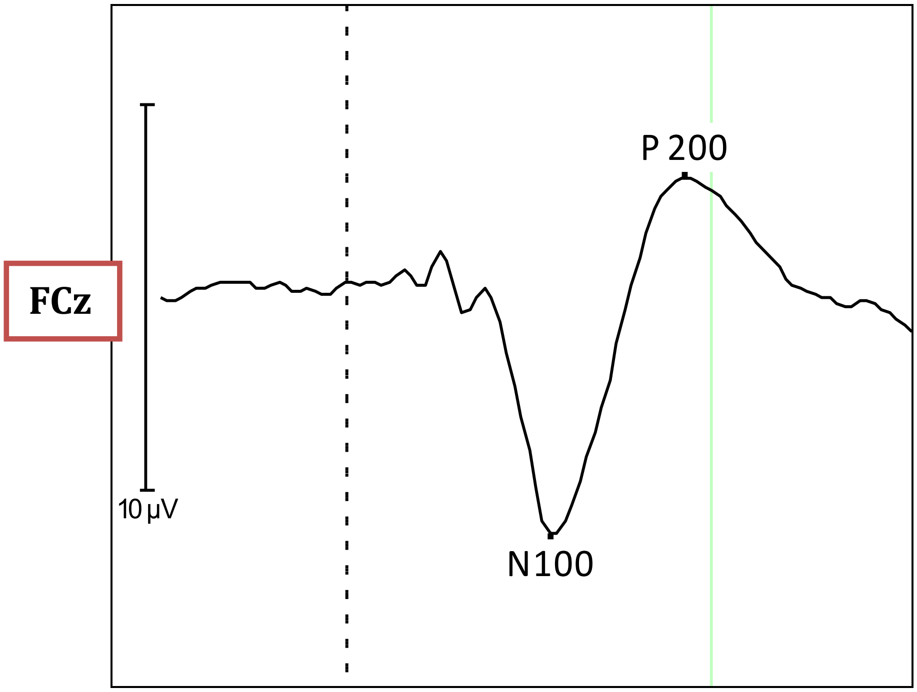

Figure 6. Enregistrement d'un PÉA chez nos participants adultes dans la région fronto-centrale (Cz) suite à la présentation d'un ton pur de 1000 Hz.

1.9.3 Limites de l'utilisation des PÉs

L'observation des PÉs représente la forme d'analyse traditionnelle de l'EEG pour évaluer le traitement des réponses cérébrales évoquées par une stimulation ou un traitement cognitif. Tel que mentionné précédemment, les PÉs sont obtenus par le *moyennage* de tous les essais qui suivent une même condition expérimentale et se limitent à l'étude des réponses cérébrales, en termes d'amplitude, qui apparaissent au même moment dans le temps et donc à latence similaire.

Ceci étant dit, la combinaison des changements développementaux en termes de densité synaptique, de myélinisation et d'autres processus de maturation physiologique (p. ex., changement dans l'épaisseur de la boîte crânienne, fermeture de la fontanelle) peuvent influencer la morphologie des courbes EEG avec l'âge (Luciana & Nelson, 1998). Les études développementales ont d'ailleurs mis en évidence une diminution de la latence et des changements dans l'amplitude des composantes EEG reliés à l'immaturité et au développement des systèmes visuels et auditifs (Bishop, Hardiman, Uwer, & Von Suchodoletz, 2007; Lippé et al., 2009; Lippé, Roy, Perchet, & Lassonde, 2006; Wunderlich et al., 2006). Une telle variabilité dans le signal EEG peut rendre difficile la lecture visuelle traditionnelle des PÉs et ainsi se répercuter dans son interprétation. De même, une des difficultés majeures dans l'application de cette technique auprès de la population pédiatrique est reliée aux artefacts lesquels peuvent créer de fausses asymétries et ainsi compliquer l'interprétation du tracé EEG. D'ailleurs, la réduction de la densité synaptique au cours des premières années de vie se traduit notamment par une plus grande proportion d'ondes lentes plutôt que par des pics d'activité cérébrale aussi bien définis que ceux des adultes (Soto-Icaza, Aboitiz, & Billeke, 2015).

Afin d'outrepasser les limites susmentionnées, l'analyse spectrale des signaux EEG nous apparaît comme une méthode de choix pour étudier les processus d'intégration AV ne pouvant pas être détectés par l'analyse traditionnelle des PÉs (Van der Lubbe, Szumska, & Fajkowska, 2016).

1.9.4 Analyse spectrale

La dynamique électrophysiologique du traitement de l'information du cerveau est composée de variations d'énergies dans les domaines temporels, mais aussi fréquentiels. Les phénomènes liés à un évènement sont en effet associés à des variations de fréquences de l'activité EEG de fond, possiblement produites par des variations de synchronies de populations neuronales locales (Pfurtscheller & Da Silva, 1999). Ainsi, les signaux EEG peuvent faire l'objet d'une décomposition en différentes oscillations de type sinusoïdales dont le cycle correspond à des bandes de fréquences distinctes et associées à certaines fonctions ou processus physiologiques. Parmi ces dernières, on recense les fréquences delta (1-4 Hz), thêta (4-7 Hz), alpha (8-14 Hz), bêta (15-29 Hz) et gamma (30-50 Hz) (Başar, Başar-Eroğlu, Karakaş, & Schürmann, 2000; Figure 7). Plusieurs études ont démontré que l'activité oscillatoire dans ces bandes de fréquences est associée à un éventail de processus reliés à la perception, au traitement sensorimoteur ainsi qu'à la cognition (Fries, 2005; Herrmann, Munk, & Engel, 2004; Klimesch, Doppelmayr, & Hanslmayr, 2006; Palva & Palva, 2007).

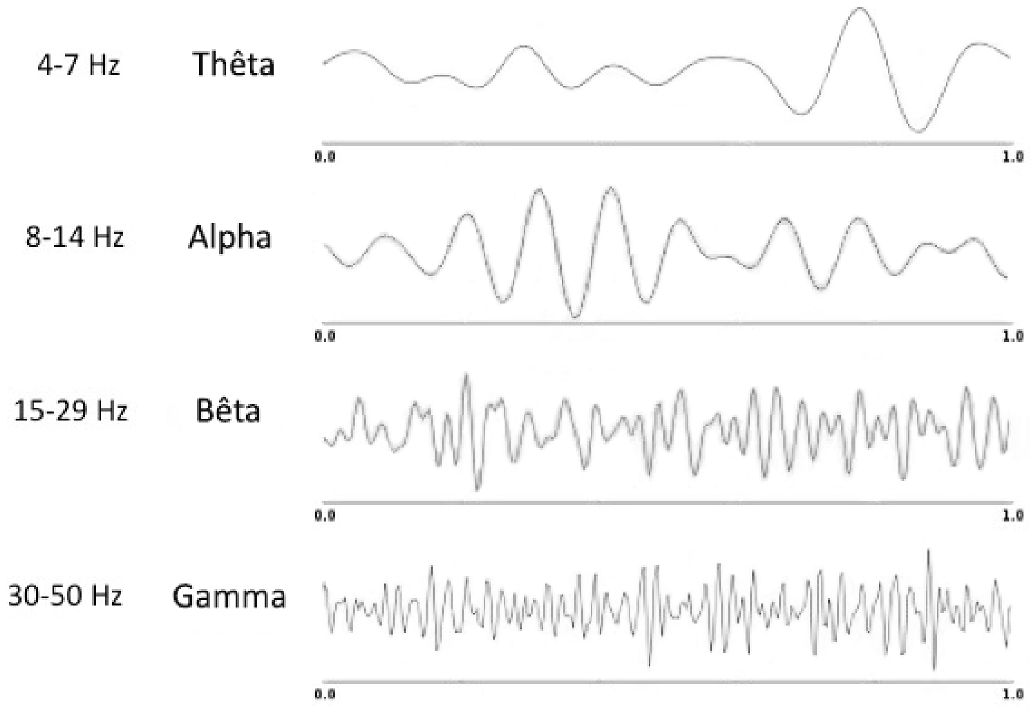

Figure 7. Décomposition du signal EEG dans les bandes de fréquences thêta, alpha, bêta et gamma.

Dans le cadre de notre étude (article 2), une décomposition temps-fréquence a été appliquée sur les réponses neuronales dites « évoquées » par les stimulations sensorielles. Les réponses évoquées sont strictement calées temporellement avec le début de la stimulation (*stimulus-locked*) et peuvent être mesurées en moyennant les réponses à la stimulation (Tallon-Baudry & Bertrand, 1999). La puissance d'activation des réponses neuronales a ensuite été extraite et analysée dans les bandes de fréquences thêta, alpha, bêta et gamma à l'intérieur d'une fenêtre temporelle fixe. L'augmentation de puissance dans une ou plusieurs bandes de fréquences mesurée au niveau d'une ou plusieurs électrodes reflète une augmentation de la synchronisation locale de l'activité oscillatoire des neurones suite à la présentation d'un évènement. D'ailleurs, des études en EEG chez les adultes ont révélé des réponses oscillatoires évoquées dans l'ensemble des bandes de fréquences soit, de thêta à gamma, en réponse à des stimuli AV simples (Kisley & Cornwell, 2006; Sakowitz et al., 2001, 2005, 2000).

1.9.4.1 Analyse temps-fréquence

L'étude des rythmes oscillatoires suppose à la fois un traitement du signal EEG et des analyses mathématiques complexes (Gross, 2014) qui ne seront pas discutées en détail dans cette thèse. Toutes ces analyses sont fondées sur la décomposition du signal dans le domaine fréquentiel, permettant d'obtenir la puissance (μV^2) des oscillations dans chaque bande de fréquences au cours du temps et pour chaque électrode. Dans le cadre de notre recherche, la transformation du signal EEG en oscillations évoquées a été réalisée par le biais de l'analyse en ondelettes de Morlet, méthode permettant de représenter le signal EEG en temps et en fréquence (Daubechies, 1992; Downing et al., 2015; Mallat, 1999). En plus de connaître les différentes fréquences excitées dans un signal, c'est-à-dire son spectre, l'avantage de cette décomposition est qu'elle permet de déterminer à quels instants ces fréquences ont été émises.

En fonction de l'âge, il n'est pas à exclure que l'IMS puisse s'exprimer différemment dans chacune des bandes de fréquences neuronales. L'analyse temps-fréquence en EEG apparaît ainsi l'outil le plus adapté pour caractériser la progression développementale des processus d'intégration AV dans la population pédiatrique.

2. OBJECTIFS ET HYPOTHÈSES

L’objectif principal de cette thèse vise à faire état des connaissances sur le développement neurotypique de l’IMS et à documenter la progression et la maturation des capacités d’intégration AV liées au développement neurotypique. Deux articles composent ainsi le corps de la thèse.

2.1 Article 1

Le premier article est une revue de la littérature et vise à dresser un portrait des connaissances sur le développement neurotypique de l’IMS dans l’ensemble des modalités sensorielles. En plus de dresser les données comportementales et neuronales en faveur du caractère inné ou acquis des processus d’IMS, cette revue a permis de mieux cibler le manque de littérature quant au développement neuronal des capacités d’intégration, ce qui a mené à la tenue de l’étude expérimentale présentée dans l’article 2. Enfin, cette revue de littérature met en lumière la pertinence d’étudier les processus d’IMS pour la compréhension de certains troubles neurodéveloppementaux et troubles d’apprentissage présentant des difficultés sensorielles, par exemple la dyslexie et le TDA/H.

2.2 Article 2

L’objectif principal de cette étude est de caractériser la progression développementale neurotypique des mécanismes d’intégration d’informations AV non linguistiques dès l’âge de 3 mois jusqu’à l’âge adulte par l’entremise de l’EEG et, plus spécifiquement, par le biais d’analyses temps-fréquence en ondelettes. Cette étude vise également à confirmer l'âge où les mécanismes d’intégration AV fonctionnent de façon similaire aux adultes et atteignent leur pleine maturité. Ainsi, le développement des capacités d’intégration AV est examiné en comparant les réponses oscillatoires AV évoquées à la sommation des réponses oscillatoires auditives et visuelles évoquées, et ce, dans les bandes thêta, alpha, bêta et gamma. À la lecture des données relevées dans la littérature, nous émettons l’hypothèse d’une maturation progressive avec l’âge des processus d’intégration AV. Plus spécifiquement, compte tenu des résultats EEG de Brandwein et collaborateurs (2011), nous émettons l’hypothèse que les mécanismes d’intégration AV atteignent leur maturité au cours de l’adolescence soit entre les âges de 13 et 16 ans. Par ailleurs, puisqu’aucune étude n’a proposé l’utilisation des ondelettes pour étudier les capacités d’intégration AV chez l’enfant, nous n’émettons aucune hypothèse formelle quant à l’expression spectrale de cette habileté en fonction de l’âge. Une meilleure compréhension du développement des mécanismes d’intégration chez les individus neurotypiques fournit un point de comparaison pour étudier ces processus chez certaines populations cliniques souffrant de problèmes sensoriels, notamment les individus présentant un TSA, une dyslexie, un trouble du langage oral et un TDA/H.

3. MÉTHODOLOGIE ET RÉSULTAS

3.1 Article 1

Multisensory Integration and Child Neurodevelopment

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Review

Multisensory Integration and Child Neurodevelopment

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Abstract

A considerable number of cognitive processes depend on the integration of multisensory information. The brain integrates this information, providing a complete representation of our surrounding world and giving us the ability to react optimally to the environment. Infancy is a period of great changes in brain structure and function that are reflected by the increase of processing capacities of the developing child. However, it is unclear if the optimal use of multisensory information is present early in childhood or develops only later, with experience. The first part of this review has focused on the typical development of multisensory integration (MSI). We have described the two hypotheses on the developmental process of MSI in neurotypical infants and children, and have introduced MSI and its neuroanatomic correlates. The second section has discussed the neurodevelopmental trajectory of MSI in cognitively-challenged infants and children. A few studies have brought to light various difficulties to integrate sensory information in children with a neurodevelopmental disorder. Consequently, we have exposed certain possible neurophysiological relationships between MSI deficits and neurodevelopmental disorders, especially dyslexia and attention deficit disorder with/without hyperactivity.

Keywords: infancy; multisensory integration; neurodevelopment; cognition; developmental dyslexia; attention deficit disorder with/without hyperactivity

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1. Introduction to Multisensory Information

Most species, including humans, are equipped with various highly specialized sensory systems that give them access to numerous types of information on the surrounding environment. Each sensory modality gives us a unique outlook on the world: Color, for instance, can only be perceived through sight, sound through hearing and temperature feel through the somatosensory system. However, our surroundings never cease to present us with situations that stimulate several senses at once. In day-to-day life, events are rarely unimodal; they are multisensory experiences, deriving from a combination of information acquired through several sensory modalities. The brain integrates this multisensory information to provide a complete and coherent representation of what is being perceived and consequently for appropriate behavioral responses to be generated [1]. For example, if we hear the sound of a siren at a distance and then see a vehicle approaching, the association of visual image and sound leads us instantly to perceive an ambulance. Our perception and behavior are not based on the juxtaposition of independent sensory experience but on the global impression resulting from the combination of information acquired through various modalities. This phenomenon has been called Multisensory Integration (MSI).

In many cases, the survival of an organism depends on appropriate responses to multisensory stimuli. Therefore, our ability to integrate sensory information becomes a fundamental element of our everyday behavior, allowing us to identify events and apply optimal responses to these events. From that perspective, many studies conducted to investigate the behavioral effects of a multisensory presentation have shown that it has beneficial effects. Incidentally, it has been noted that the combination of two sensory modalities could, in various contexts, decrease response time [2–4], increase target detection accuracy [5,6], increase acuity in one of the modalities [7], reduce detection thresholds [8] and even facilitate and optimize learning applied to a single sensory modality [9]. Furthermore, these facilitative behavioral benefits are noted regardless of which sensory modalities are being tested.

To improve our understanding of the benefits afforded by the simultaneous presentation, studies have used various type of stimulation. For instance, several studies have shown behaviorally that viewing a stimulated body part can enhance tactile detection and perception at the stimulated site [5] and that this visuo-tactile enhancement may last up to minutes [7,10]. Thus, using visual and proprioceptive stimuli, seeing one's own arm may shorten the response time to an unseen tactile stimulus to the arm [2]. In return, somatosensory information can also facilitate visual processing [11]. For instance, the response time to a light projected on one's own finger is shorter than when the light is projected on an object far removed from the body [11]. Similarly, studies have shown that vibrotactile stimuli (for example, short vibrations applied to the palm) shorten the response time to visual stimuli [3]. Finally, the integration of tactile and auditory inputs was also investigated, albeit succinctly, revealing that tactile stimuli can be beneficial to auditory perception. It appears that a tactile signal, even non-pertinent, can sometimes facilitate the detection of a sound, thus increasing the impression of loudness [6–8]. In that perspective, research in healthy adults has repeatedly shown behavioral benefit of MSI that might be linked to the underlying ability of the brain to integrate different sensory inputs related to a single event [12].

2. MSI and Development

2.1. Innate or Acquired

Although MSI capacity has been extensively studied in adults, little has been done to study it in young children. The first important question would be: Does this capacity exist at birth, or does it develop as a result of experience? One school of thought (early integration) argues for the innate nature of MSI while another (late integration) emphasizes the role of experience in the development of MSI.

2.1.1. Early Integration Approach

According to the Early Integration Approach, the nervous system is multisensorial right from its early development stage, possessing the capacities to detect redundant aspects of the surrounding environment [13]. In support of this approach, Bower, Broughton and Moore (1970) [14], have observed that infants are able to move their hands toward visual targets as early as six days after birth, which indicates that hand-eye coordination occurs very early on in life. Even in the first months of life, infants are able to perceive and derive meaning from the abundance of multisensorial information. Although the literature on infants is relatively recent and small, a few authors have suggested that MSI is not a unitary process and that different mechanisms might be implicated depending on the specific type of multisensory interaction [15].

Bahrick and Lickliter (2000) [16] proposed the "intersensory redundancy hypothesis", in order to explain how infants perceive coherent, unified multimodal objects and events through different sensory modalities. This hypothesis refers to the presentation of the same information spatially coordinated and temporally synchronous across two or more sensory modalities, and is only possible for amodal properties that are not specific to a single sense modality (e.g., shape, rhythm, duration, intensity) [17]. In other words, regardless of which sensory modality, similar qualities are perceived when we integrate information. For instance, when we hear and look at a bouncing ball, we detect that the auditory and visual stimulations that originate from the same location share a common tempo and rhythm. This sensitivity to amodal properties allows the infant to direct his attention to unitary and meaningful events in which information from different sensory modalities originates from a unique point of origin [18,19].

Studies on the cross-modal transfer of information from touch to vision revealed that neonates are able to process and encode shape information about manually experienced objects and to discriminate between subsequently presented visual objects [20,21]. Newborns are also able to visually recognize the texture that they previously felt and tactually recognize the texture that they previously saw [22]. Others have reported that one-month-old infants can benefit from the tactile-oral properties of an object during visual recognition, showing a clear visual preference for objects with which they had been familiarized through oral presentation [23–25].

It has been demonstrated that the ability to perceive audio-visual relations also emerges early in human development. For example, Lewkowicz and Turkewitz (1980) [26] have shown that three-week-old infants responded to the equivalence of different levels of auditory loudness and visual brightness inputs on the basis of intensity. Therefore, sound presented concurrently with visual stimulation modified visual behavior. It has been shown that in the first few months of life, infants benefit from temporally and/or spatially associated multisensory information [16,27,28]. While temporal synchrony refers to the capacity to specify whether a particular sound and image go together or not, spatial synchrony concerns whether signals in diverse modalities comes from a common or different location. The importance of synchrony for infant perception has been well documented [29–31] and is also reflected in the intermodal preference procedure, in which the bimodal information is typically presented synchronously. It has been reported that on the basis of synchrony, newborn infants are able to associate objects and linguistic stimuli [32] and that just a few hours old infants can learn sight-sound pairings [31]. Bahrick (2001) [28] found that early as four weeks after birth, infants are sensitive and able to learn arbitrary relations between audiovisual inputs, Moreover, it has been demonstrated that infants between three and six months old have the ability to detect the difference and discriminate temporal information of audio-visual inputs [33,34]. In addition, four-month-old infants can connect and bind visual objects to the specific sounds produced by these objects [35,36]. For instance, they are able to look longer at a puppet whose bouncing rate is the same as the rate at which the sound occurred [35]. These signs of integration, detected early on in life, remind us that the temporal synchrony is an important characteristic for MSI.

Behavioral benefits of early integration are imperative in the development of face and emotion recognition and are important features in a child's abilities to adapt to his environment later in life. Studies using a visual preference paradigm in a multimodal context for human faces have reported interesting results in infants [36–39]. For instance, two-month-old babies can link phonetic information between voices and lip movements [39] and show an enhanced response when lip movements are synchronized with sounds in contrast to unsynchronized ones [40]. In addition, four-month-old infants can perceive affect (joy, sadness or anger) in words that are supported by audio-visual presentations [41], and discriminate these affects in a multimodal context (*i.e.*, establishing relations between faces (visual modality) and voices (auditory modality) [41,42]. Overall, this data might support a form of multisensory association present early on in life, favoring the innate hypothesis for MSI development. However, all studies include post-natal investigations, which limits the opportunity to draw firm conclusions. Studies on children born prematurely could be used to make more compelling arguments in favor of this hypothesis and could be an interesting avenue of research. Also, evidence of multisensory processes in newborns and infants has been demonstrated largely by behavioral data and needs further investigation. Few researches have been carried to study the presence of multisensory mechanisms using neuroimaging techniques. Ethical and practical limitations such as recruitment may have diminished the possibility to undertake such studies on newborns. Nevertheless, the few studies found in the literature will be discussed in Section 2.2.

2.1.2. The Late Integration Approach

In opposition to the Early Integration Approach, the Late Integration Approach emphasizes the acquired nature of MSI. According to this hypothesis, all sensory systems work independently of each other at birth. At this time, these systems are not mature and become increasingly refined during the child's development. This is a long-term process during which cognitive changes and neuronal reorganization keep going on until adolescence in which the brain must continuously adapt its neuronal networks between sensory and motor communications [43]. In support of this, Putzar and colleagues (2007) [44] have recently shown that temporary visual deprivation in the first two years of life affects the level of audio-visual integration that can be achieved once normal vision is restored. These difficulties also persisted into adulthood [44]. This suggests that a critical period in infant's development might underlie the emergence and maturation of MSI, therefore reaching maturity ontogenetically late. During the first months of life, contact with multisensory information seems to be a prerequisite to develop and refine integration of these various sources of information. Thus, if relevant experience is not gained in infancy, individuals cannot compensate for this loss later in life [45].

Furthermore, the various senses do not develop at the same rate. For instance, in humans, all the sensory systems are functional at varying degrees by the end of gestation as these systems progress towards full structural and functional maturity. Sensory structures underlying touch seem to be the first to emerge during ontogenesis [46], followed by the onset of functional hearing (third trimester) and the development of the visual system (largely after birth) [47,48]. While these findings indicate that there is a difference in the rate at which the various sensory systems develop between one another, there is also a difference in the way diverse characteristics develop within each of these systems. For instance, visual acuity and contrast sensitivity keep improving until the child is five- or six-years-old [49], while the period between two and five years of age is the time of development of perceptual language [50], which corresponds to the processing of speech signal, both acoustically and visually. A study by

Morrongiello *et al.* (1994) [51] found an age effect in their study on object exploration and object recognition in children between 3 and 8 years of age with common objects of different sizes. Their results showed a distinct developmental pattern: Older children were faster, recognized more objects and were more thorough in their exploratory strategies than the younger children [51]. Moreover, object handling skills improve until the child is 8- to 14-year-old [52]. Thus, the child will have to learn to integrate multisensory information during his development [13].

Recent studies conducted on very young infants have also suggested that post-natal experience might contribute to MSI development [53]. Neil and colleagues (2006) [54] have studied the development of eye and head movements in 1- to 10-month-old infants while they were subjected to auditory, visual and audio-visual stimuli. Results showed that only 8- to 10-month-old infants responded significantly faster in bimodal conditions than in unimodal conditions, suggesting that audio-visual integration emerges at a late stage in the first year of life. Other studies have supported the assumption that the integration of different modalities does not become optimal until relatively late in childhood. In contrast to adults, when confronted to different sources of information from various sensory modalities, children do not optimally integrate the information from the two sensory modalities but make their perceptual judgments based only on one or the other sense. This unisensory dominance has been found in visuo-tactile integration task [55], visual and tactile cues for size and orientation discrimination [27], nonvisual self-motion and visual landmark information [56], in judgments of surface slant based on stereoscopic and texture information [57] and in audio and visual space and time perception [58]. According to Burr and Gorri (2011) [59], this unisensory dominance in which the most robust modality is employed to tune the others could reflect a process of cross-sensory calibration. As stated in the previous studies, MSI has not reached maturity in children younger than eight years old [27,55–58].

A number of authors have also put forward the presence of a MSI temporal window over which the strength of multisensory interactions is dependent on the spatial and temporal synchrony between different sensory inputs [60–62]. The more remote in space and time two sensory stimuli are, the less likely they are to fuse. A behavioral study by Hillock and colleagues (2011) [63], reported that the audio-visual integration temporal window is still immature in 10- and 11-year-old children, which supports the hypothesis that the underlying plasticity and maturation of MSI continues through development.

Unlike adults, behavioral studies have reported immature multisensory processing capacities in children and adolescents in audio-visual discrimination tasks [63–65] and in other sensory modalities [56]. For instance, Barutchu and colleagues [64,65] reported that multisensory facilitation is still immature in 10-year-old children during a simple audio-visual detection task. In accordance with the Late Integration Theory, results from these studies suggest that information acquired through various sensory modalities might not be integrated optimally in very young infants and that optimal MSI only occurs in children older than eight years [27,56] with changes occurring over a prolonged time course that may extend into adolescence.

Animal studies have corroborated the notion that the brain is immature and must learn to combine the various types of sensory information. One of the most studied neural structure in MSI is the cat superior colliculus (SC), a midbrain structure in which neurons located in the deep layers are responsible to converge multisensory inputs [66]. These multisensory neurons are responsible, among other things, to detect and orient one's behavior to external events and sensory stimuli [67–70]. Visual, auditory and somatosensory inputs stimulate the SC and each sensory modality is represented in a map-like representation in which all the different maps overlap each other and are in close topographic register. Therefore, the alignment among the sensory maps is fundamental for multisensory neurons to integrate the inputs from various senses manifesting itself into an adequately behavioral response [71]. Nevertheless, according to Wallace and colleagues (1997,2006) [72,73] multisensory neurons found in the SC are not present at the cortical and sub-cortical levels immediately after birth and it is only after several months of life and exposure to a multisensory environment that the integration-specialized neurons progressively appear and mature in the cat. Although the appearance of the first multisensory neurons in kittens is at about ten days of age, their ability to integrate inputs from multiple sensory modalities that can be considered adult-like is not seen until three post-natal months [72]. As in the cat multisensory SC neurons, the newborn rhesus monkey also fails to integrate coincident cross-modal inputs [74,75]. Thus, this capacity might indeed be strongly dependent on experiences [73,76].

Early post-natal experience is critical and deprivation of sensory information during this time can lead to an inability to integrate signals neurologically [45,77]. Studies conducted on the effects of sensory deprivation have demonstrated the significance of sensory organ stimulation to the proper functioning and development of sensorineural structures. It is possible that MSI capacities increase in precision over the course of human development and that they are progressively enriched through both the maturation of brain systems and the accumulation of experience. Since newborns from all species are first introduced with a complex and multisensorial environment, they ought to possess some neural mechanisms allowing them to adapt to that environment promptly. Although these coping mechanisms remain fragile and rudimentary, it is these mechanisms that allow their survival. This review exposes a discrepancy in the data revealing that newborn animals cannot perform MSI at birth while there is evidence that newborn humans can. This divergence may be accountable in the fact that animal adaptation is specific to natural environments, and "does not occur when the animal is viewing artificial stimuli such as gratings" [78]. Nevertheless, the question whether MSI is innate or a product of our environment remains debatable and requires further investigation.

2.2. Neuroanatomical Correlated of MSI and Pediatric Brain Activity

The recent explosion of EEG's and neuroimaging techniques has allowed the identification of numerous multisensory convergence zones in the brain. Numerous cortical and subcortical brain regions have been identified to receive afferent inputs from multiple senses. Subcortically, the SC and the basal ganglia as well as association and other cortical regions including the superior temporal sulcus, the parietal, premotor and prefrontal cortex [79–82] are also implicated in MSI, including feedback as well as feedforward anatomical projections [83,84]. Moreover, recent evidence at the earliest stages of perceptual processing reveals multisensory modulations, activations and connectivity in sensory sensory-specific brain areas [85,86].

To date, knowledge of the development of the neurophysiological processes that underlie MSI comes largely from animal and adult studies. To our knowledge, one recent study using electrophysiology (ERP) [87] has investigated the development of MSI capacities in infants. In this study, Reynolds and colleagues (2014) [87] have shown evidence of enhance neural responsiveness to synchronous audiovisual stimulation compared to asynchronous stimulation in five-month-old infants. Besides, only a few studies have dealt with the underlying cerebral mechanisms of MSI in older children and teenagers. It is in particular the case of Brandwein, Foxe, Russo, Altschuler, Gomes and Molholm (2011) [88] who used ERP to characterize the developmental trajectory of brain processes underlying audiovisual MSI in forty-nine neurotypical children and adolescents aged between 7- and 16-years-old. The data suggest that mature levels of multisensory facilitation are only reached by approximately 15 years of age. Another ERP study in typically developing children aged between 6- and 13-years-old suggests that like adults, they integrate multisensory audio-somatosensory input during multiple stages of sensory information processing [89]. However, a study in magnetoencephalography revealed a robust audio-somatosensory integration response in 11- and 13-month-old infants, which suggest the development of MSI during the first year of life [90].

As outlined above, these studies provide encouraging evidence for cortical MSI in typical children. However, considering the important discrepancy in neurophysiological data, further exploration of MSI in neurotypical children is required. The use of neuroimaging approach is of great interest for the scientific community and could fill the current gap of knowledge on developmental MSI.

3. MSI and Cognitive Development

As previously stated, multisensory stimuli provide an enhanced representation of the environment [91] and MSI processes facilitate the speed and accuracy of a variety of behaviors and perceptual processes. The benefits of multisensory information derive from empirical support with infants in various domains showing that multisensory stimulation can enhance early perceptual, affective, and cognitive discrimination. For instance, the combined use of information from several senses has been found to enhance time discrimination abilities in infants [16,33] as well as affect discrimination [41] and even numerical cognition in infants [92,93] and preschool children [94]. Multisensory stimulation promotes heightened attention, perceptual processing and memory in adults as well as in infants [16,95]. Some authors have put forward that the capacity to perceive a complete and coherent representation of multimodal information provides the groundwork for the development of perception, cognition and behavioral abilities, which, in turn, are critical elements to the development of higher-level perceptual and cognitive functions [96,97]. The acquisition of MSI capacity would influence perceptual learning [16] and the acquisition of global cognitive and intellectual abilities [98,99]. Therefore, these MSI capacities in infancy may provide an important developmental foundation for the emergence of cognitive abilities in adulthood.

The premise that MSI can contribute to cognitive development has been supported by studies showing lower intellectual functioning in children with MSI deficits [99–101]. Some studies showed that information transfer across different modalities predict verbal performance in school age children, suggesting that primary MSI skills can impact the acquisition of verbal aptitudes [99,100]. For instance, recent findings showed that children who did not demonstrate good MSI skills had weaker verbal processing scores than what was expected when considering their age and global intellectual quotient [101]. Moreover, sensory integration deficits might result in various difficulties such as learning new skills, getting organized, regulating attention and engaging in positive social experiences in some children [102]. These kinds of difficulties in integrating multisensory information might be associated with particular neurodevelopmental disorders in children.

4. MSI in Neurodevelopmental Disorders

According to the World Health Organization, neurodevelopmental disorders affect one in six children in industrialized countries [103]. Impacting cerebral growth and development, neurodevelopmental disorders encompass a wide range of disorders, such as intellectual disability, Tourette syndrome, autism spectrum disorder, learning disabilities and attention deficit disorder with or without hyperactivity (ADD/ADHD). Children with neurodevelopmental disorders also represent a significant proportion of students who are struggling or failing in school [104,105]. A better understanding of these disorders thus appears to be a crucial concern, particularly when embracing a therapeutic and preventive perspective. Therefore, the following sections will examine the relationship between MSI deficits and two neurodevelopmental disorders commonly found in children: Developmental dyslexia [106] and attention deficit disorder with or without hyperactivity (ADD/ADHD).

4.1. MSI and Dyslexia

Developmental dyslexia is a specific reading and spelling deficit affecting 4% to 10% of the population [107]. According to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [106], this neurodevelopmental disorder manifests itself during the years of formal schooling and is characterized by persistent and impairing difficulties with learning foundational academic skills in reading, such as reading fluently with an accurate comprehension, despite average or above-average intelligence [106,108].

Deficits in the phonological domain have consistently been found to be the primary cause of developmental dyslexia [109–112], although other cognitive deficits, such as in working memory [113,114], executive functions [115–118], processing speed [119–121] and attention [122] have been linked to this disorder. Although a number of conceptual frameworks have been put forward to explain the spectrum of neurological deficits seen in dyslexia, we will review the phonological-deficit hypothesis and the temporal processing hypothesis, two models of particular interest for developmental MSI.

4.1.1. MSI and the Phonological-Deficit and Temporal Processing Hypothesis

The phonological-deficit hypothesis supposes that reading and spelling difficulties result from impaired phonological processes specific to language [107,123,124]. MSI is undoubtedly an important competence in the acquisition of reading skills, since they rely upon rapid and accurate associations between the visual (written) and auditory (verbal) labels [125–127]. Regardless of phonological awareness difficulties, authors have suggested that children with dyslexia have difficulties associating verbal labels to the appropriate visual stimuli and thus, establishing appropriate associations between a word and its spelling [127,128]. A number of studies have put forward that unstable letter-speech sound associations could be a critical factor in dyslexia [129,130]. It has been found that children with developmental dyslexia showed significant deficits in processing letter and digit strings (verbal material) [131]. These results receive strong support from a neuroimaging study by Blau and colleagues (2010) [132] showing fundamental deficits in letter-sound integration in children with dyslexia. Similarly, recent findings on the influence of processing speed on reading acquisition in six-year-old children revealed that, whatever the modality (audio-verbal, visuo-verbal, visual, and visuo-visual), children with reading difficulties displayed poor performances in rapid intermodal processing speed in audio-verbal (phonological awareness) and visuo-verbal (rapid naming) tasks [133]. These results support the influence of MSI in rapid naming and phonological processes involved in reading, suggesting that the neural mechanisms underlying audio-visual integration in children with dyslexia differ from normal reading children.

Other studies postulated that not only unimodal [125,134,135] but also multisensory verbal and nonverbal information processing is temporally impaired in children with dyslexia. Some evidence suggests that the core deficit of dyslexia is based on atypical temporal processing of audio-visual multisensory information [125,135–138]. An interesting paradigm to investigate intermodal temporal processing is the McGurk effect [139]. This effect occurs when an individual sees and hears a speaker producing speech segments that are incongruent with their visual perception. For instance, a classic McGurk effect is hearing the syllable /ta/ while the speaker uttered /ga/. Thus, the auditor usually perceives the sound /pa/. This robust effect in neurotypical individuals was found to be impaired in subjects with dyslexia, suggesting a deficit of MSI. For that matter, instead of perceiving the normal illusion, individuals with dyslexia tend to pronounce the sound perceived visually [140]. Similarly, children with reading difficulties showed low performances in comparing two patterns of brief nonverbal audio-visual stimuli [141]. Moreover, decreased segregation acuity and prolonged cross-modal segregation times were also evident using trains of brief stimuli in three different sensory modalities (audio-visual, audio-tactile and visuo-tactile) in 8- to 12-year-old children with dyslexia, especially in the audio-visual condition [142]. These findings suggest the implication of a general impairment of the nervous system in children with dyslexia when processing audio-visual information rather than a sole deficit in the sensory, motor or phonological systems.

4.1.2. Other Sensory Deficits in Dyslexia

An array of subtle sensory defects unrelated to audio-visual stimuli has also been reported in individuals with dyslexia. For instance, previous studies involving a dual task reported that postural control was highly impaired in children with dyslexia when compared to age- and gender-matched controls [143,144]. Recent findings have also shown that children with dyslexia had difficulty maintaining balance while fixing a point in front of them [145] and that coupling between visual information to body sway was weaker and more variable compare to normal reading children [146]. Poor postural control in children with dyslexia might reflect an inability to integrate multiple sensorimotor inputs, such as proprioceptive signals, that are necessary for proper motor activity. Even though sensory motor deficits were put forth to explain dyslexia, there is a current gap in the literature concerning this hypothesis. Future research on this matter should be considered and would be an interesting avenue to pursue.

Based upon these results, the impairments suggested to underlie the causes of dyslexia could be directly related to atypical audio-visual temporal processing, rapid and accurate associations of visual and auditory stimuli and sensory-motor integration. These findings provide additional information about the neurophysiological causes and evidence of the MSI hypothesis to explain developmental dyslexia.

4.1.3. Anatomical and Structural Differences in Dyslexia and MSI

Recent neuroimaging studies have investigated neuronal activity in multisensory cortical regions of normal readers and individuals with specific learning disabilities in reading. Given its role in language processing, the most consistent finding is altered morphology in the left temporal lobe. For instance, Welcome and colleagues (2011) [147] recently reported reduced asymmetry in gray matter thickness within the temporo-parietal region and smaller brain sizes in the right inferior frontal region in children with reading difficulties. Using fMRI during a phonological task, Temple (2001) [148], reported reduced left temporo-parietal activity in 8- to 12-year-old children with dyslexia compared to normal reading children. Likewise, two magnetoencephalography (MEG) studies from Simos *et al.* (2000) [149,150] supported these results and found decreased left temporo-parietal activity in children with dyslexia while they were reading words and pseudowords. The temporo-parietal region is known to be involved in the integration of letters and speech sounds [151,152], a crucial ability for reading in beginning readers. In addition to atypical activity within the temporal lobe, pediatric functional magnetic resonance imaging (fMRI) studies have also reported deviant patterns of activation [153–155] and morphological brain alterations [156] in frontal brain regions of children with dyslexia. One possible explanation for these cerebral differences might be the reduced specialization for processing letters and letter-sound associations.

Altered connectivity patterns in primary sensory and multisensory processing regions were also found in individuals with dyslexia [157,158]. More precisely, the heteromodal superior temporal cortical regions as well as the auditory cortex (Heschl sulcus and planum temporale) have been identified as integration sites for letters and speech sounds in normal readers [151,159]. However, it has been found that children with dyslexia that failed to recognize speech sounds presented together with visual letters (congruent or incongruent) also showed reduced neural integration in the left planum temporale and Heschl sulcus and the left superior temporal sulcus [132]. Overall, these studies suggest that an interrelated network of visual, auditory and heteromodal brain areas might contribute to the skilled use of letter-speech sound integration necessary for learning to read. Reduced congruency between letters and speech sounds in children with dyslexia are likely to indicate less successful letter-speech sound integration [132]. The presence of deviant patterns of activation and morphological brain alterations associated with MSI may play a critical role in the neural basis of dyslexia. Despite the gap of knowledge on this matter, these results highlight the importance of pursuing such neuroimaging studies in order to better understand the impact of MSI deficits on children with reading disabilities.

Atypical development of MSI capacities during infancy can have a momentous impact on children’s neurodevelopment. The previous findings suggest that children with dyslexia have difficulties in MSI and may suffer from integrating sensory cues coming from multiple sources. The hypothesis that MSI deficits might be responsible for impaired reading is still premature. The impact of such difficulties remains unclear and requires greater attention from researchers. However, the development of this integrative ability may offer a cue that may be useful in identifying children likely to develop later difficulties. Therefore, we can speculate that children with dyslexia would take advantage of intervention protocols directed to improve sensory integration.

4.2. MSI and Attention Deficit Disorder with or without Hyperactivity (ADD/ADHD)

ADHD occurs in most cultures in about 3% to 5% of children [107,160] and accounts for approximately half of all pediatric referrals to mental health services in the United States [161,162]. ADD/ADHD is a neurodevelopmental disorder characterized by impairing levels of inattention, disorganization, and/or hyperactivity-impulsivity that interferes with functioning or development. Inattention and disorganization entail inability to stay on task, to give close attention to details, to listen when spoken to, to follow through on instructions, to be easily distracted by extraneous stimuli and to have difficulty organizing tasks and activities, at levels that are inconsistent with age or developmental level [107]. Hyperactivity refers to excessive motor activity when it is not appropriate or excessive fidgeting or tapping hands or feet when seated, difficulty to remain seated in situations where it is expected, overactivity, talking excessively, at levels that are inconsistent with age or developmental level [107]. Impulsivity implies a desire for immediate rewards or an inability to delay gratification which can manifest into behaviors such as a difficulty to wait for her/his turn, interrupting or intruding into other people's activities and making important decisions without consideration of long-term consequences, at levels that are inconsistent with age or developmental level [107]. According to the DSM-V, ADHD symptoms must be present in at least two settings, impact directly on social and academic activities and must be present before the age of 12-years-old [107]. While the predominantly inattentive type (ADHD-I) is the most common subtype in the population (38%–57% of all individuals with ADHD), individuals with the combined inattention-hyperactivity type (ADHD-C) (22%–26%) are more likely to be referred for clinical services [163].

Additionally to attention problems, ADHD is often accompanied by deficits other than those subsumed under the ADHD diagnosis. In terms of cognitive profile, children with ADHD often have difficulty with executive functions (e.g., planning, set shifting, organization, inhibition and regulation of behavior) as well as processing speed and working memory [164–176]. A high percentage of children with attention disorders also have sensory processing problems, exemplified by behavioral evidence of difficulty modulating sensory responses [177–179]. It has been reported that boys with ADHD aged between 6- and 10-years-old have more sensory processing difficulties than neurotypical boys [180]. It has also been suggested that these children may not be perceiving and processing sensory information properly as well as having difficulty producing appropriate responses at school, at home and in the community [181]. Compared with children without neurodevelopmental disorders, children with ADHD exhibit greater difficulties in the sensorimotor domain such as the vestibular and balance control systems [182,183]. For instance, in contrast to neurotypical children, Hassan and Azzam (2012) [184] showed that children with ADHD-C aged between 8- and 10-years-old had lower somatosensory, visual and vestibular ratios by 1%, 9%, and 18%, respectively. According to Guskiewicz and Perrin (1996) [185], this could be the result of a lack of adequate interaction among the three sensory inputs that provide orientation information to the postural control system. Furthermore, children with ADHD also have more difficulties to process tactile [186], visual [187] and auditory stimuli [188–191]. More precisely, while Hern and Hynd (1992) [186] found that 6- and 12-year-old children with ADHD-C exhibit more soft signs than the normal group on a prototype sensorimotor soft sign battery. Ghanizadeh (2010) [187] demonstrated that children with ADHD give poorer performances on visual acuity and visual field. In the audition realm, a number of studies reported auditory processing problems in children with ADHD [188–191].

4.3. Neuroanatomical Model for ADHD

Studies investigating the neural basis of ADHD have steadily showed structural and/or functional anomalies in cortical areas, basal ganglia, and cerebellar brain regions in children with ADHD [192–194]. This circuit has been extensively investigated using methods such as structural volumetric brain imaging and fMRI and has been linked to ADHD behavioral deficits such as inhibitory response, working memory and executive functioning impairments [194–203]. For instance, using volumetric brain imaging to examine anatomic brain abnormalities, an extensive study compared regional brain volumes in 152 children and adolescents with ADHD aged 5 to 18 years old and 139 age- and sex-matched controls [204]. Children with ADHD exhibited smaller total cerebral and cerebellar volumes in contrast to control children and these volumetric differences persisted into adulthood. Furthermore, frontal and temporal gray matter, caudate nucleus and cerebellar volumes correlated with the severity of ADHD symptoms [204]. Other studies investigating volumetric differences between children with

ADHD and typically developing children also reported smaller cerebral volume in frontal and prefrontal cortices [205–207]. Such cortical volume reductions were also associated with altered brain activation in sensory cortices (auditory, visual and somatosensory cortices) [184,208], which could explain sensorimotor deficits in this population. The frontal lobes both receive a multitude of inputs from sensory association areas and have influence over a wide region of the nervous system to direct behavior. Moreover, working memory, planning, and reasoning, often affected in ADHD, are associated to the frontal lobes and depend on the recognition and integration of a vast network of signals.

Research evidence in favor of the existence of bidirectional influences between attention and MSI is thus considerable and allows the possibility to make neuroanatomical connections between ADHD and MSI networks. Attentional processes and MSI share subcortical networks such as the SC [209] and operate with cortical regions, including the fronto-parietal and temporo-parietal networks [210]. Moreover, top-down attention is controlled by a fronto-parietal network of brain areas, which sends signals that modulate the sensitivity of neurons in sensory brain regions [211]. Recently, Koziol *et al.* (2011,2012) [192,212] integrated SPD/SMD symptoms in relation to their impacts upon the development of inhibitory control, working memory, academic skill, and behavioral automation in children with ADHD, proposing the first neuroanatomical conceptualization model of sensory processing deficits in ADHD. They suggested that an integrative network of specific brain regions is involved in both cognitive development and sensorimotor integration of the environment [212,213]. According to their model, the cortex encodes specific sensory information (visual, auditory, spatial, perceptual and sensory) by interacting with the basal ganglia that act as a selection mechanism and is important to voluntary motor movement, perceptual learning and inhibitory response. Then, the cerebellum receives sensory information inputs from the involved cortical regions and basal ganglia in order to integrate stimuli and modulate or regulate the intensity of experienced stimulation [212,213]. As previously mentioned, similarly to the neurons in the SC and related structures, previous studies have demonstrated the presence of multisensory neurons in the basal ganglia [85]. Neurons sensitive to visual, auditory or somatosensory modalities have been found in both the substantia nigra (SN) and the caudate nucleus (CN) in which a high proportions of neurons with multisensory properties have been described in these neuronal populations [214,215]. MSI deficits in the CN and the SN may lead to a disruption in the processing of complex sensory stimuli which, indirectly will affect the sensory feedback of motor actions controlled by the basal ganglia. Studies have documented anatomical abnormalities, such as volume decrease, asymmetric and connectivity differences, in the basal ganglia [203,208] and cerebellum of children with ADHD [203,216–219].

Overall, the neural basis of ADHD has been widely documented by functional and structural studies. Anatomical evidence has provided a reasonable framework for the suggestion that ineffective MSI cortical maps underlying sensory-related behaviors as well as physiological reactivity to sensory stimuli found in children with both ADHD and sensory processing problems may possibly explain their comorbidity.

5. Conclusions

One of the most impressive features of the central nervous system is its ability to process information from a variety of stimuli to produce an integrated, comprehensive representation of the external world. Research in neurotypical adults has repeatedly shown behavioral benefits of MSI that might be linked to the underlying ability of the brain to integrate different sensory inputs related to a single event [11]. The benefits of the combined use of information from several senses have been exposed in numerous studies and reveal notably that MSI aids detection and speed response [2–9]. Although MSI capacity has been extensively studied in adults, the literature is scarcer regarding the ability to integrate multisensory information in infants. This review firstly aimed to describe MSI developmental processes of neurotypical infants and children and its neuroanatomic correlates. Moreover, we addressed the question whether the capacity to integrate multisensory information exist from birth or develops as a result of experience. The debate between MSI being innate or acquired remains. Neurophysiological data on animals [59,60,63] and ERP studies on children and adolescents [65,66] suggest that our optimal capacity to integrate multisensory information reaches its maturity late during childhood and is strongly dependent on early experience.

The second section of this article reviewed the presence of sensory integration impairments in children affected with a neurodevelopmental disorder. We first studied dyslexia and paid a particular attention to the phonological-deficit and the temporal processing hypothesis, two models of special interest for developmental MSI. Overall, the literature suggests that an interrelated network of visual, auditory and heteromodal brain areas contributing to the skilled use of letter–speech sound integration might be impaired in children with dyslexia. Studies on ADHD also reported potential alterations of MSI. Children with ADHD often show sensory deficits including sensorimotor [166,167], somatosensory [168], visual [171] and auditory [172–175] processing impairments. Moreover, anatomical evidence suggested that ineffective MSI cortical maps underlying sensory-related behaviors as well as physiological reactivity to sensory stimuli found in both children with ADHD and sensory processing problems may possibly explain their comorbidity. Although certain neurodevelopmental disorders can cause MSI impairments, research and clinical applications in development are in progress and constitute promising research avenues.

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Author Contributions

All authors have been involved in the preparation and have approved the submitted manuscript. Emmanuelle Dionne-Dostie was lead author and responsible for conducting the literature review and writing the manuscript. Natacha Paquette participated in the redaction of the "MSI and neurodevelopmental disorders" section. Maryse Lassonde reviewed and edited the manuscript. As the senior author, Anne Gallagher supervised Mrs. Dionne-Dostie and Paquette's work, reviewed and edited the manuscript.

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3.2 Article 2

Development of the electrophysiological correlates of audiovisual integration from infancy to adulthood

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Title: Development of the electrophysiological correlates of audiovisual integration from infancy to adulthood

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Abstract

Behavioral studies suggest that some multisensory processes emerge in early childhood. However, little is known about the developmental course of the neurophysiological correlates of multisensory integration (MSI) and the age when this process reaches maturity. This cross-sectional study aims to characterize the developmental progress of audiovisual (AV) integration from the age of 3 months to adulthood in a large cohort of 121 individuals. Using time-frequency decomposition of high-density electrophysiological (EEG) activity, AV integration was investigated in the evoked theta, alpha, beta and gamma bands during a passive task. Our results revealed precursors of AV integration in children as young as 2 years old in the theta band, with theta activation increasing gradually with age until 11 to 14 years old. At that age, adolescents have strong responses to AV stimulations in both theta and alpha bands. AV integration mechanisms, however, seem to reach full maturity between 15 and 17 years of age when theta responses are no longer present and the alpha activation reach an intensity level similar to that observed in adults. This systematic relationship between age and neuronal processes underlying AV integration suggests that MSI is a long process that emerges during childhood and matures until late adolescence.

Keywords: multisensory integration; neurodevelopment; audiovisual evoked potentials; electrophysiology; wavelet analysis.

1. Introduction

The natural environment provides a plethora of concurrent stimulation to all our senses. Subsets of the incoming stimulation across different modalities arise from common external objects or events, as when we both see and smell a flower or both see and hear a vocalist singing or a train moving. Although the senses can function independently of each other, our perceptual experience relies on crossmodal connections and Multisensory Integration (MSI) of information across senses (Stein & Stanford, 2008). Research in adults has shown behavioral benefits of MSI as it enables to adaptively guide behavior by identifying and applying optimal responses to objects or events, consequently having enormous survival value. In the present article, we will concentrate on audiovisual (AV) integration. In the behavioral domain, multisensory circumstances confer strong advantages including enhanced orientation and discrimination (Corneil & Munoz, 1996; Stein, Huneycutt, & Meredith, 1988; Stein, Meredith, Huneycutt, & McDade, 1989; von Saldern & Noppeney, 2013), improved target detection (Frassinetti, Bolognini, & Làdavas, 2002; Gillmeister & Eimer, 2007; Girard, Collignon, & Lepore, 2011; Girard, Pelland, Lepore, & Collignon, 2013; Lovelace, Stein, & Wallace, 2003; Molholm, Ritter, Javitt, & Foxe, 2004) and reaction time (Amlôt, Walker, Driver, & Spence, 2003; Calvert & Thesen, 2004; Corneil, Van Wanrooij, Munoz, & Van Opstal, 2002; Diederich, Colonius, Bockhorst, & Tabeling, 2003; Forster, Cavina-Pratesi, Aglioti, & Berlucchi, 2002; Molholm et al., 2002). Likewise, on the cerebral level, recent functional magnetic resonance imaging (fMRI) experiments (Alpert, Hein, Tsai, Naumer, & Knight, 2008; Beauchamp, Lee, Argall, & Martin, 2004; Calvert, 2001; Calvert, Hansen, Iversen, & Brammer, 2001; Kayser, Petkov, Augath, & Logothetis, 2007) and electrophysiological (EEG) studies (Fort, Delpuech, Pernier, & Giard, 2002a, 2002b; Giard & Peronnet, 1999; Molholm et al., 2004; Molholm et al., 2002; Sakowitz, Schürmann, & Başar, 2000; Santangelo, Van der Lubbe, Belardinelli, & Postma, 2008; Talsma & Woldorff, 2005; Teder-Sälejärvi, McDonald, Di Russo, & Hillyard, 2002; Yordanova et al., 2002) have shown significantly greater responses following AV stimulation than unisensory ones.

To date, knowledge of the development of neuronal basis of MSI comes largely from animal and human adult studies. Neurophysiological animal studies have revealed that, during early postnatal life, subcortical and cortical multisensory neurons remain immature and lack the ability to synthesize multisensory information, requiring considerable sensory experience to reach maturation (Wallace, Carriere, Perrault, Vaughan, & Stein, 2006; Wallace & Stein, 1997; Xu, Yu, Rowland, Stanford, & Stein, 2014). Single-unit recording experiments in animals deprived of sensory experience (Carriere et al., 2007; Royal, Krueger, Fister, & Wallace, 2010; Wallace, Perrault, Hairston, & Stein, 2004; Wallace & Stein, 2007) have also shown a reduction in the ability of neurons to integrate multisensory inputs. Moreover, humans deprived of visual experience during the first months following birth as a result of congenital cataracts do not exhibit MSI at the behavioural level in adulthood (Putzar, Goerendt, Lange, Rösler, & Röder, 2007). FMRI evidence has also revealed that these individuals show a reorganisation of crossmodal auditory and visual functions (Collignon et al., 2015; Guerreiro, Putzar, & Röder, 2015; Putzar et al., 2007), as well as alteration and reduction of neuronal and behavioral responses to AV signals (Collignon et al., 2015; de Heering et al., 2016; Guerreiro et al., 2015; Putzar et al., 2007). Altogether, these studies suggest that the neurophysiological underpinning of MSI is not innate but develops with experience, and that this early experience plays a crucial role for the emergence of typical MSI mechanisms (Stein, Stanford, & Rowland, 2009).

Like adults, neonates are sensitive to redundant information of objects and events (Bahrick & Lickliter, 2002; Bahrick, Lickliter, & Flom, 2004; Bahrick & Pickens, 1994; Lewkowicz, 2000; Lickliter & Bahrick, 2004) and learn to perceive increasingly more subtle differences and more complex experiences through interaction with their environment (Gibson, 1969; Gibson, 1966). For instance, behavioral findings revealed that a few-hours- and months-old infants are skilled perceivers to detect the rhythm, tempo, intensity and discriminate synchrony from asynchrony between objects and sounds produced by a single event, for instance when we hear and see the audible beat produced by a visible swinging pendulum of a metronome (for review see Dionne-Dostie and others 2015; Lewkowicz and Lickliter, 2013). These experiments suggest that within the first 6 months of postnatal development, human infants can perceive multisensory associations and detect temporal equivalencies or differences across information from different senses. Although these abilities appear to be present in early infancy, developmental studies have also highlighted that some multisensory processes are generally found to develop gradually throughout childhood and continue changing during adolescence (Barutchu, Crewther, & Crewther, 2009; Barutchu et al., 2010; Brandwein et al., 2011; Hillock-Dunn & Wallace, 2012; Hillock, Powers, & Wallace, 2011; Lewkowicz, 1996; Nardini, Bales, & Mareschal, 2016). For instance, while adults perceive visual and auditory events as synchronous when their onsets fall within a certain time window, often called a temporal binding window (for review see Keetels and Vroomen 2012), this window of temporal integration remains wider in pre-schoolers' and continues to narrow during school years (Hillock-Dunn & Wallace, 2012; Hillock et al., 2011; Lewkowicz, 1996). Developmental behavioral findings have also reported that multisensory facilitation of behavioral performance occurs after 8 years of age during simple AV detection tasks (Barutchu et al., 2009; Barutchu et al., 2010; Brandwein et al., 2011) and seems to be fully mature around 14 years-old (Brandwein et al., 2011). While a bulk of behavioral studies has demonstrated infants' capacity for crossmodal perception and their sensitivity to redundant information, others support that MSI occurs late in a child's development, fueling the nurture-nature debate of the development of MSI.

Only a few authors have begun to delve on the neuronal activations underlying AV integration in early life, leading to a paucity of data on the development and maturation of integration of AV stimuli in humans. While event-related potential (ERP) evidence has demonstrated the early ability of humans to use redundant AV information in 3- to 6-month-old infants (Hyde, Jones, Porter, & Flom, 2010; Kopp, 2014), to our knowledge, only one study attempted to characterize neurodevelopmental changes through ages in AV integration (Brandwein et al., 2011). In this interesting study, Brandwein and colleagues (2011) used ERPs to investigate AV integration in participants aged between 7 years of age and early adulthood. They found larger brain response amplitude in 13- to 16-year-olds and adults in the AV condition compared to the sum of the unisensory conditions in frontocentral scalp regions. In contrast, the amplitude of the sum of the unisensory responses was much larger than that of the AV multisensory response in 7-to 9-year-old children.

To date, no neuroimaging or electrophysiological studies have yet looked at the developmental course of MSI before the age of 7 years old. Moreover, the behavioral literature remains controversial and the development of MSI still needs to be characterized in terms of brain response. Thus, the aim of this experiment is to investigate the developmental pattern of AV integration from the age of 3 months to adulthood and to specify when MSI mechanisms reach full maturity. Time-frequency decomposition of high-density EEG activity will allow us to characterize the developmental course of AV and reveal how this ability may be expressed differently in distinctive EEG frequency bands according to the age.

2. Materials and methods

2.1 Participants

A total of 131 neurotypical French-speaking participants aged from 3 months to 17 years old were recruited. Participants were recruited primarily from Sainte-Justine University Hospital Center and the Université de Montréal through electronic and paper advertisements. Data from 10 participants were withdrawn from the original sample because of excessive movement artifacts (2 participants), premature ending of the testing due to fatigability and irritability (4 participants) or because of presence of spike-waves on the EEG (4 participants). A final sample of 108 infants, children and adolescents was divided into seven age groups [3–6 months ($n = 13$), 6–12 months ($n = 16$), 2-4 years ($n = 21$), 5-7 years ($n = 16$), 8-10 years ($n = 14$), 11-14 years ($n = 17$), 15-17 years ($n = 11$)] in order to enable comparisons of AV responses between developmental stages. Age groups were defined based on auditory and visual cortical maturation (Lippé, Martinez-Montes, Arcand, & Lassonde, 2009; Lippé, Roy, Perchet, & Lassonde, 2007) and typical developmental stages (Borgers, De Leeuw, & Hox, 2000; McNeely & Blanchard, 2010; Piaget, 2000). In addition, 13 young adults aged between 18 to 30 years of age were tested in order to have a measure of mature brain response of AV integration, for a total sample size of 121 participants. Table 1 shows the demographic characteristics of the sample. All participants were born at term, had no history of neurological, congenital or chromosomal anomalies, had no psychiatric, neurodevelopmental or learning difficulties, and had normal hearing and normal or corrected-to-normal vision.

Exclusion criteria for all age groups also included a history of intrauterine growth retardation (IUGR) or seizures, the use of psychotropic medication and major infectious diseases during pregnancy (e.g., AIDS, toxoplasmosis, rubella, tuberculosis). Developmental information was gathered from interviews and a developmental questionnaire completed by the parents. Participants' consent was obtained according to the Declaration of Helsinki, and this study was approved by the Ethical, Administrative and Scientific Committees of the Sainte-Justine University Hospital Center and the Université de Montréal. Informed written parental and adult consent was obtained before data acquisition.

Insert Table 1 about here

2.2 Stimuli and paradigm

Participants viewed unisensory-auditory (A), unisensory-visual (V) and audiovisual (AV) stimuli. The visual stimulus had a luminance of 37cd/m^2 and was presented centrally on a computer monitor at a distance of 114 cm from the participant's eyes. Auditory stimulation consisted of a 1000Hz tone delivered binaurally (Optimus XTS 24) through loudspeakers located laterally at a distance of 30cm from the participant's head. The intensity was 65dB SPL (sound-pressure level) and the tone duration was 150ms including 10ms rise and fall time. Visual stimulation consisted of a black and white checkerboard stimulus with each square subtending a visual angle of 20.1° X 15.1°. AV stimulation consisted of a simultaneous presentation of the black and white checkerboard synchronized to the 1000Hz tone. Moreover, to reduce visual consecutive effects (*afterimage effect*), a uniform gray Gaussian mask (combination of red 125/255, green 125/255 and blue 125/255) was presented during unisensory-auditory and right after unisensory-visual and multisensory stimuli presentation. The interstimulus interval varied randomly between 700 and 1000ms. Stimuli were presented in random order and with equal probability in five blocks of 175 trials. Each stimulus had an exposure duration of 150ms and were generated by E-Prime Psychology Software (Psychology Software Tools Inc., Pittsburgh, USA), on a Dell GX 150 PC computer located in an adjacent room.

2.3 Procedure

All conditions were presented in a single data acquisition session. Simultaneously to stimulus presentation, all participants underwent an EEG recording of approximately 11 minutes that was conducted in a dark and soundproof Faraday room. They were instructed to maintain fixation in the center of the stimulus screen while they sat in a comfortable chair or on their parent's lap. During EEG data acquisition, participants' state of alertness was monitored through observation of their behavior and EEG data. An EEG technician (P.V.) located in an adjacent room was responsible for monitoring EEG data. In addition, an experimenter (E.D.-D.) located in the same room as the participant, ensured that fixation was maintained and verbally prompted them to re-engage if necessary. Stimuli were only presented when the participant was looking at the computer screen and stimulus presentation was paused when the participants looked away from the screen. As it is standard in cognitive EEG experiments in infants, ERPs were only recorded when infants and children were still and their gaze was focused on the center of the screen (Lippé, Kovacevic, & McIntosh, 2009; Roy, Barsoum-Homsy, Orquin, & Benoit, 1995; Sayeur et al., 2015). Stimulation was immediately aborted if participants became weary, found difficulty in fixation or when subtle shifts from vigilance to drowsiness were identified by quantifying changes in EEG waveforms (Åkerstedt & Gillberg, 1990). Rest periods were provided to maintain concentration, prevent fatigue and verify electrode impedance and stimulation was restarted afterwards.

2.4 Data acquisition and Analysis

EEG data were recorded using a high density Geodesic Sensor Net equipped with 128 electrodes (Electrical Geodesics Inc., Eugene, OH, USA), with the reference located at the vertex. Electrode impedance was maintained below 50KΩ (Tucker, 1993). EEG signals were acquired at a sampling rate of 250 Hz with an analog bandpass of 0.01-100Hz using the NetStation EEG Software (Electrical Geodesics Inc., Eugene, OH, USA) on a G4 Macintosh computer. Raw EEG data were analyzed using BrainVision Analyzer software version 2.1 (Brain Products, Germany). Preprocessing included offline digital filtering of the 1.0-50Hz bandwidth (24dB/octave). EEG was referenced off-line to an average of left and right mastoid. Noisy channels were replaced by a linear interpolation of adjacent electrodes. Ocular correction was conducted using the regression-based approach (Gratton, Coles, & Donchin, 1983). Raw data were segmented into epochs ranging from -500 pre-stimulus to +1000ms relative to stimulus onset. Afterwards, artifact rejection (threshold of ±100uV) and visual inspection of the data for further artefacts were conducted. For each participant, the artifact-free segments were averaged across trials for each stimulus type (averaged good segments: A = 84.19 ± 34.42, V = 84.32 ± 33.84, and AV = 82.90 ± 34.29 on electrode FCz).

2.5 ERPs and Morlet Wavelet transformation

An established method to assess multisensory interactions in ERPs is to compare AV multisensory responses with the summation of the responses to the respective unisensory-A and unisensory-V constituents (A+V) (Calvert, 2001; Fort et al., 2002b; Foxe et al., 2002; Giard & Peronnet, 1999; Molholm et al., 2002; Talsma & Woldorff, 2005; Teder-Sälejärvi et al., 2002). Typically, the presence of AV integration is characterized by a difference between AV and (A+V) responses. In order to investigate AV integration, the sum of the unisensory-A and unisensory-V stimuli were computed for each participant, and compared to AV responses.

For each participant, a continuous time-frequency analysis over AV and (A+V) averaged ERPs was performed with complex Gaussian Morlet's wavelets (Burrus, Gopinath, & Guo, 1997) in the frequency range from 4 to 50Hz, allowing to investigate theta, alpha, beta and gamma band activity. Since previous EEG studies have observed multisensory effects in theta, alpha, beta and gamma activity (Doesburg, Emberson, Rahi, Cameron, & Ward, 2008; Klimesch, Sauseng, & Hanslmayr, 2007; Sakowitz, Quiroga, Schürmann, & Başar, 2005; Sakowitz et al., 2000; Yordanova et al., 2002), the aforementioned frequency bands were selected to study and characterize the developmental course of AV integration. It is especially interesting to study MSI in the time-frequency domain since this approach might allow a more accurate and stable examination of multisensory interactions in a specific frequency range than traditional ERP peak detection (Van der Lubbe, Szumska, & Fajkowska, 2016). The presence of greater slow wave activity and EEG noise in infant and young child ERPs (Luciana & Nelson, 1998) explains, therefore, the choice of wavelet analyses in the present study.

Wavelet Transform analyses were performed using Brain Vision Analyzer 2.1 (Brain Products, Germany). Two different Morlet parameters were chosen for the low- and high-frequency range in order to improve the temporal resolution of these frequencies. The width of the wavelet was determined according to the Morlet parameter of $2\pi\sigma_t f = 3.8$ (logarithmic frequency steps) for frequencies between 4 and 14Hz and of $2\pi\sigma_t f = 7.0$ for frequencies ranging between 15 to 50Hz, both with 10 frequency steps (Zion-Golumbic, Kutas, & Bentin, 2010). In addition, a baseline correction (-150ms to -50ms prior to stimulus onset) was applied. For each participant, time-frequency mean power values time-locked to the responses in theta (4-7Hz), alpha (8-14Hz), beta (15-29Hz), and gamma (30-50Hz) bands (Klimesch et al., 2007) were calculated for AV and summed (A+V) conditions from 100 to 300ms, corresponding to the ERPs' time window (Figure 1). In fact, grand-mean AV ERP waveforms revealed different morphologies across ages as it is typically observed in the development of auditory and visual ERPs. As previously documented in the literature (Brandwein et al., 2011), N1 and P2 components have been found to reflect AV integration. Our data also revealed different changes in overall peak amplitudes and latencies of the N1 and P2 responses between 100 and 300ms across ages (Figure 1). Consequently, a time window between 100 and 300ms was selected to constrain our Morlet Wavelet transformations. Mean power values of each participant were then exported for further statistical analyses.

Insert Figure 1 about here

2.6 Topographic t-test on the AV versus sum responses (A+V)

Electrodes of interest were selected based on the results of a topographical distribution *t*-test revealing the maximum power of the difference of (AV - [A+V]) (Figure 2; Brain

Products, Germany). *T*-tests ($p < 0.05$, two-sided, unpaired) were computed on the power topography of 128-channel responses at the 150ms time point showing maximum difference power between the responses evoked by AV and (A+V) stimulations. Topographic scalp distribution revealed that the maximal difference activations between AV and (A+V) conditions ($T > 2$; $p < 0.05$) were located predominantly over the frontocentral regions in all age groups at 150ms (Figure 2). Thus, the following frontocentral electrodes of interest were used for the subsequent analyses: Fz, FCz, Cz.

Insert Figure 2 about here

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3. Statistical Analyses

The relationship between age group and wavelet magnitude power was investigated using linear regression analyses using a jackknife procedure (Obiora-Ilouno & Mbegbu 2012; Figure 3). For each subject, wavelet magnitude power peaks were taken from 80% of the maximum activation within the previously selected time window (100-300ms) and all frequencies for AV and (A+V) conditions on all electrodes. In order to investigate statistical differences between the progression of each condition with age, a *t*-test was performed to compare the slopes of both linear regressions.

Further statistical analyses were carried out using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Mixed-design analyses of variance (ANOVAs) with factors of age group (3-6 and 6-12 months, 2-4, 5-7, 8-10, 11-14 and 15-17 years, adults), stimulus condition (AV, [A+V]), and electrode (Fz, FCz, Cz) were performed separately on each frequency band (theta, alpha, beta and gamma). Outlier values were replaced with the next highest value plus one, value that has a z-score of 3.29 (Field, 2009). Greenhouse-Geisser adjustment for violation of sphericity was performed when necessary. To identify significant differences, multiple comparisons were corrected using Bonferroni's procedure (corrected *p* values reported) as post-hoc analyses.

4. Results

4.1 Linear regression analyses

The relationship between age and wavelet power was investigated using linear regression analyses in AV and (A+V) conditions within all frequencies and 128 electrodes between 100 and 300ms. Wavelet power had a positive linear increase with age on both conditions. This increase was stronger for the AV condition, compared to the summed unisensory (A+V) condition, and was predominantly located over the frontocentral regions. As illustrated in Figure 3 the slope of the regression line represents the rate of change in wavelet power in function of age. Table 2 summarizes significant regression equations obtained on Fz, FCz and Cz in both conditions. For example, on electrode FCz, while wavelet power increased significantly by 15.14 μV^2 for each year of age in response to AV stimuli, it increased significantly of 6.42 μV^2 in response to (A+V) stimuli.

Insert Table 2 about here

Insert Figure 3 about here

4.2 ANOVA

4.2.1 Theta

The ANOVA also revealed significant interactions between condition and age group ($F_{7,113} = 2.070$, p = 0.052, $h_p^2 = 0.114$). Post-hoc analyses revealed that theta band power was greater for AV responses compared with the sum response (A+V) in groups 2-4 (p = 0.028), 5-7 (p = 0.002) and 11-14 (p = 0.0001) years old (Figure 4a), suggesting that AV response is already present at these young ages, although different from adults. No activation differences in theta were found in either of the condition in the 3-6 and 6-12-month-old groups, in the 8-10 and 15-17-year-old groups or in the adults. No significant interactions between stimulus condition, electrode and age group were found. The ANOVA revealed significant main effect for condition ($F_{1,\ 113} = 23.042$ p = 0.0001, $h_p^2 = 0.169$) reflecting higher theta activation to the AV condition compared with the summed response (A+V). Results also showed a main effect for electrode ($F_{1.53,\ 172.58} = 11.964$, p = 0.0001, $h_p^2 = 0.096$) revealing significantly higher theta power on electrode FCz compared to Fz (p = 0.0001).

4.2.2 Alpha

The ANOVA revealed significant interactions between condition and age group ($F_{7,\ 113} = 7.778$; p = 0.0001; $h_p^2 = 0.325$), condition and electrode ($F_{1.65,\ 186.59}$) = 5.963; p = 0.005; $h_p^2 = 0.050$), as well as between condition, electrode and age group ($F_{11.56,\ 186.59} = 2.080$; p =

0.022; $h_p^2 = 0.114$). Post-hoc analyses revealed that adults ($p = 0.0001$) as well as participants in age groups 11-14 ($p = 0.001$) and 15-17 ($p = 0.0001$) years showed significantly enhanced alpha band power in response to AV stimuli compared to the summation of A and V stimuli on all electrodes (Figure 4b) whereas no difference of condition was found in the younger groups. In the AV condition, electrode FCz showed a significantly greater activation in the alpha band in comparison to electrode Fz ($p = 0.0001$). No significant differences of activation were found between electrodes in the (A+V) condition. For the condition by electrode by age group interaction, the activation difference between 11-14 year-olds and adults reached a statistical trend ($p = 0.092$) on electrode Cz, for the AV condition only while none was observed between other age groups or electrodes. No (A+V) activation differences were found between all age groups and electrodes. Post-hoc analyses also revealed that AV activations were significantly stronger in contrast to (A+V) activations for all electrodes in adults (Fz [$p = 0.0001$], FCz [$p = 0.0001$], Cz [$p = 0.007$]), 15-17 year-olds (Fz [$p = 0.0001$], FCz [$p = 0.0001$], Cz [$p = 0.0001$]) and 11-14 year-olds (Fz [$p = 0.003$], FCz [$p = 0.001$], Cz [$p = 0.007$]) but not in participants aged between 3 months and 10 years old ($p < 0.05$). No significant interaction was found between electrode and age group, suggesting that the nature of the condition explains the differences of activation in alpha band. The ANOVA revealed significant main effects for condition ($F_{1,\ 113} = 47.088$; $p = 0.0001$; $h_p^2 = 0.294$) reflecting higher alpha activation to the AV condition compared with the summed response (A+V). Results also indicated a main effect for electrode ($F_{1.61,\ 182.07} = 5.046$; $p = 0.012$, $h_p^2 = 0.043$) showing significantly higher alpha power on FCz compared to Fz ($p = 0.0001$).

4.2.3 Beta

A main effect of condition ($F_{1, 113} = 27.120$; $p = 0.0001$; $h_p^2 = 0.194$) confirmed that the AV response was significantly higher in the beta band as compared with the summed response. The ANOVA also indicated a significant main effect of electrode ($F_{1.66, 187.25} = 3.847$; $p = 0.030$; $h_p^2 = 0.033$) revealing significantly higher beta power on electrode FCz compared to Fz ($p = 0.018$). Since no main effect of group or interactions were found, no further description is provided.

4.2.4 Gamma

The ANOVA revealed significant interactions were found between age group and electrode ($F_{11.56, 186.59} = 2.080$; $p = 0.022$; $h_p^2 = 0.114$) as well as condition and electrode ($F_{1, 787} = 2.980$; $p = 0.059$; $h_p^2 = 0.026$). Post-hoc analyses revealed that gamma activations were stronger in adults (Cz > FCz [$p = 0.004$] and Fz [$p = 0.0001$]; FCz > Fz [$p = 0.039$]), in 15-17 (FCz > Fz [$p = 0.024$]) and in 11-14 year-olds (Cz > Fz [$p = 0.038$]). Post-hoc analyses also revealed that AV activations were significantly stronger in contrast to (A+V) activations on electrodes Cz ($p = 0.002$) and FCz ($p = 0.0001$) compared to Fz. No significant interactions between condition and age group were found. The ANOVA revealed significant main effect for condition ($F_{1, 113} = 6.986$; $p = 0.009$; $h_p^2 = 0.058$) reflecting higher gamma activation for AV stimuli as compared to summed (A+V) stimuli. Results also showed a main effect for electrode ($F_{1.62, 183.05} = 8.961$; $p = 0.001$; $h_p^2 = 0.073$) revealing significantly higher gamma power on electrodes FCz ($p = 0.0001$) and Cz ($p = 0.002$) compared to Fz.

Insert Figure 4 about here

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5. Discussion

While behavioral evidence suggests that young infants seem to benefit from multisensory information across senses, no neuroimaging or electrophysiological studies had yet looked at the developmental course of MSI from early infancy. We therefore conducted a cross-sectional study on a large cohort of 121 individuals to investigate the integration of non linguistic AV information through time-frequency decomposition of high-density EEG. The aim of this experiment is to investigate the developmental patterns of AV integration from the age of 3 months old to adulthood and to specify when MSI mechanisms reach maturity. The literature concerning the development of MSI remains controversial and, to our knowledge, the neuronal data available on the study of AV integration in early childhood remains scarce. While Brandwein and colleagues (2011) did not found clear neurophysiological evidence of AV integration before the age of 13 years old, animal and human findings indicate that the structural and functional architecture to integrate information are already present in the first months of life (Sours et al., 2016; Wallace et al., 2006). The present study reveals that AV integration emerges between 2 and 4 years of age but that the maturation of MSI processes occurs gradually during the course of childhood and adolescence, reaching a mature pattern of AV integration between 15 and 17 years old. In order to characterize precisely the developmental course of AV integration we have sought the use of time-frequency analyses.

The specificity of this analysis methodology allowed to characterize precisely the development of AV integration from 3 months of age to young adulthood and revealed how this ability may be expressed differently in distinctive EEG frequency bands according to the age. Time-frequency decomposition of high-density EEG activity may thus allow a more accurate and stable examination of multisensory effects, compared to ERP peak detection, since the transient electric potential shape change with age (Figure 2). Indeed, young children do not exhibit as many well-defined peaked responses when compared to older children and adult responses. Consequently, MSI brain responses may be reflected in a specific frequency range that cannot be detected in traditional ERP peak detection (Van der Lubbe et al., 2016). Thus, the discrepancy between the current work and Brandwein et al's study (2011) may lie in these methodological differences.

Overall, our results revealed a significant increase of AV and (A+V) neuronal activations as a function of age, with a greater enhancement in response to bisensory than unisensory presentation. The Morlet wavelet analyses did not reveal any differences between AV and the summed unisensory responses in 3- to 12-month-old infants. Recent ERP evidence has shown that auditory ERPs are increased by the simultaneous presentation of a visual stimulus compared to auditory stimulus presentation when the visual component was factored out (Hyde et al., 2010). Similarly, 6-month-old infants demonstrate greater amplitude of auditory ERPs in response to synchronous compared to slightly delayed AV stimuli yet within the temporal binding window (Kopp, 2014). While showing that the combination and the synchronous presentation of AV information enhances auditory processing (Hyde et al., 2010; Kopp, 2014), these investigations did not bring out a real indication of MSI in 3- to 6-month-old infants. As previously documented in the behavioral literature, the facilitation effect of visual information to auditory cues and the sensitivity to temporal AV synchrony seem to be mechanisms prioritized in the first few months of life (Bahrick & Lickliter, 2002; Hyde et al., 2010; Lewkowicz, 2010), but the combination of different sensory information using more complex integration models (Ernst & Banks, 2002) emerges later. It has been argued that, before middle childhood, calibration of one sensory modality by another sensory modality may be more likely to occur than real integration (Burr & Gori, 2011). While our findings cannot conclude to the presence of AV integration in infants, it is possible that the limited number of trials, due to movements, that could be analyzed in our 3- to 12-month-old participants may have affected the signal-to-noise ratio of the averaged wavelet, reducing our ability to detect differences in these frequency bands.

Although our findings may suggest the absence of AV integration in these young children, an alternate explanation related to the impact of low attentional resources in these infants is also plausible. While no explicit task was required from our participants, how neuronal activity related to MSI may be associated with maturation differences in attentional capacity (Konrad, 2005; Posner & Rothbart, 1998) remains an open question. From 6 to 12 months of age, infants have better voluntary control over their visual fixations and show brief looks to basic AV stimuli (Courage, Reynolds, & Richards, 2006). Beyond that age, the anterior attention system, including areas of prefrontal cortex, becomes increasingly influential in the voluntary selection and maintenance of attention (Posner & Petersen, 1990) and may play a role in the ability to interpret information from multiple sources. The immaturity in attentional processes might thus explain the absence of AV integration before the age of 24 months old. Future research should integrate behavioral and electrophysiological measures in studies examining infant attention to multisensory stimuli.

From the age of 2 until 7 years old, children exhibit stronger theta activations in response to AV stimulation compared to the summed response suggesting early forms of MSI during early childhood. Theta activity is abundant in the EEG of infants and young children and this feature is generally considered as a sign of neuronal immaturity (Clarke, Barry, McCarthy, & Selikowitz, 2001; Somsen, van't Klooster, van der Molen, van Leeuwen, & Licht, 1997). While no MSI response was reflected in the alpha band, as observed in adults, significant differences found between the AV and (A+V) conditions in the theta band suggest the presence of AV integration precursors in these age groups. As documented in the literature, slower frequencies in the broad theta frequency range dominate in childhood and are closely associated with the encoding of new information (Klimesch, 1997). In our 2- to 7-year-old children, the processing of AV information elicited a strong event-related increase in the theta frequency band and may reflect higher demands on sustained attention to the processing of new information for this age group (Jensen, Gelfand, Kounios, & Lisman, 2002). This difference in theta activation is also exhibited by children aged between 11 and 14 years. Previous work on brain maturation reported gradual changes in EEG spectral power between 5 and 12 years old (Somsen et al., 1997). While the power of lower frequencies (delta, theta) decreases with age, the power of higher frequencies (alpha, beta and gamma) increases (Somsen et al., 1997; Whitford et al., 2007). In fact, from early infancy to puberty, there is a strong decrease in theta frequency and a strong increase in alpha frequency (Harmony et al., 1990; Klimesch et al., 2007; Somsen et al., 1997; Yordanova et al., 2002). Interestingly, in addition to the stronger response to AV compared to (A+V) stimuli in the theta frequency band exhibited by the 11- to 14-year-old group, a difference between AV and (A+V) responses in the alpha band from 11 years old to adulthood was also found. The increase of alpha frequency with age, documented in the literature and illustrated in our data, may thus be associated with brain maturation and heightened sensory processing and cognitive aptitudes.

Given the predominance of theta band during childhood, the absence of significant results in the group of children between 8 and 10 years of age was unexpected. In this age group, no significant differences were observed in the theta or alpha band. These results may suggest a transitional phase at this age period resulting notably by maturational changes in frequency bands. In fact, between the age of 8 and 11 years, theta and alpha bands reach a crossing point where the predominance of theta reaches that of alpha (Somsen et al., 1997). This transition may explain the absence of significant differences between conditions in both theta and alpha, since MSI effect may be diluted in both frequency bands. The presence of several major morphological and functional changes occurring in the human brain during adolescence (Giedd et al., 1999), may also contribute to this absence of activation difference. For example, an important linear increase in global white matter volumes and an inverted U-shaped developmental trajectory for global gray matter structures, with peak volumes occurring between 7 and 11 years of age are documented (Gogtay & Thompson, 2010; Thatcher, 1994). Thus, the absence of differences between AV and the summed unisensory responses between the age of 8 and 11 years old may not reflect an absence of AV integration, but rather individual variability in EEG signal resulting from cerebral maturation and cognitive development during puberty, a critical phase where the brain undergoes profound changes.

In our study, while adults and 15- to 17- year-olds seemed to respond in a similar manner to AV stimuli as revealed by the absence of difference in the alpha band between the two groups, adults tended to show a difference of alpha activation compared to 11- to 14- year-old adolescents. More specifically, adults tended to have higher level of alpha activation compared to the 11 to 14 years-old group. Although this difference did not reach the statistical threshold, which might be due to the variability in our data, results suggest that AV integration mechanisms have not yet reached full maturity at this developmental period. Furthermore, these findings suggest that 11- to 14-year-old adolescents begin to integrate in a similar manner to adults, as both show greater alpha activation to AV compared to (A+V) stimulations. However, AV integration mechanisms seem to reach full maturity between 15 and 17 years of age, as the intensity level of alpha activation is similar to adults. Our results confirm Brandwein and colleagues' (2011) previous findings that showed significantly larger ERP amplitude in 13- to 16-year-olds and adults in the AV condition compared with the sum of the unisensory ones in frontocentral scalp regions. Contrary to our findings, Brandwein et al. did not find electrophysiological indices of AV integration before the age of 13 years old (Brandwein et al., 2011). It is possible that the use of wavelet analyses in the current study has allowed a more precise examination of multisensory effects reflected in specific frequency ranges (Van der Lubbe et al., 2016).

Overall, our results suggest that the maturity of AV integration mechanisms is a long and gradual process starting in the early childhood and culminating in late adolescence. According to the literature, these processes might depend, among others, on structural and functional maturation of unisensory senses (Ernst, 2008). While all senses begin to develop in utero, they have distinct rates of neuroanatomical maturation and functional development during infancy and childhood (Lippé et al., 2009). Progressive myelination, changes in synaptic density and metabolic activity within auditory and visual cortical and subcortical systems is a decade-long course lasting through early and later childhood (Lippé et al., 2009; Kozma, Kovács, & Benedek, 2001; Moore & Linthicum, 2007). Both sensory systems have different developmental timelines and the level of visual (Atkinson, 2002; Ellemberg et al., 2003; Kovacs, Kozma, Feher, & Benedek, 1999; Sayeur et al., 2015) and auditory (Draganova et al., 2005; Kuhl, 2000) processing complexity develops as a function of age expressed by more stable and accurate behavioral performance. Moreover, on the neuronal level, the development of visual and auditory ERP responses show morphological differences in their waveforms from infancy to adulthood (Lippé et al., 2009; Lippé et al., 2007). Thus, the maturation of unisensory systems and responsiveness might shape and be interconnected to parallel maturation of structural and functional multisensory structures and pathways. Ernst (2008) suggested that such late development of multisensory integration could depend on the continuous calibration of the sensory systems required during development (Ernst, 2008). We also presume that the extended time course of MSI may depend on incomplete myelination of white matter pathways (Cappe, Rouiller, & Barone, 2009) and maturational differences of cortical and subcortical structures and networks (Driver & Noesselt, 2008) underlying the capacity to integrate AV information. In fact, recent behavioral studies have suggested a hierarchy of different multisensory processing abilities (Barutchu et al., 2010; Nardini, Jones, Bedford, & Braddick, 2008; Neil, Chee-Ruiter, Scheier, Lewkowicz, & Shimojo, 2006) with age.

Another important determinant in the development of MSI is the acquisition of increasing amounts of sensory experience. While anatomical and physiological animal studies have demonstrated the importance of multisensory exposure on the acquisition of MSI capacities (Wallace, Meredith, & Stein, 1993; Wallace & Stein, 1997, 2001; Yu, Rowland, & Stein, 2010; Yu, Stein, & Rowland, 2009), prenatal and postnatal exposure to environmental stimulation may have an impact on the human child’s development and functional state of

MSI. Findings such as these may be applied to our data, as they suggest that adult-like MSI maturity in humans do not emerge until several years following birth. This research corroborates previous studies using AV tasks in children ranging from 6 years old to early twenties suggesting that the capacity to integrate AV information extends well into development and does not reach its full developmental peak until late adolescence (Barutchu et al., 2009; Barutchu et al., 2010; Downing, Barutchu, & Crewther, 2015; Gori, Sandini, & Burr, 2012; Nardini et al., 2016).

Our data did not reveal any differences between the AV and the summed responses in either beta or gamma bands for all age groups. This result might be explained by the nature of the paradigm. While beta activity has been related to AV integration in adults (Sakowitz, Quiroga, Schürmann, & Başar, 2001; Sakowitz et al., 2005), this component has been most frequently related to sensory-motor processing and reaction times (Jenkinson & Brown, 2011; Liang, Bressler, Ding, Truccolo, & Nakamura, 2002; Pfurtscheller, Graimann, Huggins, Levine, & Schuh, 2003; Senkowski, Molholm, Gomez-Ramirez, & Foxe, 2006). Many EEG studies investigating multisensory effects in beta activity have required a motor response from the participant. Therefore, the type of paradigm used in the present study, a passive task, might be a possible explanation for the absence of integration measured in beta responses. While no significant activation differences between AV and the summed responses were found in the gamma band, previous EEG studies have found enhanced evoked gamma activity in response to AV stimulation in adults (Sakowitz et al., 2001). In contrast to these studies, the simultaneous presentation of our flashing checkerboard and tone stimuli may not imply higher order cognitive processing, such as language (Bastiaansen & Hagoort, 2006) or memory processes (Busch, Groh-Bordin, Zimmer, & Herrmann, 2008; Kaiser, Heidegger, Wibral, Altmann, & Lutzenberger, 2008; Kaiser & Lutzenberger, 2005), that have been associated with gamma responses. Moreover, it is possible that the key to understanding the discrepancy in the AV integration literature results might rely on the use of different paradigms and stimuli that may elicit distinct cognitive processes. Ultimately, a longitudinal developmental research design would minimize certain confounding and contextual effects mentioned above and allow assessing the stability and continuity of MSI developmental course.

6. Conclusion

This is the first electrophysiological study that characterizes the developmental progression of AV integration mechanisms from 3 months old to adulthood and indicates the age at which these processes reach full maturity. Here, we undertook a cross-sectional investigation on a large cohort of 121 individuals using electrophysiological measures during a simple passive task. The current results indicate that AV integration emerges slowly over the second year of life, that 11- to 14-year-old adolescents start to integrate these information in an adult-like manner and that AV integration mechanisms reach maturity as late as 15 to 17 years of age. These results corroborate findings from neurophysiological animal models and behavioral studies in children and adolescents suggesting that the fine-tuning of optimal AV integration continues gradually throughout childhood and reaches maturity during late adolescence as a consequence of environmental exposure and brain maturation. This study may provide an electrophysiological marker of AV integration in infants that can be used to understand how information is integrated across the senses to form a unitary perception of the world. The benchmarks and chronology of typical MSI development brought to light in this study could be crucial in the screening of certain neurodevelopmental disorders where multisensory processing deficits are reported (Charbonneau et al., 2013; Collignon et al., 2013; Dionne-Dostie, Paquette, Lassonde, & Gallagher, 2015).

Conflicts of Interest

The authors declare no conflict of interest.

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Tables

Table 1. Demographic data for each age group.

Age group	N	Mean Age (SD)	Male: Female
3-6 months-old	13	4.26 m (1.24)	8:5
6-12 months-old	16	10.41 m (2.98)	6:10
2-4 years-old	21	3.30 y (1.05)	12:9
5-7 years-old	16	6.14 y (0.76)	8:8
8-10 years-old	14	8.67 y (1.02)	8:6
11-14 years-old	17	12.88 y (1.09)	9:8
15-17 years-old	11	16.18 y (0.60)	5:6
Adults	13	24.19 y (2.94)	7:6

N = number of participants; SD = standard deviation; m = months; y = years

Table 2. Linear regression equations between age and wavelet power in both conditions within all frequencies on frontocentral electrodes.

Electrode	**Equation**	**R^2**	**t**	**p**
FCz	AV = 15.14*X + 62.70	0.20	327	< 0.0001
	(A+V) = 6.42*X + 38.98	0.20		< 0.0001
Fz	AV = 10.28*X + 77.66	0.14	267	< 0.0001
	(A+V) = 5.27*X + 39.90	0.11		< 0.0001
Cz	AV = 16.24*X + 63.41	0.16	336	< 0.0001
	(A+V) = 6.47*X + 42.11	0.21		< 0.0001

Figure Legends

Figure 1. Grand-averaged AV ERPs on electrode FCz are depicted in panel (a) for groups 2-4, 5-7, 8-10, 11-14 and 15-17 years old and adults and (b) for groups 3-6 and 6-12 months old. Time is plotted on the *x*-axis and amplitude on the *y*-axis. A time window between 100 and 300ms was selected based on the development of AV N1 and P2 components as a function of age (horizontal grey bar).

Figure 2. Topographic brain activities elicited when comparing both multisensory (AV) and sum (A+V) averaged wavelet responses for all age groups and electrode sites. Note that both conditions elicited significantly greater magnitude power of activation over the frontocentral region. Results from the topological scalp distribution *t*-test reveal that the frontocentral activation is stronger for the AV condition compared to (A+V), justifying the chosen electrodes of interest to study AV integration.

Figure 3.The linear regression illustrates the relationship between age and wavelet power in both conditions a) on electrode FCz (*in blue*: AV and *in red*: [A+V]). Topographic map representation of the slope regression between age and wavelet power for b) AV and c) (A+V) conditions on all electrodes. The scalp distribution is predominantly located over the frontocentral regions for the AV integration (b) and, at a lower intensity, for the (A+V) condition (c).

Figure 4. Significant mean power differences between multisensory (AV: *in white*) and ([A+V]: *in dark grey*) responses are shown in theta, alpha, beta and gamma across age groups on electrode FCz. Light grey bars show no statistical differences between conditions (AV and [A+V]).

Figure 1.

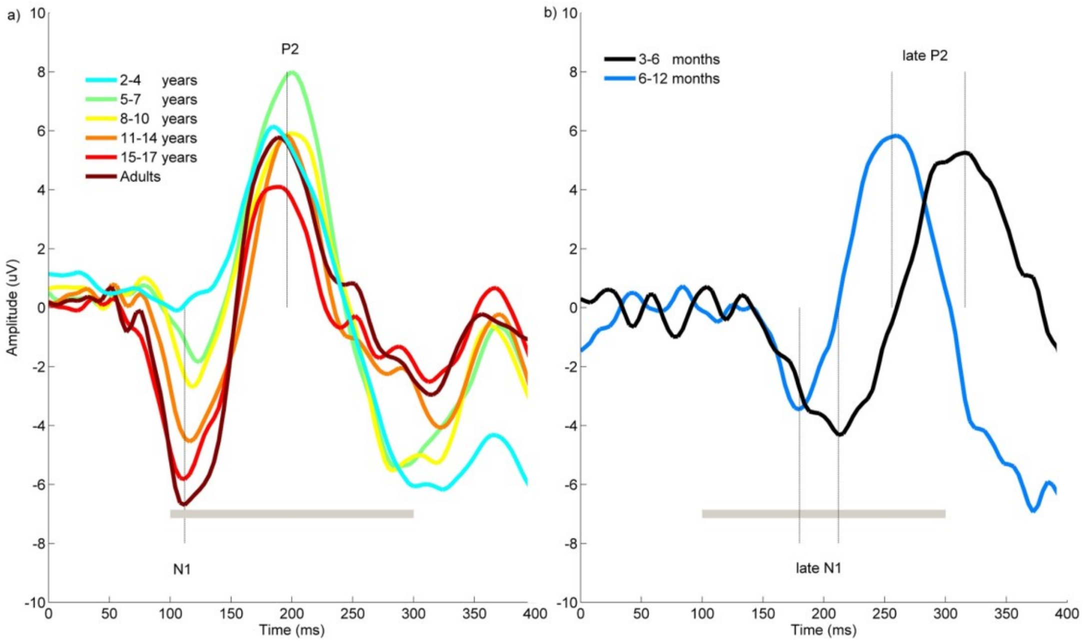

a)
b)
P2
N1
late P2
late N1
2-4 years
5-7 years
8-10 years
11-14 years
15-17 years
Adults
3-6 months
6-12 months
Amplitude (uV)
Time (ms)
10
8
6
4
2
0
-2
-4
-6
-8
-10
0
50
100
150
200
250
300
350
400

Figure 2.

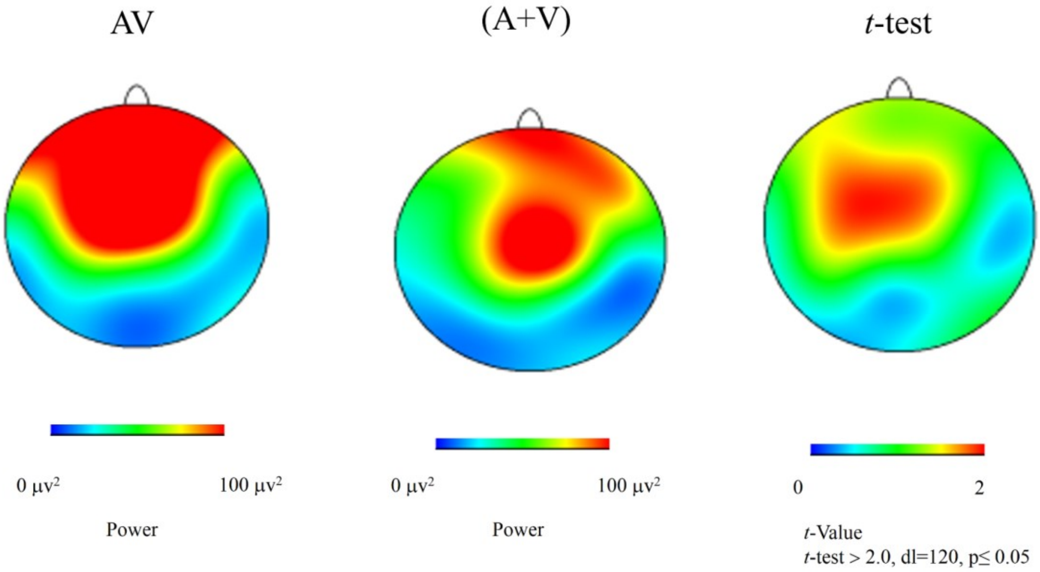

AV
(A+V)
t-test
0 µv²
100 µv²
Power
0 µv²
100 µv²
Power
0
2
t-Value
t-test > 2.0, dl=120, p≤ 0.05

Figure 3.

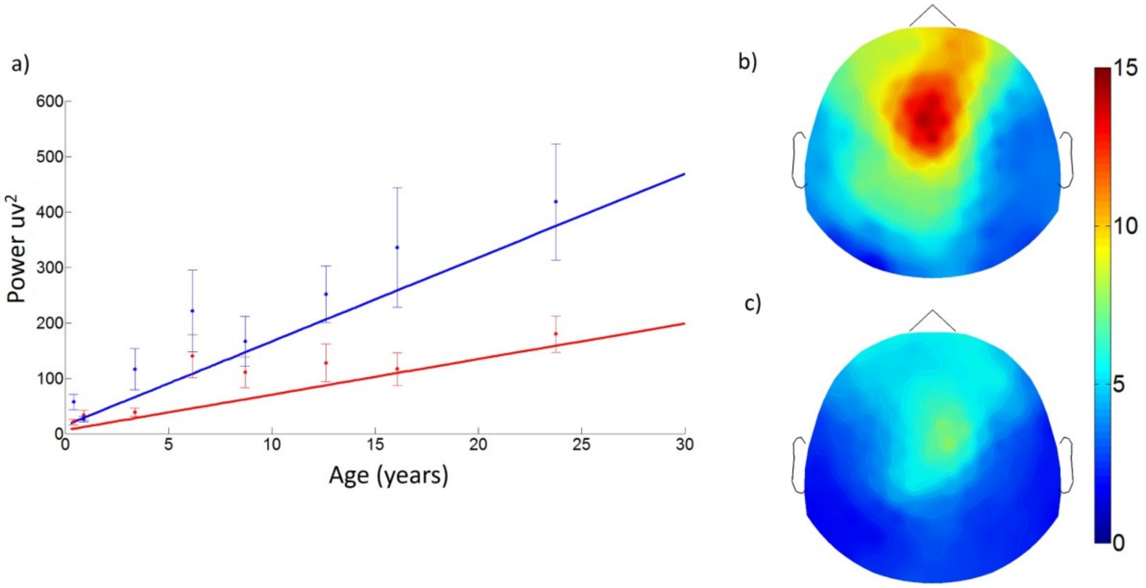
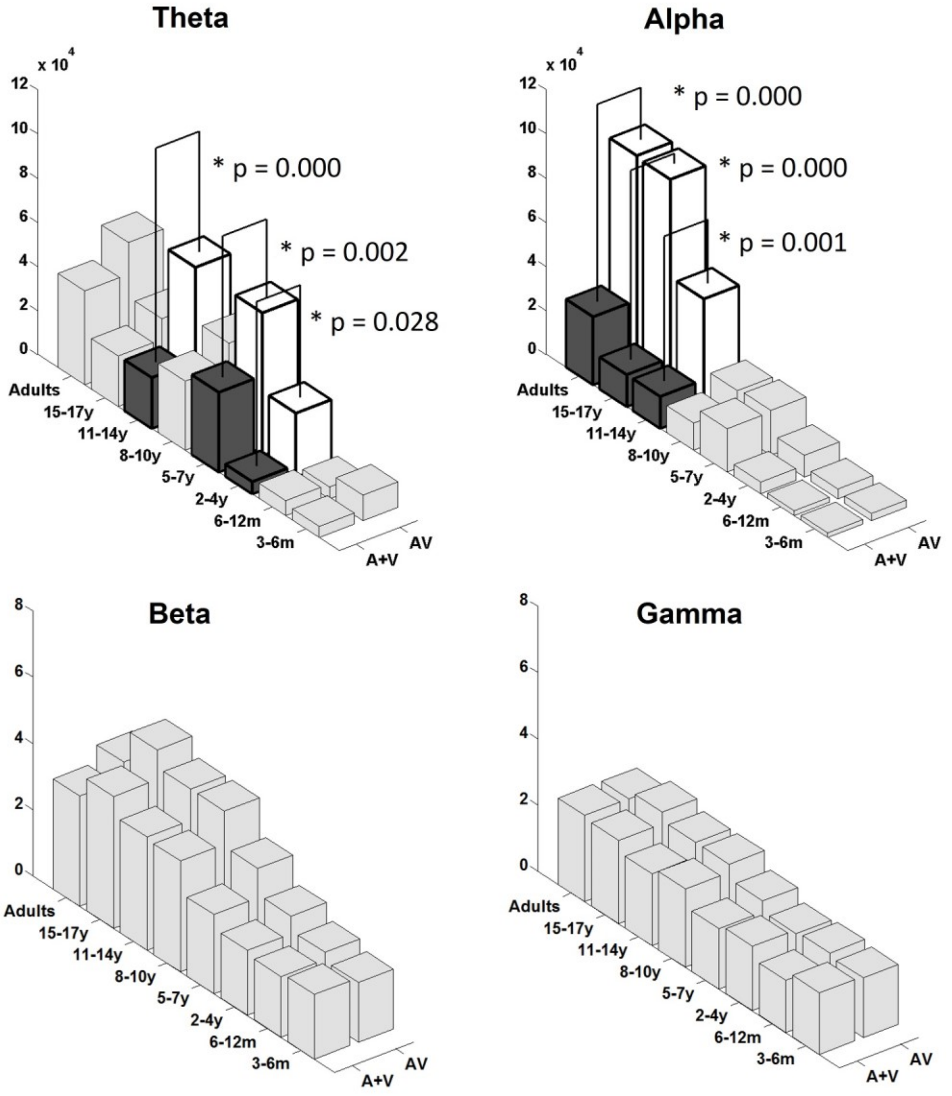

a)
Power uv^2
600
500
400
300
200
100
0
0
5
10
15
20
25
30
Age (years)
b)
c)
15
10
5
0

Figure 4.


Theta
x 10^4
12
10
8
6
4
2
0
* p = 0.000
* p = 0.002
* p = 0.028
Adults
15-17y
11-14y
8-10y
5-7y
2-4y
6-12m
3-6m
AV
A+V
Alpha
x 10^4
12
10
8
6
4
2
0
* p = 0.000
* p = 0.000
* p = 0.001
Adults
15-17y
11-14y
8-10y
5-7y
2-4y
6-12m
3-6m
AV
A+V
Beta
8
6
4
2
0
Adults
15-17y
11-14y
8-10y
5-7y
2-4y
6-12m
3-6m
AV
A+V
Gamma
8
6
4
2
0
Adults
15-17y
11-14y
8-10y
5-7y
2-4y
6-12m
3-6m
AV
A+V

4. DISCUSSION GÉNÉRALE

4.1 Rappel des objectifs et résultats

Les objectifs généraux de cette thèse consistaient tout d'abord à faire un survol des connaissances sur le développement neurotypique de l'IMS et à documenter la progression et la maturation des capacités d'intégration AV liées au développement neurotypique. Pour ce faire, nous avons effectué une revue de la littérature sur les connaissances du développement neurotypique de l'IMS, toutes modalités sensorielles confondues. Cette revue présentait les études comportementales et neuronales en faveur du caractère inné ou acquis des processus d'IMS, ce qui nous a permis de mieux cibler le manque de littérature quant au développement neuronal des capacités d'intégration AV. Ce constat a justifié la tenue de l'étude expérimentale présentée dans l'article 2. Cette dernière avait pour but de caractériser la progression développementale neurotypique des mécanismes d'intégration d'informations AV non linguistiques dès l'âge de 3 mois jusqu'à l'âge adulte, en examinant les réponses oscillatoires. Cette recherche visait également à confirmer l'âge où les mécanismes d'intégration AV, d'une part, fonctionnent de façon similaire aux adultes et, d'autre part, atteignent leur pleine maturité. Dans les sections suivantes, les résultats de notre étude seront résumés et discutés au regard de la littérature existante. Nous aborderons ensuite les limites inhérentes à notre étude et proposerons des avenues de recherches futures.

4.1.1 Article 1

Le premier objectif de notre revue de la littérature consistait à documenter l'état des connaissances sur le développement des capacités d'IMS. Nous avons recensé un total de 219 études portant sur les enregistrements unitaires chez l'animal, la réponse des populations neuronales, les travaux en neuroimagerie ainsi que les données comportementales chez l'homme, et ce, toutes modalités sensorielles confondues. Les études animales relevées dans la littérature indiquent que ce n'est qu'après plusieurs mois de vie et d'exposition aux expériences environnementales que les neurones spécialisés dans l'IMS se manifestent et se développent progressivement (Wallace et al., 2006; Wallace & Stein, 1997). Par ailleurs, l'ensemble des travaux chez le nourrisson suggère qu'il serait possible de former des associations multisensorielles à des stades de développement précoces (Bahrick, & Lickliter, 2000), tandis que d'autres études mentionnent que les capacités à intégrer les informations multisensorielles de façon optimale demeurent un long processus qui se développe tardivement à l'enfance (Barutchu et al., 2010; Brandwein et al., 2011; Downing et al., 2015; Gori et al., 2012; Nardini et al., 2016). Considérant les gains comportementaux associés à l'IMS (Corneil, Van Wanrooij, Munoz, & Van Opstal, 2002; Girard, Pelland, Lepore, & Collignon, 2013; von Saldern & Noppeney, 2013), notre revue de la littérature a également mis en relief le rôle important que peuvent jouer les habiletés multisensorielles dans le développement cognitif et intellectuel des enfants. Nous avons d'ailleurs mis en relation la présence de difficultés à traiter et intégrer les informations sensorielles et certains troubles neurodéveloppementaux, notamment la dyslexie et le TDA/H. Globalement, la littérature suggère que l'altération de l'activité de certaines structures corticales et sous-corticales ainsi qu'une inefficacité des réseaux cérébraux peuvent être responsables (Blau et al., 2010; Simos et al., 2000; Shaywitz et al., 1998; Stevens et al., 2009; Tian et al., 2008; Yeo et al., 2003), d'une part, des difficultés d'association, de traitement temporel et d'intégration de l'information AV retrouvées chez le dyslexique (Laasonen, & Virsu, 2001; Windfuhr & Snowling, 2001) et, d'autre part, des déficits sensoriels, de même que des difficultés sensorimotrices et de modulation des réponses sensorielles chez les individus avec un TDA/H (Engel-Yeger & Ziv-On, 2011; Hassan, & Azzam, 2012). Depuis la publication de notre revue de la littérature, de nouveaux articles se sont ajoutés dans l'étude du développement des capacités d'intégration AV. Comme nous l'avons déjà vu précédemment (voir section 1.4.2), il semble que la synchronie stricte entre les différents évènements sensoriels ne soit pas fondamentale dans la perception d'un évènement multisensoriel. En effet, le cerveau peut percevoir deux informations sensorielles décalées dans le temps comme synchrones dans la mesure où celles-ci surviennent à l'intérieur d'un certain intervalle de temps, désigné sous le nom de « fenêtre temporelle d'intégration » (Dixon & Spitz, 1980; Noesselt et al., 2007). De récentes études sont venues appuyer le caractère acquis de l'IMS en révélant que la capacité à détecter la synchronie AV continue de se peaufiner tout au long de l'adolescence (Kaganovich, 2016; Lewkowicz, 2014) et dépend, en partie, de la maturation prolongée de la fenêtre temporelle d'intégration. De nouvelles études développementales ayant examiné les temps de réaction chez des enfants d'âge scolaire jusqu'à l'âge adulte ont démontré des effets de facilitation multisensorielle à 9 (Downing et al., 2015) et 12 ans (Barrett & Newell, 2015; Viggiano et al., 2017) dépendamment de la complexité de la tâche (tâche d'identification et de discrimination) à exécuter et des stimuli à traiter.

Le deuxième objectif de notre recension des écrits consistait à identifier dans la littérature les manquements du développement des capacités d'intégration AV. À ce titre, bien que les travaux sur les capacités d'IMS à l'âge scolaire soient nombreux, une infime quantité de travaux en neuroimagerie et en EEG s'est penchée sur la progression développementale de l'IMS (Brett-Green et al., 2008; Kaganovich & Schumaker, 2014; Knowland et al., 2014) et ce, toute modalité sensorielle confondue. On constate également un manque de données notables sur le développement des capacités d'IMS à l'âge préscolaire (entre 3 et 5 ans). Notre revue de la littérature nous a permis d'identifier une seule étude en EEG, celle de Brandwein et collaborateurs (2011), laquelle a examiné la progression développementale de l'intégration d'informations AV non linguistiques de l'âge de 7 à 16 ans et, aussi, chez les adultes. Les résultats issus de cette recherche ont révélé que l'amplitude de la réponse AV était significativement plus grande que la sommation des réponses auditives et visuelles (A+V), et ce, uniquement chez les adultes et les enfants âgés entre 13 et 16 ans. Il n'y a aucune autre étude en EEG traitant de la progression développementale de l'intégration AV et cette dernière se concentre sur la période d'âge scolaire, ce qui nous a permis de constater un manque de données en EEG sur la progression développementale de l'intégration d'informations AV non linguistiques en bas âge. La prochaine section traitera plus en détails des résultats de notre étude expérimentale.

4.1.2 Article 2

Nous avons mené une étude expérimentale transversale sur un vaste échantillon composé de 121 participants neurotypiques afin d'étudier la progression développementale des mécanismes d'intégration d'informations AV non linguistiques en utilisant l'EEG à haute densité. Notre recherche visait plus spécifiquement à étudier les patrons développementaux de l'intégration AV dès l'âge de 3 mois jusqu'à l'âge adulte et de spécifier le moment où les mécanismes d'IMS atteignent leur pleine maturité. Afin de caractériser plus précisément la progression développementale de l'intégration AV, nous avons examiné l'activation oscillatoire du cerveau des participants dans la majorité des bandes de fréquences (thêta, alpha, bêta et gamma) en utilisant les analyses temps-fréquence en ondelettes. En effet, ce type d'analyses nous apparaît comme une technique de choix pour étudier les processus d'intégration AV puisqu'elle permet une investigation plus précise et stable des processus d'intégration comparativement à la détection des pics des PÉs (Van der Lubbe et al., 2016). En effet, le tracé EEG du nourrisson et du jeune enfant est souvent bruité et se caractérise par une plus grande activité en ondes lentes (Luciana & Nelson, 1998) ce qui influence la polarisation des PÉs et a justifié notre recours à l'analyse en ondelettes dans notre étude. Cette technique nous a également permis de voir comment l'intégration AV s'exprime dans une bande de fréquences spécifique. Ainsi, nous avons comparé la puissance d'activation oscillatoire des enfants (3-6 mois, 6-12 mois, 2-4 ans, 5-7 ans, 8-10 ans), des adolescents (11-14 ans, 15-17 ans) et des adultes (18 ans et plus) neurotypiques en réponse à des stimuli bisensoriels (AV) et unisensoriels (A+V) dans un intervalle de temps de 100 à 300 ms.

L'analyse de régression linéaire a illustré une augmentation significative et progressive de l'ensemble des activations oscillatoires AV et (A+V) en fonction de l'âge, avec une augmentation significativement plus importante de la puissance d'activation en réponse aux stimuli bisensoriels qu'unisensoriels.

Quant à elles, nos analyses en ondelettes n'ont révélé aucune différence significative dans l'ensemble des bandes de fréquences entre les réponses AV et la somme des réponses unisensorielles auditives et visuelles chez les nourrissons âgés entre 3 et 12 mois. Par ailleurs, entre 2 et 7 ans, les enfants ont présenté des activations plus importantes en thêta en réponse aux stimulations AV qu'aux stimulations (A+V). Les enfants de 8 à 10 ans n'ont démontré aucune différence significative d'activation entre les réponses AV et (A+V) dans l'ensemble des bandes de fréquences. Quant aux jeunes de 11 à 14 ans, ils ont démontré une activation en thêta plus importante aux stimuli AV que la somme des réponses auditives et visuelles. De plus, ils ont également affiché une activation plus importante en alpha. De la même manière, les adolescents de 15 à 17 ans ainsi que les adultes ont démontré une puissance d'activation en alpha significativement plus élevée en réponse à la stimulation AV comparativement à la stimulation (A+V).

Par ailleurs, nos résultats suggèrent que les adolescents de 11-14 ans présentent un patron d'intégration similaire à celui des adultes, puisque ces deux groupes affichent une plus grande activation en alpha en réponse aux stimuli AV comparativement à la somme des stimuli auditifs et visuels. Néanmoins, les adultes ont démontré une tendance à présenter un niveau d'activation plus élevé en alpha que le groupe des 11-14 ans. Bien que cette différence d'activation n'ait pas atteint le seuil statistique, possiblement en raison de la variabilité de nos données, les résultats suggèrent que les mécanismes d'intégration AV n'ont pas encore atteint leur pleine maturité au cours de cette période d'âge. De plus, la comparaison de la puissance d'activation en alpha entre les 15-17 ans et les adultes ne révèle aucune différence significative suggérant que ces deux groupes répondent de façon similaire aux stimulations AV. Ceci indique que les mécanismes d'intégration AV semblent atteindre leur pleine maturité entre les âges de 15 et 17 ans, vu la similitude de leur niveau d'intensité d'activation en alpha avec celui des adultes ainsi que l'absence de différence dans les autres bandes de fréquences, notamment en thêta. Enfin, que ce soit en bêta ou en gamma, nos résultats n'ont démontré aucune différence significative entre les réponses AV et la somme des réponses (A+V) pour tous les groupes d'âge.

4.2 Discussion et interprétation des résultats en lien avec la littérature

Il n'y a pas de consensus évident dans la littérature sur le caractère inné ou acquis de l'IMS. De façon générale, notre revue de littérature indique que les réponses neuronales chez l'animal militent en faveur du caractère acquis. Bien que les données chez le nourrisson appuient l'idée d'une capacité précoce à traiter les informations multisensorielles, les études effectuées chez les enfants d'âge scolaire (6 ans et plus), mettent en évidence une variabilité des capacités à combiner et intégrer ces informations, qui demeurent sous-optimales jusqu'à l'adolescence (Barutchu, Crewther, & Crewther, 2009; Barutchu et al., 2010; Downing, Barutchu, & Crewther, 2015; Gori, Sandini, & Burr, 2012; Nardini, Bales, & Mareschal, 2016). Ainsi, l'ensemble de la revue de la littérature effectuée dans le cadre de cette thèse a permis de mettre en lumière le débat inné-acquis de l'IMS avec une attention particulière sur le développement des capacités d'intégration AV d'informations non linguistiques.

4.2.1 Existe-il vraiment un débat inné ou acquis ?

Lors de la recension des différents travaux sur le développement des capacités d'IMS l'identification des études ayant réellement étudié ce phénomène fut ardue. Cette difficulté semble découler d'une confusion sémantique dans la définition de l'IMS comme tel (Stein et al., 2010). En effet, un nombre d'études utilise différentes expressions telles que « hétéromodal », « polymodal », « intersensoriel », « polysensoriel », « crossmodal » pour décrire le même concept qu'est l'IMS. De plus, cette confusion sémantique prend aussi ses origines sur une utilisation polysémique du terme « intégration multisensorielle » que l'on retrouve dans différentes études abordant l'analyse de différents processus multisensoriels comme « la sensibilité à la synchronie », « l'appariement multisensoriel », « le transfert intersensoriel » sans toutefois étudier la capacité à intégrer les informations de plusieurs modalités sensorielles. Depuis les dernières années, on constate une amélioration sémantique dans l'utilisation de termes plus appropriés pour décrire un processus multisensoriel distinct sous étude. En sus de l'imbroglio dans cette nomenclature, les paradigmes comportementaux employés dans l'étude du développement des capacités d'IMS chez le nourrisson, tels, entre autres, le test de regard préférentiel, le test d'habituation-reconnaissance, portent davantage sur l'investigation de différents processus multisensoriels plutôt que les mécanismes inhérents à l'IMS. Comme discuté dans la section 1.8 de la présente thèse, il n'est pas exclu que les paradigmes comportementaux utilisés chez les enfants d'âge scolaire, s'appuyant majoritairement sur des temps de réaction, puissent représenter des mesures plus fiables que la répartition des temps de regard pour étudier les processus multisensoriels. Notre revue de la littérature sur le développement de la capacité à intégrer les différentes informations sensorielles met en évidence des résultats mitigés quant à l'âge d'émergence de l'IMS et soulève un débat dichotomique *inné* ou *acquis*. Dans ce contexte, nous nous sommes questionnés sur la pertinence d'un tel débat qui, bien que tangible, puisse découler, en partie, de la confusion sémantique et des différents paradigmes employés tel qu'abordé précédemment. Le besoin actuel dans la littérature semble consister davantage à dresser un portrait de l'évolution des différentes habiletés de traitement des informations multisensorielles qui mènerait à l'intégration et de statuer sur l'âge de maturité de l'IMS.

4.2.2 Progression développementale des habiletés de traitement AV

Depuis les dernières années, il semble y avoir un certain consensus à l'effet de la présence d'une séquence développementale dans la capacité du nourrisson à évaluer les relations multisensorielles. L'architecture cérébrale permettant d'intégrer les informations multisensorielles semble être présente dès les premiers jours de vie (Sours et al., 2016; Wallace et al., 2006). Bien que nous n'ayons trouvé aucun indice d'intégration AV chez les nourrissons de 3 à 12 mois (article 2), notre revue de la littérature suggère une capacité précoce des nourrissons à détecter des relations simples d'un stimulus multisensoriel telles que le tempo, le rythme, la synchronie temporelle (Bahrick, 1992; Bahrick, Flom, & Lickliter, 2002; Baumgartner & Oakes, 2011; Lewkowicz, 1992, 2014; Lewkowicz & Ghazanfar, 2009; Neil et al., 2006; Vouloumanos, Druhen, Hauser, & Huizink, 2009). Sur le plan comportemental, il a été démontré notamment que dès l'âge de 4 mois, les nourrissons vont regarder plus longtemps les évènements multisensoriels qui coïncident dans le temps et l'espace provenant d'une source commune (p. ex., voir et entendre le rebondissement d'une balle; Lewkowicz, 1992). De même, sur le plan neuronal, les nourrissons de 3 et 6 mois semblent afficher une augmentation de l'amplitude de certaines composantes PÉAs en réponse à des stimuli AV synchrones tel qu'un cercle et un ton (Hyde et al., 2010; Kopp, 2014). Bien que cette réponse neuronale soit immature comparativement à celle observée chez les adultes (Besle et al., 2009; Giard & Peronnet, 1999; Stekelenburg & Vroomen, 2007), ces résultats démontrent une certaine capacité précoce de traitement multisensoriel dans cette tranche d'âge.

S’appuyant sur ces capacités de bas niveau, l’enfant développe ensuite des habiletés à combiner et intégrer des caractéristiques de complexité croissante. À ce titre, nous avons d’ailleurs observé une plus grande réponse neuronale à la présentation de stimuli AV dès l’âge de 2 ans, s’exprimant dans la bande thêta, largement prédominante durant l’enfance (Orekhova, Stroganova, Posikera, & Elam, 2006). En effet, comme le montre la littérature, l’EEG du nourrisson et de l’enfant se caractérise par un tracé de fond lent (delta, thêta) et cette caractéristique est généralement considérée comme un signe d’immaturité neuronale (Clarke, Barry, McCarthy, & Selikowitz, 2001; Somsen, van't Klooster, van der Molen, van Leeuwen, & Licht, 1997). Ces réponses neuronales en thêta à la présentation de stimulations AV demeurent ainsi immatures, mais semblent constituer des précurseurs de l’intégration AV.

La littérature démontre que ces habiletés se raffinent et s’améliorent jusqu’à l’adolescence (Barutchu et al., 2009; 2010; Brandwein et al., 2011; Downing et al., 2015; Hillock-Dunn & Wallace, 2012; Hillock et al., 2011; Nardini et al., 2016) au cours de laquelle on mesure des réponses d’intégration AV comportementales et neuronales à proprement parler. Notre article a d’ailleurs démontré, dès l’âge de 11 ans, la présence d’intégration AV dans la bande alpha, fréquences davantage présentes à l’âge adulte (Stroganova, Orekhova, & Posikera, 1999). En effet, nos résultats ont suggéré que les adolescents de 11-14 ans présentent un patron d’intégration similaire à celui des adultes, puisque ces deux groupes affichent une plus grande activation en alpha en réponse aux stimuli AV comparativement à la somme des stimuli auditifs et visuels. Néanmoins, les adultes tendent à présenter un niveau d’activation plus élevé en alpha que les 11-14 ans, suggérant que les mécanismes d’intégration AV n’ont pas encore atteint leur pleine maturité au cours de cette période d’âge. De plus, les 11-14 ans présentent également une intégration AV dans la bande thêta, ce qui sera abordé de manière plus spécifique dans une section ultérieure. Ainsi, notre article a d'ailleurs suggéré que les mécanismes d'IMS atteignent leur pleine maturité entre les âges de 15 et 17 ans, compte tenu de la similitude de leur niveau d'intensité d'activation en alpha avec celui des adultes à la présentation de stimuli AV. En effet, la comparaison de la puissance d'activation en alpha entre les 15-17 ans et les adultes ne révèle aucune différence significative, et les deux groupes ne montrent aucune différence significative dans les autres bandes de fréquences, suggérant que ces deux groupes répondent de façon similaire aux stimulations AV.

Des résultats similaires ont été rapportés dans l'étude développementale EEG de Brandwein et collaborateurs (2011), ceux-ci ayant démontré que les mécanismes d'intégration AV atteignent leur maturité tardivement au cours de l'adolescence, soit entre les âges de 13-16 ans. Ces données neuronales sont également appuyées par la littérature comportementale dans laquelle une facilitation multisensorielle est observée chez la plupart des enfants autour de l'âge de 7 ans dans des tâches de discrimination AV (Barutchu et al., 2009), tandis que d'autres études démontrent que l'intégration de stimuli auditifs et visuels ne devient pas optimale avant l'âge de 15 ans (Brandwein et al., 2011; Downing et al., 2015). Ainsi, on observe des indices neuronaux d'intégration AV dès l'âge de 11 ans, lesquels se perfectionnent toutefois au cours de l'adolescence pour atteindre leur maturité entre 15 et 17 ans.

4.2.3 Rôle de l'attention dans l'IMS chez le nourrisson

Bien que nos données suggèrent l'absence d'intégration AV chez les nourrissons âgés de 3 à 12 mois, il est possible, d'une part, qu'une immaturité des ressources attentionnelles puisse contribuer à ces résultats. L'association entre les différences de maturation des capacités attentionnelles et les réponses neuronales reliées à l'IMS mérite que l'on s'y attarde davantage. Chez les nourrissons âgés de moins de 1 an, bien qu'on observe un regard préférentiel pour les stimuli multisensoriels (Reynolds, Zhang, & Guy, 2013), les mesures de temps de regard et de battement cardiaque suggèrent que ces ressources attentionnelles demeurent immatures. Par exemple, entre 3 et 7 mois, la littérature documente amplement une diminution du temps de regard avec l'âge, reflétant une amélioration progressive de l'efficacité à traiter l'information (Courage, Reynolds, & Richards, 2006; Frick, Colombo, & Saxon, 1999; Rose, Feldman, & Jankowski, 2002). Par la suite, grâce au développement du cortex préfrontal, les nourrissons développent une meilleure capacité à sélectionner et maintenir leur attention de façon volontaire (Colombo, 2001; Posner & Petersen, 1990). Ceci pourrait influencer considérablement les capacités à traiter et interpréter des informations sensorielles provenant de plusieurs modalités et pourrait expliquer que nous n'observions pas d'indices d'intégration AV avant l'âge de 24 mois. D'autre part, bien que contradictoires, les résultats des études ayant examiné les réponses attentionnelles élicitées par la présentation de stimuli AV (Hyde & Spelke, 2011) ont révélé une augmentation de l'amplitude de la composante attentionnelle Nc en réponse à ces stimuli. Chez les nourrissons âgés de moins de 1 an, cette composante PÉ survient toutefois tardivement, soit environ entre 350 et 750 ms après la présentation du stimulus (Hyde, Jones, Flom, & Porter, 2011; Reynolds, Bahrick, Lickliter, & Guy, 2014), ce qui milite également en faveur d'une immaturité des processus attentionnels à cet âge. Dans notre étude, puisque nous nous sommes intéressés spécifiquement aux processus d'IMS à proprement parler et que nous n'avons pas ciblé cette composante attentionnelle, nous avons sélectionné une fenêtre temporelle d'intérêt comprise entre 100 à 300 ms. Ceci est susceptible d'expliquer l'absence de différence de puissance neuronale significative entre la présentation de stimuli uni- et bisensoriels chez nos groupes de nourrissons de 3 à 12 mois. Par ailleurs, bien qu'une augmentation de l'amplitude de cette composante attentionnelle ait été observée, il est possible que la nature sociale et linguistique des stimuli employés dans ces études facilite la réponse neuronale chez ces nourrissons. Enfin, il n'est pas à exclure que le nombre d'essais limité des 3 à 12 mois, relié à la contamination du signal par des artéfacts de mouvements du bébé lors de l'expérimentation, puisse avoir affecté le rapport signal-bruit de nos données, réduisant ainsi notre habileté à détecter des différences entre les conditions AV et (A+V).

4.2.4 Intégration AV tributaire du développement de l'audition et de la vision

La littérature ainsi que nos résultats confirment une maturation tardive des processus d'intégration AV. Cette séquence développementale des capacités d'IMS concorde avec la chronologie développementale anatomique et fonctionnelle du cerveau en soi. Il est possible que le développement tardif des mécanismes d'intégration soit tributaire du développement et de la maturation de chacun des sens notamment les organes sensoriels, le raffinement du fonctionnement cérébral ainsi que les expériences de vie individuelles. Tel que présenté dans l'introduction de cette thèse, les différents sens ne se développent pas tous au même rythme et possèdent des vitesses de maturation neuroanatomique et fonctionnelle distinctes qui se raffinent au cours de l'enfance et de l'adolescence. En effet, le développement sensoriel du fœtus suit une séquence temporelle fixe voyant apparaître d'abord les structures auditives suivi par le système visuel (Gottlieb, 1971). De même, la myélinisation progressive, les changements dans la densité synaptique et dans l'activité métabolique des systèmes visuel et auditif corticaux et sous-corticaux représentent un parcours s'échelonnant sur une dizaine d'années pouvant durer jusqu'à la fin de l'enfance (Lippé, Kovacevic, & McIntosh, 2009; Kozma, Kovács, & Benedek, 2001; Moore & Linthicum, 2007). De plus, d'un point de vu neuronal, le développement des réponses en PÉs présente des différences morphologiques notamment au niveau de la latence et de l'amplitude retrouvées autant dans le système auditif que visuel (Brecelj, 2003; Lenassi, Likar, Stirn-Kranjc, & Brecelj, 2008; Lippé, Roy, Perchet, & Lassonde, 2007; Paquette et al., 2013; Wunderlich et al., 2006) de la petite enfance à l'âge adulte. De même, bien que certaines habiletés visuelles et auditives apparaissent au cours des premiers mois de vie, le niveau de complexité du traitement visuel et auditif se raffine et poursuit son développement au cours de l'enfance et de l'adolescence. Par exemple, la sensibilité aux contrastes et la perception du mouvement et des formes complexes s'améliorent au cours des premières années, mais se prolongent et n'atteindront un niveau adulte qu'en début de l'adolescence soit vers 11-12 ans (György Benedek, Benedek, Kéri, & Janáky, 2003; Ellemberg et al., 2003; Kovacs, Kozma, Feher, & Benedek, 1999). Ainsi, le cerveau doit continuellement calibrer et adapter sa circuiterie neuronale afin de tenir compte des changements associés au développement normal de chacun des systèmes sensoriels. L'émergence des habiletés d'intégration AV peut ainsi être tributaire du développement respectif des sens de l'audition et de la vision.

4.2.5 Signature neuronale de l'intégration AV

Depuis les années trente, plusieurs travaux se sont penchés sur l'étude des changements développementaux de l'EEG au repos (Lindsley, 1938; Smith, 1939). Au cours de l'enfance, le tracé EEG est caractérisé par sa transformation progressive dans le temps traduisant les différentes étapes de maturation cérébrale. L'évolution de l'électrogénèse apparaît ainsi être une mesure pertinente pour apprécier la maturation chronologique des processus d'IMS.

En sus de sa prépondérance dans le tracé EEG spontané au cours de l'enfance, l'activité oscillatoire en thêta est également associée à la mobilisation des ressources attentionnelles et à l'encodage de nouvelles informations sensorielles (Gevins & Smith, 2000; Jaušovec & Jaušovec, 2004; Klimesch, 1997; Orekhova, Stroganova, & Posikera, 1999). Dans notre étude, les enfants âgés entre 2 et 7 ans ont démontré une augmentation de la puissance neuronale spécifique à la bande thêta suite à la présentation des stimuli AV, pouvant refléter la demande attentionnelle soutenue nécessaire pour traiter cette information (Jensen, Gelfand, Kounios, & Lisman, 2002). De la même façon, les jeunes de 11-14 ans ont également présenté une différence de puissance d'activation significative en thêta entre les conditions AV et (A+V).

De manière intéressante, aucune différence de puissance neuronale significative entre les conditions AV et (A+V) n'a été observée dans la bande thêta chez les enfants de 8 à 10 ans. Étant donné la prédominance des ondes thêta durant l'enfance (Clarke et al., 2001; Somsen et al., 1997, l'absence de résultats significatifs chez nos 8-10 ans était inattendue, mais pourrait refléter davantage une variabilité individuelle dans le signal EEG résultant de changements morphologiques et fonctionnels cérébraux importants survenant à la puberté

(Giedd et al., 1999). Sur le plan fonctionnel, entre les âges de 8 et 11 ans, les ondes thêta et alpha atteignent un point de croisement où la prédominance en thêta laisse tranquillement sa place aux ondes alpha (Somsen et al., 1997). Ces changements fonctionnels sont sous-tendus par des changements anatomiques, tels que la myélinisation croissante des fibres de matière blanche. À ce titre, il ressort de la littérature que la progression développementale de la maturation de la matière grise suit une courbe en « U » inversée, dont les pics de croissance du volume total surviennent entre 7 et 11 ans (Gogtay & Thompson, 2010; Thatcher, 1994). Nos résultats illustreraient ainsi la phase de transition caractéristique de cette tranche d'âge résultant probablement de changements de maturation dans les bandes de fréquences. Cette absence de différence significative retrouvée entre les deux conditions dans les bandes thêta et alpha illustrerait cette phase de transition plutôt que de suggérer une incapacité des enfants de 8-10 ans à traiter l'information multisensorielle. D'ailleurs, il est intéressant de constater que dans leur étude en EEG, Brandwein et all. (2011) ont également suggéré la présence d'une phase de transition entre les âges de 10 et 12 ans. En effet, c'est entre 10-12 ans qu'une différence d'amplitude s'installe entre les réponses PÉs AV et (A+V) sans toutefois que celle-ci n'atteigne un seuil significatif à cet âge (Brandwein et al., 2011).

Fait intéressant, en plus d'afficher une puissance d'activation plus importante en thêta suite à la présentation des stimuli AV, les 11-14 ans ont également présenté une puissance d'activation plus importante en alpha. Des travaux antérieurs sur la maturation cérébrale ont rapporté des changements graduels dans la puissance spectrale EEG entre 5 et 12 ans (Somsen et al., 1997). En effet, certains auteurs suggèrent que l'activité de basses fréquences est graduellement remplacée par l'activité de fréquences plus élevées (Marshall, Bar-Haim, & Fox, 2002; Somsen et al., 1997; Stroganova et al., 1999; Whitford et al., 2007). D'ailleurs, de la petite enfance jusqu'à la puberté, la littérature fait état d'une diminution progressive de l'activité des basses fréquences (delta, thêta) et d'une augmentation de l'activité des hautes fréquences (alpha, bêta, gamma) lors de la maturation cérébrale (Harmony et al., 1990; Klimesch, Sauseng, & Hanslmayr, 2007; Somsen et al., 1997; Yordanova et al., 2002). En lien avec la littérature, nos données suggèrent ainsi que cette augmentation de l'alpha avec l'âge est étroitement reliée à la maturation cérébrale et au développement des habiletés de traitement sensoriel et cognitives. De manière similaire à nos résultats, Brandwein et collaborateurs (2011) ont également observé une réponse explicite d'intégration AV à partir de l'âge de 13 ans.

De plus, nos résultats ont également démontré une augmentation de la puissance neuronale exclusivement en alpha suite à la présentation de stimuli AV chez les adolescents de 15-17 ans et les adultes. Il n'est pas étonnant d'observer une telle réponse dans cette bande étant donné la prédominance de l'activité alpha dans le tracé EEG spontané de l'adulte (Stroganova et al.,1999). D'ailleurs, certains travaux chez les adultes rapportent une augmentation de l'activation en alpha 250 ms suite à la présentation d'une stimulation sensorielle (Başar & Schürmann, 1996; Erol, 1999; Schürmann et al., 1997). Par ailleurs, d'autres études rapportent une augmentation de l'activation en alpha enregistrée dans les régions frontales durant les processus d'imagerie mentale, d'associations libres ainsi que lors des tâches faisant appel à des processus d'idéation et de créativité (*creative ideation*) (Benedek, Bergner, Könen, Fink, & Neubauer, 2011; Cooper, Burgess, Croft, & Gruzelier, 2006; Von Stein & Sarnthein, 2000). Étant donné la facilité et la passivité de notre tâche, il n'est également pas à exclure que les adolescents et les adultes se soient engagés dans une forme d'autostimulation cognitive. Par exemple, un participant adulte nous mentionne avoir imaginé un chat sur le bruit blanc présenté entre chaque stimulus.

Enfin, notre étude n'a révélé aucune différence significative entre la condition AV et (A+V) dans les bandes bêta et gamma, et ce, pour tous les groupes d'âges. Un certain nombre d'études en EEG chez l'adulte ont observé une augmentation de l'activation en bêta et en gamma lors de tâches d'intégration AV (Sakowitz et al., 2001, 2005; Senkowski, Molholm, et al., 2005). Contrairement à notre recherche, ces études requéraient une réponse motrice de la part des participants, associée à l'activation en bêta, (Jenkinson & Brown, 2011; Liang, Bressler, Ding, Truccolo, & Nakamura, 2002; Pfurtscheller, Graimann, Huggins, Levine, & Schuh, 2003; Senkowski, Molholm, et al., 2005) et sollicitaient des processus cognitifs de plus haut niveau tels que la mémoire ou le langage associés à l'activation en gamma (Bastiaansen & Hagoort, 2006; Busch, Groh-Bordin, Zimmer, & Herrmann, 2008; Kaiser & Lutzenberger, 2005). Ainsi, l'absence de différence significative entre les conditions AV et (A+V) s'explique possiblement par la simplicité des stimuli employés ainsi que la passivité de la tâche. L'absence de différence significative entre les deux conditions dans les bandes bêta et gamma peut également s'expliquer par la rapidité de leur signal oscillatoire. En effet, les activités de ces hautes fréquences ont plus facilement tendance à être déphasées d'un essai à l'autre et se sont potentiellement annulées lors du grand moyennage de l'activité évoquée. L'analyse de l'activité induite par les stimulations sensorielles pourrait contourner cet aspect en révélant de l'information supplémentaire sur le patron de maturation des processus d'intégration AV.

4.3 Limites des études et avenues de recherches futures

4.3.1 Étude transversale

Si notre étude expérimentale a fait appel à un devis transversal, un devis longitudinal aurait été le choix d’étude à privilégier afin d’examiner la trajectoire développementale de l’intégration AV dans le temps. En effet, il aurait été idéal de sélectionner un groupe de nouveau-nés et de les suivre jusqu'à l'âge adulte en effectuant annuellement des mesures EEG. Un devis longitudinal permettrait d’identifier clairement ce qui relève, dans l'évolution des réponses EEG, de l'effet de l'âge tout en contrôlant l’effet de la variabilité interindividuelle et de la génération. Par exemple, à âge égal, des personnes nées à des périodes différentes peuvent avoir des caractéristiques très dissemblables. En termes de variabilité interindividuelle, la littérature a notamment démontré une influence génétique et du sexe sur les mécanismes neuronaux générant l’activité des différentes bandes de fréquences (Hughes et al., 2011; Steriade and Timofeev, 2003). Bien qu’il soit idéal pour documenter la trajectoire développementale de l’intégration AV, le devis longitudinal pose certains défis majeurs sur le plan pratique et méthodologique notamment quant au taux d’attrition des participants ainsi que sur la faisabilité d’un tel projet à long terme dans le cadre d’une thèse doctorale.

4.3.2 Utilisation d’une plage fréquentielle fixe

Comme plusieurs études, la méthodologie de notre recherche (article 2) repose sur l’utilisation d’une plage fréquentielle fixe définissant chacune des bandes de fréquences soit thêta, alpha, bêta et gamma. Ainsi, nous avons sélectionné une plage fréquentielle fixe pour définir chaque bande (4-7 Hz pour thêta, 8-14 Hz pour alpha, 15-29 Hz pour bêta et 30-50 Hz pour gamma; Klimesch et al., 2007) dans un intervalle de temps prédéfini (100-300 ms) que nous avons ensuite appliqué à chaque participant. Cette méthodologie nous a permis de détecter des différences significatives entre les deux conditions (AV et [A+V]) et, par le fait même, de mesurer les effets associés à la signature neuronale de l'intégration AV. Certains chercheurs suggèrent toutefois que l'utilisation d'une bande fréquentielle de largeur fixe pour définir le niveau d'activation neuronale est susceptible de diminuer la sensibilité expérimentale et d'accroître les risques d'erreur (Klimesch et al., 1993; Bazanova & Aftanas, 2008; Kaiser, 2001; Bazanova, 2010; Segrave et al., 2011). Il a été allégué qu'une évaluation plus précise de la puissance d'activation oscillatoire reliée aux conditions (AV et [A+V]) devrait s'appuyer sur la sélection d'une bande de fréquences déterminée individuellement (Bazanova, 2010).

Ceci étant dit, il est possible que l'utilisation d'une plage fréquentielle fixe puisse voiler le pic d'activation « réel » en thêta, alpha, bêta ou gamma, masquant ainsi les fines modifications associées aux processus d'intégration AV en fonction de l'âge. Ainsi, il aurait été intéressant d'employer une mesure d'IMS encore plus spécifique à chaque participant en se reposant sur l'activation maximale dans chacune des bandes propre à chaque individu. L'obtention de la valeur d'activation maximale associée à l'intégration AV peut s'effectuer en identifiant la moyenne autour du pic d'activation maximale (environ 50 ms autour du pic) de chaque participant. En plus d'augmenter la spécificité de la mesure des capacités d'intégration, l'utilisation du pic individuel permettrait de connaître le niveau de maturité de l'intégration AV propre à chaque participant. Par exemple, un enfant de 11 ans pourrait avoir un niveau d'activation en alpha de 12 Hz tandis qu'un autre du même âge pourrait n'avoir qu'un niveau d'activation en alpha de 8 Hz.

Par ailleurs, il serait intéressant d'étudier les capacités d'IMS dans une approche multisystémique en combinant et appuyant cette mesure neuronale par l'administration d'épreuves neuropsychologiques sollicitant les capacités d'intégration, notamment le test d'intégration visuomotrice du Beery VMI et des tests évaluant la correspondance graphème-phonème (BALE, Odédys). Une analyse de corrélation entre les valeurs individuelles de pic d'activation et les scores neuropsychologiques nous permettrait, par exemple, d'associer la puissance d'activation en alpha aux scores pondérés des épreuves neuropsychologiques.

4.3.3 Complémentarité des techniques de neuroimagerie

De façon générale, le compromis spatio-temporel entre l'EEG et l'IRMf a mené, d'une part, à l'utilisation de l'EEG comme principal outil pour étudier *quand* les processus d'intégration surviennent et, d'autre part, à l'utilisation de l'IRMf pour étudier *où* les interactions multisensorielles prennent place dans le cerveau. Bien qu'une localisation précise ne soit pas possible avec la technique d'EEG, la topographie des activations neuronales obtenues dans notre étude suggère une contribution des régions fronto-centrales, telle que révélée par le test-*t* topographique employé dans l'article 2 (voir Figure 2 dans l'article). Comme nous l'avons vu dans la section 1.3.2.3, des études chez l'animal et l'homme adulte ont notamment mis en évidence le rôle des cortex préfrontal (Bushara et al., 2001; Paraskevopoulos et al., 2012) et cingulaire antérieur (Benoit et al., 2010; Laurienti et al., 2003) lors de l'intégration d'informations AV non linguistiques. Bien qu'une localisation précise ne soit pas possible avec la technique d'EEG, la topographie des activations neuronales obtenues dans notre étude suggère une contribution des régions fronto-centrales, telle que révélée par le test-*t* topographique et l'analyse de régression linéaire employés dans l'article 2 (voir Figure 2 dans l’article). Comme nous l’avons vu dans la section 1.3.2.3, des études chez l’animal et l’homme adulte ont notamment mis en évidence le rôle des cortex préfrontal (Bushara et al., 2001; Paraskevopoulos et al., 2012) et cingulaire antérieur (Benoit et al., 2010; Laurienti et al., 2003) lors de l’intégration d’informations AV non linguistiques. Ainsi, l’augmentation de la puissance d’activation obtenue en fronto-central suite à la présentation d’un stimulus AV peut également provenir d’une augmentation de la synchronie temporelle entre les assemblées neuronales de différentes régions cérébrales, plus ou moins distantes les unes des autres, pour parvenir à un percept unifié. D’ailleurs, la littérature a mise en évidence l’existence de réseaux distribués lors de l’étude des processus multisensoriels (Ghazanfar & Schroeder, 2006). En effet, des interactions ascendantes, descendantes et latérales entre le cortex frontal, les régions temporo-pariétales aisni que les cortex unisensoriels ont été relevés dans plusieurs études (Driver & Spence, 2000; Foxe & Schroeder, 2005; Kayser & Logothetis, 2007). L’étude de la cohérence neuronale pourrait préciser la contribution de diverses régions cérébrales dans l’intégration AV (Senkowski et al., 2008) et en documenter l’évolution en fonction du développement.

De plus, afin de mieux préciser les caractéristiques spatiales reliées à la progression développementale de l’intégration AV parmi les groupes d'âge, de futures études pourraient procéder à des analyses de sources sur les données électrophysiologiques ou utiliser la neuroimagerie en concomitance avec notre tâche d'intégration. La question concernant quelles régions cérébrales sont impliquées dans l’intégration d’informations AV non linguistiques chez le nourrisson et si celles-ci changent ou non au cours du développement, demeure largement sous-explorée. Ce manque de recherche découle probablement, en partie, d’une difficulté à appliquer les techniques de neuroimagerie à haute résolution spatiale auprès de la population pédiatrique. Toutefois, de nouvelles méthodes émergentes telles que la spectroscopie proche infrarouge (NIRS), technique employée dans notre laboratoire (Gallagher, 2013; Gallagher, Tremblay, & Vannasing, 2016; Lassonde et al., 2011), ainsi que les développements technologiques reliés à l'application de la NIRS aux enfants pourraient permettre de répondre à ces questions dans le futur.

Enfin, il serait d'intérêt d'aborder la question de la multisensorialité chez les aînés (Diederich, Colonius, & Schomburg, 2008), mais à notre connaissance, seules des études de facilitation multisensorielle ont été effectuées. Nous proposons ici d'utiliser dans de prochaines recherches des tâches de stimulation AV telles que celle employée dans notre étude. La connaissance du parcours développemental de la modification de l'intégration des sens dans la population gériatrique pourrait en effet compléter le tableau des processus d'intégration AV à travers les différentes étapes de la vie.

4.3.4 Impacts cliniques de l'IMS dans les troubles neurodéveloppementaux

Nous percevons et interprétons chacun les informations sensorielles de façon unique selon nos récepteurs, notre seuil de tolérance, nos émotions, notre capacité à moduler les informations ainsi que nos expériences antérieures (Anzalone & Lane, 2011). Les différences individuelles et la nature subjective du traitement de l'information sensorielle ne constituent cependant pas d'emblée un problème. Il s'agira d'un trouble lorsque ces différences au niveau du traitement sensoriel produisent des réponses non adaptées à l'environnement et entravent le fonctionnement ainsi que la participation d'une personne à ses occupations quotidiennes

(Miller, Anzalone, Lane, Cermak, & Osten, 2007). Tel que mentionné dans notre revue de la littérature, il a été démontré que plusieurs conditions neurodéveloppementales telles que le TSA, la dyslexie, le TDA/H s'accompagnent souvent de déficits sensoriels et d'une inefficacité à intégrer l'information multisensorielle (Bao et al., 2017; Benn, 2017; Collignon et al., 2013; Fransisco et al., 2017; Ghanizadeh, 2011; Ye et al., 2017) lesquels peuvent découler d'altérations anatomiques et fonctionnelles des régions cérébrales dédiées au traitement de l'information multisensorielle (Blau et al., 2010; Simos et al., 2000; Shaywitz et al., 1998; Stevens et al., 2009; Tian et al., 2008; Yeo et al., 2003; Zilbovicius et al., 2006).

À titre d'exemple, revoyons la situation de la dyslexie discutée dans notre revue de la littérature (article 1). Un traitement temporel atypique de l'information AV est une hypothèse en cause proposée pour expliquer certaines difficultés de langage écrit qu'éprouvent les dyslexiques. Par exemple, Harinston et collaborateurs (2005) ont démontré que même lorsque le stimulus auditif intervient très tardivement (350 ms) après le stimulus visuel, il facilite la performance d'enfants dyslexiques dans une épreuve de jugement d'ordre temporel, prouvant qu'ils ont une fenêtre d'intégration plus étendue (Hairston, Burdette, Flowers, Wood, & Wallace, 2005). Pour illustrer ce propos, un élargissement anormal de la fenêtre de temps pourrait affecter les processus associés au couplage rapide et précis de deux informations provenant de modalités différentes, par exemple, ceux mis en jeu lors de la conversion de graphèmes en phonèmes. Conséquemment, ceci pourrait conduire à des erreurs de transcodage, occasionnant une production d'erreurs accrue en lecture ainsi qu'un ralentissement dans la vitesse de lecture. Cet exemple illustre bien l'importance des habiletés à traiter les informations multisensorielles dans les fonctionnements perceptuel, comportemental et cognitif. La question n'est pas tant de savoir si l'IMS explique ou non certains troubles neurodéveloppementaux que de constater la concomitance des déficits sensoriels dans ces conditions.

Secondée par la littérature (Barutchu et al., 2009; Brandwein et al., 2011), notre étude (article 2) illustre l'émergence progressive du développement des capacités à intégrer les informations AV dont la maturation semble survenir entre les âges de 15 et 17 ans. Cette période de maturation prolongée nous permet de supposer qu'il existe une période de temps optimale au cours de laquelle il pourrait être opportun de stimuler les fonctions multisensorielles. D'ailleurs, l'implantation de programmes d'entraînement multisensoriel pourrait soutenir le développement des précurseurs à l'IMS pour minimiser l'impact de tels déficits dans le fonctionnement des individus présentant des troubles neurodéveloppementaux.

Il a été démontré que l'information multisensorielle vient faciliter les apprentissages (Jordan & Baker, 2011; Joshi, Dahlgren, & Boulware-Gooden, 2002) et moduler l'attention des enfants (Bahrick et al., 2002; Bahrick & Lickliter, 2000; Gogate & Bahrick, 1998; Richardson & Kirkham, 2004), et qu'un environnement multisensoriel enrichi peut stimuler le développement neuronal, améliorant les capacités de traitement sensoriel de l'enfant (Reynolds, Lane, & Richards, 2010). Une prise en charge adaptée et une participation précoce à des programmes d'entraînement multisensoriel rehausserait ainsi la qualité de vie des enfants présentant des troubles neurodéveloppementaux et souffrant de déficits sensoriels.

5. CONCLUSION GÉNÉRALE

En conclusion, la présente thèse a permis de faire état des connaissances et de mettre en lumière le débat inné-acquis portant sur le développement des capacités d’IMS. Ainsi, le premier article de cette thèse documente la capacité précoce du nourrisson à traiter des informations multisensorielles de bas niveau où cette capacité s’appuie sur le développement progressif des habiletés à combiner et intégrer des informations multisensorielles de complexité croissante qui se raffinent et s’améliorent jusqu’à l’adolescence.

Le deuxième article de cette thèse a permis de caractériser la progression développementale neurotypique des mécanismes d’intégration AV dès 3 mois jusqu’à l’âge adulte et d’exposer l’âge auquel ces mécanismes atteignent leur maturité. À notre connaissance, il s’agit de la toute première étude électrophysiologique de cette ampleur à caractériser l’émergence progressive du développement des capacités à intégrer les informations AV grâce à l’utilisation des analyses temps-fréquence combinée à la couverture d’une plage d’âges étendue. En effet, nos résultats ont permis d’identifier des précurseurs de l’intégration AV dès l’âge de 2 ans dont la maturation des mécanismes d’intégration AV semble survenir entre les âges de 15 et 17 ans. Les résultats de notre étude appuient la littérature quant à la présence d’une séquence développementale des habiletés à traiter et intégrer l’information multisensorielle et se veut une réponse à l’absence de littérature sur la progression développementale de la réponse neuronale de l’intégration AV chez le nourrisson et l’enfant d’âge préscolaire.

L’établissement d’une telle trajectoire permet de mieux comprendre les mécanismes cérébraux sous-jacents à cette capacité chez les enfants neurotypiques et sert de point d’ancrage pour étudier la progression développementale des enfants présentant des troubles neurodéveloppementaux qui s’accompagnent fréquemment de problèmes sensoriels. La période de maturation prolongée de l'intégration AV nous permet de supposer qu'il existe un intervalle de temps optimal au cours duquel il pourrait être opportun de stimuler les fonctions multisensorielles. Un tel constat confirme ainsi la pertinence d'intervention précoce auprès d'enfants présentant des déficits sensoriels en participant notamment à des programmes d'entraînement multisensoriel.

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ANNEXES

Annexe 1

Voice Perception in Newborns and Infants

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Voice perception in newborns 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

Tableau 1. Nombre total de pauses prises lors de l'enregistrement EEG pour chaque groupe d'âge.

Groupes	**Adultes**	**15-17 ans**	**11-14 ans**	**8-10 ans**	**5-7 ans**	**2-4 ans**	**6-12 mois**	**3-6 mois**
Pauses	19	12	20	17	30	43	46	52
Durée totale de l'administration	11 minutes							

Annexe 3

Tableau 2. Nombre moyen d'essais retenu sur l'électrode FCz par condition (Audiovisuelle : AV, Visuelle : V, Auditive : A) et pour l'ensemble des groupes d'âge. Un total de 175 essais par condition a été administré.

Groupes		**Adultes**	**15-17 ans**	**11-14 ans**	**8-10 ans**	**5-7 ans**	**2-4 ans**	**6-12 mois**	**3-6 mois**
Condition AV	Moyenne	101	99	103	108	97	80	42	35
	Écart-type	4	11	9	19	35	28	24	25
Condition A	Moyenne	105	101	108	108	98	81	43	32
	Écart-type	9	7	10	21	28	25	27	23
Condition V	Moyenne	104	96	106	108	101	81	43	37
	Écart-type	12	9	10	20	32	24	25	24