



Anatomo-functional correlates of visual and auditory development: insights on the ontogeny of face and speech processing lateralization

Parvaneh Adibpour

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Thèse de doctorat
de l'université Pierre et Marie Curie
Spécialité Neurosciences Cognitives

Présentée par
Parvaneh Adibpour

**Anatomo-functional correlates of visual and auditory development:
insights on the ontogeny of face and speech processing lateralization**

Thèse soutenue le 17 Octobre 2017

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Abstract

Several cognitive functions, such as language processing, handedness, and face recognition, are lateralized in the adult human brain. The ontogeny of these functional asymmetries is still poorly understood, raising interest in studying whether they are present early on during development. To approach this issue, we attempted to map and compare the hemispheric responses in the infant brain. In particular, we aimed to evaluate the neural substrates of face and speech processing nested in the visual and auditory networks using non-invasive neuroimaging techniques and lateralized presentation of stimuli in infants.

First, we studied how the functional and structural characteristics of these two brain systems change over the first six months after birth. With event related potentials (ERP), we showed major age-related decreases in the latency of brain responses, both for early responses (visual P1 and auditory P2) and for inter-hemispheric transfer (visual P1). Using diffusion magnetic resonance imaging (MRI), we observed significant changes in myelination indices for both the visual and auditory white matter pathways. Above these relationships to infants' age, we further demonstrated that the conduction speed of visual responses is related to the maturation of underlying tracts conducting these responses. In the auditory system, we failed to establish similar structure-function relationships, suggesting that the contribution of other pathways and cortical maturation should be further considered.

In parallel, we studied the hemispheric lateralization of face processing abilities using a discrimination paradigm of faces presented in each hemifield. Based on N290 and P400 responses in the infant ERP, we first observed that only the right hemisphere, and not the left, was able to discriminate between novel and frequently presented faces. When the frequently presented face from one side appeared on the opposite hemifield, no discrimination response was raised. We suggest that this observation is related to the transfer of face-relevant information across hemispheres.

Finally, we studied the lateralization of speech processing abilities in infants. When syllables were presented binaurally, we observed a trend for higher amplitude of P2 responses in the left relative to the right hemisphere. When syllables were presented monaurally, responses tended to be of higher amplitude and shorter latency in the contra- versus ipsi-lateral hemisphere. Ipsilateral responses were particularly delayed on the left side in typical infants but not in infants with corpus callosum agenesis, suggesting an asymmetric transfer of responses mediated by callosal fibers.

In summary, our studies highlight the potential of complementary neuroimaging approaches to study the infant brain and suggest differences in the development of visual and auditory systems and their processing biases. We also underscored the role of the corpus callosum, its protracted development, and the asymmetrical transfer of auditory information that may contribute to the reinforcement of a left-hemispheric bias for speech processing

Résumé

Plusieurs grandes fonctions cognitives, comme le traitement du langage, la manualité et la reconnaissance des visages, sont latéralisées dans le cerveau de l'humain adulte. Alors que l'origine de ces asymétries fonctionnelles reste encore méconnue, il apparaît fondamental d'en étudier le développement. Dans ce contexte, nous avons essayé d'identifier et comparer les réponses hémisphériques dans le cerveau du bébé. Pour cela, nous avons cherché à évaluer les substrats neuronaux du traitement du visage et du langage imbriqués dans les réseaux visuels et auditifs grâce à des techniques de neuroimagerie non invasives et une présentation latéralisée des stimuli chez les nourrissons.

Premièrement, nous avons étudié comment les caractéristiques fonctionnelles et structurelles de ces deux systèmes cérébraux changent au cours des six premiers mois après la naissance. Avec les potentiels évoqués, nous avons constaté des diminutions majeures de la latence des réponses cérébrales en fonction de l'âge, tant pour les réponses précoces (P1 visuel et P2 auditif) que pour le transfert interhémisphérique (P1 visuel). À l'aide de l'imagerie par résonance magnétique (l'IRM) de diffusion, nous avons observé des changements significatifs dans les indices de myélinisation pour les voies visuelles et auditives de la matière blanche. En plus de ces effets liés à l'âge des nourrissons, nous avons également démontré que la vitesse de conduction des réponses visuelles est liée à la maturation des faisceaux de fibres de substance blanche conduisant ces réponses. Dans le système auditif, nous n'avons pas pu observer de relation structure-fonction équivalente, ce qui suggère que la contribution d'autres voies ainsi que la maturation corticale devraient être étudiées en perspective.

Parallèlement, nous avons étudié la latéralisation hémisphérique du traitement des visages grâce à un paradigme de discrimination des visages présentés dans chaque hémichamp. Sur la base des réponses N290 et P400 en potentiels évoqués chez le nourrisson, nous avons d'abord observé que seul l'hémisphère droit, et non le gauche, a pu discriminer les nouveaux visages de ceux fréquemment présentés. En revanche, nous n'avons observé aucune réponse de discrimination lorsque le visage fréquemment présenté d'un côté est apparu dans l'hémichamp opposé. Nous suggérons que cette observation est due au transfert d'informations pertinentes au visage entre les hémisphères.

Enfin, nous avons étudié la latéralisation du traitement de la parole chez le nourrisson. Nous rapportons une tendance à une plus grande amplitude P2 dans l'hémisphère gauche par rapport à l'hémisphère droit en réponse à des syllabes présentées de manière binaurale. En réponse à des syllabes présentées de manière monaurale, les amplitudes évoquées ont tendance à être plus élevées, avec une latence plus courte dans l'hémisphère contralatéral versus ipsilatéral. Nous rapportons des réponses ipsilatérales particulièrement retardées dans l'hémisphère gauche chez les nourrissons typiques, mais pas chez les nourrissons avec agénésie du corps calleux, ce qui suggère un transfert asymétrique des réponses via les fibres du corps calleux.

En résumé, nos études mettent en évidence le potentiel des approches complémentaires en neuroimagerie pour étudier le cerveau du nourrisson et suggèrent des différences dans le développement des systèmes visuels et auditifs et leurs biais de traitement. Nous avons également souligné le rôle du corps calleux, son développement lent et le transfert asymétrique de l'information auditive qui peut contribuer au renforcement d'un biais hémisphérique gauche pour le traitement de la parole.

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List of abbreviations

aCC Auditory fibers of Corpus Callosum
AF Arcuate Fasciculus
AgCC Agenesis of Corpus Callosum
AR Acoustic Radiations
DTI Diffusion Tensor Imaging
EEG Electroencephalography
EC External Capsules
EmC extreme Capsule
ERP Event Related Potentials
FA Fractional Anisotropy
fNIRS functional Near Infrared Spectroscopy
fMRI functional Magnetic Resonance Imaging
FFA Fusiform Face Area
HG Heschl's Gyrus
IFOF Inferior Fronto-Occipital Fasciculus
IHTT Inter-Hemispheric Transfer Time
LGN Lateral Geniculate Nucleus
LO Lateral Occipital cortex
MEG Magnetoencephalography
MGN Medial Geniculate Nucleus
MRI Magnetic Resonance Imaging
N170 face-sensitive adult's visual ERP component
N290 face-sensitive infant's visual ERP component
OR Optic Radiations
P1 First positive ERP component
P2 Second positive ERP component
P400 face-sensitive infant's visual ERP component
PET Positron Emission Tomography
PT *Planum Temporale*
SLF Superior Longitudinal Fasciculus
STS Superior Temporal Sulcus
TMS Transcranial Magnetic Stimulation
UF Uncinate Fasciculus
vCC Visual fibers of Corpus Callosum
<D> mean Diffusivity
 λ_{\perp} Transverse Diffusivity
 $\lambda_{||}$ Longitudinal Diffusivity

Chapter 1

Introduction

1. Introduction

Human way of inspecting the surrounding environment, acting on, and communicating with it, is unique in many aspects. Extensive amount of research has focused on understanding the neural mechanisms that support the human abilities. Accumulating evidence shows that the human brain is composed of several regions that are functionally specialized in performing a task or dealing with certain aspects of environmental inputs. These regions are similar across individuals with different cultural, linguistic, or socio-economic backgrounds, suggesting that the functional architecture of the human brain remains similar for the wide range of variability in the environmental inputs. They are not *isolated* with respect to the rest of the brain, but interact with other areas and send/receive information, through the connections between them, giving rise to functional circuitries and networks that have distributed regions.

The rationale behind these functionally specialized regions might be related to the speed and energy efficiency that they provide by relying on computations that are performed locally through spatially-close neuronal assemblies. **Hemispheric lateralization** is a special example of regional **functional specialization** in the brain, when certain computations remain preferentially localized in a region or a network of regions inside one hemisphere, instead of relying on neuronal assemblies across hemispheres that is limited by the timing constraints of the neural information transfer between hemispheres. It is important to note that these hemispheric lateralizations refer to hemispheric advantages rather than radical binary ability of a single hemisphere in performing a task. In the adult human brain, the existence of numerous anatomical and functional differences between the two hemispheres is supported by several *post-mortem*, behavioral and neuroimaging studies (Hugdahl & Westerhausen, 2010; Kimura, 1961; Toga & Thompson, 2003), and many functions such as handedness, language, face processing, visuospatial processing., etc. are biased toward one hemisphere. Yet, little is known about the **ontogeny** of these lateralized functions in the human brain.

The question on the ontogeny can be addressed, to some extent, by studying the infant brain, asking whether functional lateralizations and structural asymmetries are the properties of adult brain or if they are found early on as well. These questions are informative in two respects. First, infant brain provides the early machinery that facilitates the emergence of human abilities. Therefore, insights on the development of the functional lateralizations can help to understand which aspects of an early architecture, biases and constraints the architecture of the human brain to achieve its many abilities. Second, characterizing the normal development of lateralized functions is also informative for our understanding of the critical periods

and developmental outcomes. It becomes especially important, when we take into account the coincidence of developmental disturbances like dyslexia or autism spectrum disorder with abnormal lateralization for processing language or social stimuli such as faces.

With these questions in background, we aimed at investigating the neural correlates of face and language processing abilities, while studying the functional and structural characteristics of the visual and auditory development in the infant brain. This first chapter presents a context for our studies. Section 1.1 describes the main stages of early development and organization of the brain, with an attempt to illustrate which mechanisms can push this early architecture to develop lateralized functions. Sections 1.2 and 1.3 particularly focus on the emergence of language and face processing abilities. Starting from the description of the neural substrates of each function in the adult human brain, we will focus on their development early on. Section 1.4 attempts to review how hemispheric differences might interact with inter-hemispheric communications. Finally, section 1.5 contains the plan for the following chapters and the questions addressed in each chapter.

1.1. The developing human brain

Studying the human brain is especially difficult during the early developmental period. *Post-mortem* histological studies can only anatomically characterize the maturation of neural substrates and therefore lack functional significance. Behavioral studies also remain limited, not only because of the indirectness of their measures, but especially due to the limited behavioral output at this early stage. With the emergence of **non-invasive neuroimaging techniques**, the developing infant brain is now accessible, enabling a characterization of early neuronal circuitries and their maturation *in vivo*. These techniques provide information about both structural and functional development of the brain. Magnetic Resonance Imaging (MRI) provides a description of the structural development and maturation of the cerebral tissues based on their water content. A number of other techniques allow assessing the functional responsiveness of neural circuits through measuring brain electrical activity or metabolic activity. Electroencephalography (EEG) records the electrical field generated by the summation of post-synaptic potentials on the surface of the head and Magnetoencephalography (MEG) captures the magnetic field perpendicular to the generated electric field. Functional MRI (fMRI) and Near-Infrared Spectroscopy (fNIRS) measure changes in blood oxygenation related to neuronal assemblies' oxygen consumption and its vascular consequences. In the methodological appendix of this thesis, we describe in more details, the usefulness, technical

considerations and limitations of EEG and diffusion-MRI techniques when employed for studying infant population, as we used these approaches to perform the studies described in this thesis.

In section 1.1.1, we briefly review the main cellular, microscopic and macroscopic phenomena involved in the development and maturation of the brain. We then discuss their relevance for the emergence of functional maturation and hemispheric lateralizations in sections 1.1.2 and 1.1.3, respectively.

1.1.1. Micro- and macro- structural development of the human brain

Brain development extends over a long period, starting during gestation and continuing toward the end of adolescence, and is mostly intense in the prenatal and first years of postnatal life. It relies on several maturational mechanisms that occur asynchronously, i.e. different onsets, and with different rates across brain regions and time-courses of development (Brody et al., 1987; Yakovlev. & Lecours., 1967) .Formation and **maturation** of the cortical layers and white matter connections rely on a succession of cellular events, driven by **biological clocks** or entrained by the **sensory inputs**. Figure 1.1 illustrates a schematic of the sequential, yet over-lapping, occurrence of these events during development (Kostović & Judoš, 2015).

Developmental calendar of cellular and microstructural events involved in brain development

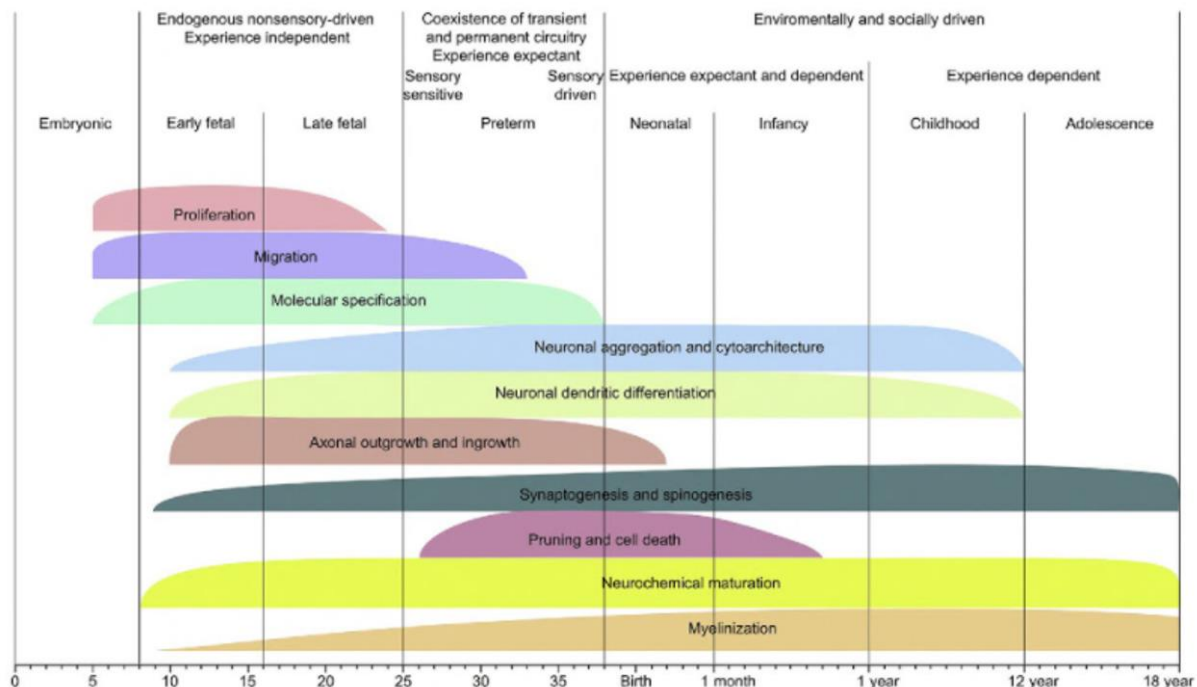


Figure 1.1. Developmental periods of occurrence and intensity of main neurogenetic events in cortical histogenesis. Note the predominance of proliferation and migration during the first trimester of gestation, growth of axons and dendrites during the second and third trimesters, and prolonged postnatal synaptogenesis, myelination and neurochemical maturation (Adapted from Kostovic and Judas., 2015).

We will first describe these cellular events, and then detail their relevance in the microscopic and macroscopic developmental changes that are measured in *post-mortem* histological (Figure 1.2) and *in vivo* neuroimaging studies (Figure 1. 3 to 1.5). To illustrate the developmental processes, we combine the insights from both type of studies, without distinguishing and detailing the methods.

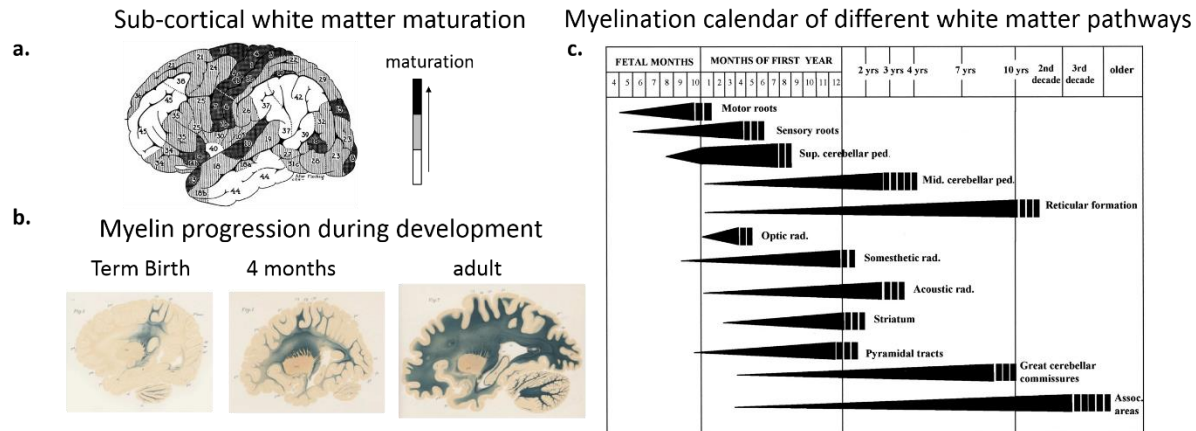


Figure 1.2. Development and maturation of gray and white matter over the course of development as revealed by post-mortem studies. Note the asynchronies across cortical regions and pathways. a) Maturation of white matter underneath cortical regions as an indicator of cortical maturation across regions (Adapted from Flechsig, 1901; 1920). The numbering of cortical regions indicates their maturation order. Darker areas are more mature than lighter areas. b) Myelin progression in developing brain. Note the progression gradient from the central to peripheral regions (Adapted from Flechsig, 1920). c) Cycles of myelination in the central nervous system during development. The width and the length of bars indicate progression in the intensity of staining corresponding to the density of myelinated fibers; the vertical stripes at the end of the graphs indicate approximate age range of termination of myelination estimated from comparison of the fetal and postnatal tissue with tissue from adults in the third and later decades of life (Adapted from Baumann & Pham-Dinh., 2001, originally adapted from Yakovlev & Lecours., 1967).

Development and maturation of cortex:

Neurons and glial cells are first produced during the embryonic period within two proliferative zones (Ventricular and Sub-Ventricular Zones). These neurons are then guided by the glial cells toward the brain periphery. They first reach the subplate zone, a transient layer underneath the future cerebral cortex that serves as a waiting compartment for the growing neurons (Pasko Rakic, 1972). The areal and laminar position of these **migrating neurons** are determined through signaling molecules secreted from patterning centers, i.e. commissural plate and cortical hem (O'Leary, Chou, & Sahara, 2007; Pasko Rakic, 1995), and their respective functional roles are further specified through the expression patterns of several genes (Bayatti et al., 2008; Wang et al., 2010). The cerebral cortex is progressively formed mostly in an inside-out manner, i.e. the last migrating neurons are settled in more superficial layers of cortex (Bystron, Blakemore, & Rakic, 2008; Rakic, 1995). Then the neurons are aggregated within the transient plates as well as in the cortical layers and form regions with specific cytoarchitectonic characteristics (Kostović & Judaš, 2015). Once neurons are in the cortical plate, their morphological characteristics (dendritic spines and axons),

start establishing (Mrzljak, Uylings, Kostovic, & van Eden, 1988; Petanjek, Judaš, Kostović, & Uylings, 2007) and cortical neural circuits are progressively formed. These circuits are first organized by **overproduction** of neuronal axons, dendrites, dendritic spines and also synapses and then refined and re-organized by processes like elimination of axons, later on with elimination of dendritic spines and synapses (Huttenlocher & Bonnier, 1991; Innocenti & Price, 2005; Petanjek et al., 2011). Following these events, myelination of intracortical axons that are not pruned occurs in two stages: first the proliferation and settlement of oligodendrocytes around the axons (Thomas et al., 2000) and secondly their spiral wrapping (Baumann & Pham-Dinh, 2001) and chemical maturation (Barkovich, Kjos, Jackson, & Norman, 1988; Poduslo & Jang, 1984).

Between the fetal period and term age, the intense cortical microstructural changes can be captured *in vivo* with diffusion MRI. The increasing branching of dendritic spines and synaptic density within the cortex at this period, make the diffusion of water molecules more isotropic, and affects diffusion MRI parameters that are sensitive to the directionality of water molecules (Ball et al., 2013; McKinstry et al., 2002). During post-term period, cortical maturation relies on myelination of intra-cortical axons on the top of the synaptogenesis and pruning of axons, dendritic spines and synapses. These changes are also reflected in signal contrasts of MRI parameters, allowing to distinguish different maturational stages (Figure 1.3) (Leroy et al., 2011), i.e. earlier maturation of primary and sensory cortices relative to the associative cortices as indicated in postmortem studies (Figure 1.2.a) (Flechsig, 1920; Yakovlev. & Lecours., 1967).

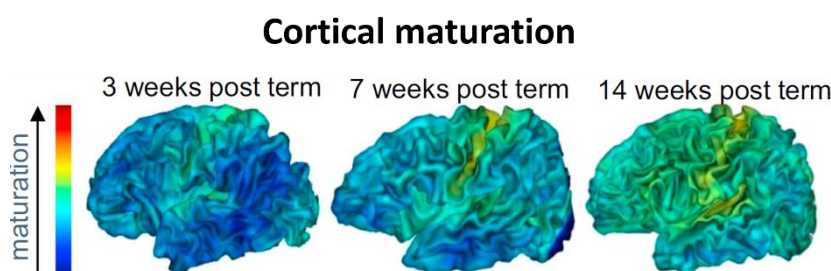


Figure 1.3. Structural imaging of cortical maturation. Asynchronous maturation of cortical regions between 3 and 14 weeks of age (Adapted from Leroy et al., 2011).

Development and maturation of connections:

The **axonal growth** produces transient connectivity patterns during the fetal period, particularly toward the subplate zone underneath the future cortex (Kostović, Judaš, Radoš, & Hrabač, 2002). This transient connectivity starts to relocate from the subplate to the cortical plate in the early preterm period.

The first connections from thalamus to cortical neurons are established during this period (Dubois, Kostovic, & Judas, 2015; Kostovic & Rakic, 1990). In addition to the thalamo-cortical connections, limbic and associative cortico-cortical connections progressively develop before term (Dubois, Kostovic, & Judas, 2015; Takahashi, Folkerth, Galaburda, & Grant, 2011). This development continues after term for short fibers connecting adjacent gyri (Kostović et al., 2014). Most of the developed connections include overproduced axons that are **pruned** after birth in interaction with the environmental inputs, refining the connectivity in parallel with the reorganization of cortical synaptic patterns (Innocenti & Price, 2005). The pruning of axons occurs most intensely in the first postnatal year, and probably continues more slowly afterwards (Kostović et al., 2014; Petanjek et al., 2011). Parallel to the pruning of the connections, connections also become functionally more efficient through **myelination** of the axons that are not subject to elimination. Myelination is most intense around the term age and in the first postnatal years (Brody et al., 1987; Yakovlev & Lecours., 1967). It accelerates the speed of neural information that travel through the axons (Baumann & Pham-Dinh, 2001; van der Knaap & Valk, 2005).

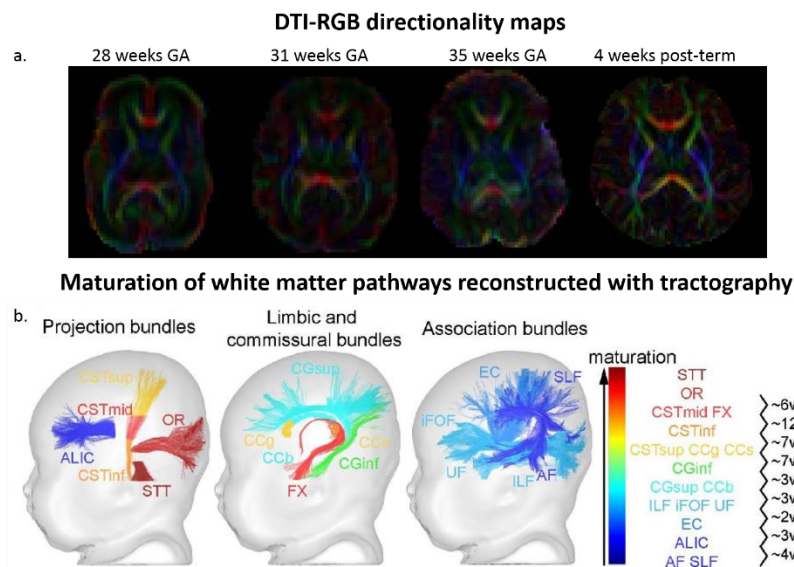


Figure 1. 4. Diffusion MRI of the developing white matter. a) DTI-RGB directionality maps of developing brain. Diffusion anisotropy increases as fibers become more compact and myelinated along development. b) The regional asynchrony in white matter maturation is highlighted in healthy infants using multi-parametric MRI. Projection, limbic, commissural and association bundles are ordered and colored according to their maturation, and maturational delays (in weeks) are computed between pairs of bundles (adapted from Dubois et al., 2015). Abbreviations: AF arcuate fasciculus; ALIC anterior limb of the internal capsule; CC corpus callosum (g/b/s genu/body/splenium); CG cingulum (inf/sup inferior/superior parts); CST cortico-spinal tract (inf/mid/sup inferior/middle/superior portions); EC external capsule; FX fornix; iFOF inferior fronto-occipital fasciculus; ILF inferior longitudinal fasciculus; OR optic radiations; SLF superior longitudinal fasciculus; STT spino-thalamic tract; UF uncinate fasciculus.

Mapping the establishment and microstructural maturation of connectivity for different pathways is possible through MRI, already from early preterm period (from ~24 gestational week onward). These

maps provide parameters that are sensitive to the coherence, compactness, density and myelination of fibers (Figure. 1.4.a) (Counsell et al., 2002; Deoni et al., 2012; Dubois et al., 2014; Hüppi et al., 1998) and can illustrate the **asynchronous myelination of different pathways** (Figure. 1.4.b) indicated by postmortem studies: It occurs earlier and faster in sensory than in motor pathways, in projection pathways (those connecting subcortical nuclei and cortical regions) than in associative ones, in proximal than distal pathways, in central regions than in peripheral ones, and in occipital lobe than in parietal, temporal and frontal lobes (Figure 1. 2.b and c)(Brody et al., 1987; Yakovlev & Lecours., 1967).

Morphological changes:

At the macroscopic level, a remarkable change is related to the **increase in the brain volume**. Cortical volume increases substantially before term age, from about 10 cm³ to 200 cm³ between the 21 – 40 weeks of gestational age (Kuklisova-Murgasova et al., 2011; Scott et al., 2011), and after term birth, from about 200 cm³ to 500 cm³ during the first two postnatal years (Gilmore et al., 2011; Knickmeyer et al., 2008). White matter volume also increases with development from about 50 cm³ to 150 cm³ between the 30– 40 weeks of gestational age (Kuklisova-Murgasova et al., 2011) and from about 150 cm³ to 200 cm³ during the first two postnatal years (Knickmeyer et al., 2008). This growth continues with a slower rate toward adolescence both for cortical areas and white matter (Groeschel, Vollmer, King, & Connelly, 2010; Shaw et al., 2008; Sowell et al., 2004).

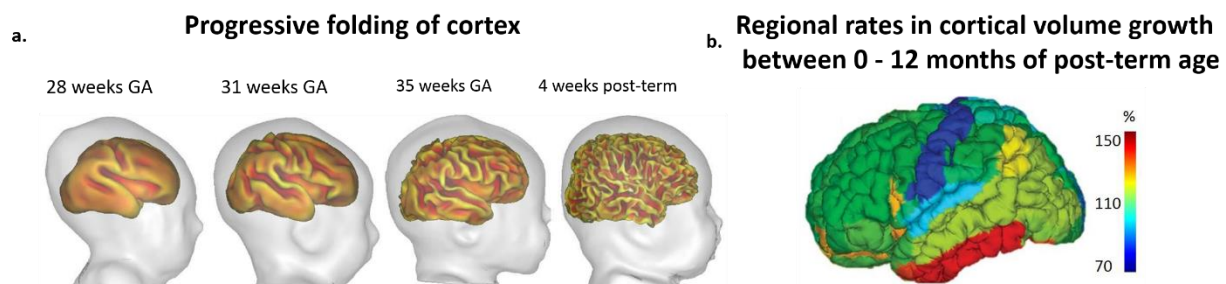


Figure 1.5. Structural imaging of cortical folding and growth. a) Inner cortical surfaces demonstrating the progressive folding and gyrification along development (Adapted from Dubois & Dehaene-Lambertz., 2015). b) Asynchronous cortical volume increase during the first post-natal year (Adapted from Gilmore et al., 2012).

Cortical volume increases asynchronously and with different rates across different regions and over different developmental periods. During the fetal period (20-28 weeks of gestation), the cortical volume increases more in the occipital and parietal regions compared to the frontal areas (Rajagopalan et al., 2011), whereas during the first two years of post-term period, it increases more rapidly in the visual ventral areas and frontal and parietal areas compared to the motor and sensory areas (Figure. 1.5.b) (Gilmore et al.,

2011). Parallel to the cortical and white matter volume growth, cortical folding and gyrification also occur sequentially for the primary, secondary and tertiary folds, and for the central, parietal, temporal, occipital and frontal gyri between the 20 weeks of gestational age and term age (Chi, Dooling, & Gilles, 1977; Dubois et al., 2008). At term, cortical gyrification is approximately adult-like (Hill et al., 2010) and changes much less significantly thereafter (Figure. 1.5.a).

The point of emphasis in all of the micro- and macro-structural maturational changes, is the **asynchrony** of occurrence onsets and rates across different regions and also developmental periods, suggesting that development of different brain networks follow very different trajectories.

1.1.2. Functional development

Parallel to the establishment and maturation of cortical circuits and structural connectivity, the activity arising from the emerging networks also changes. EEG recordings of neural activity progressively change from a **discontinuous pattern** at ~24 weeks of gestational age, recognized by sudden high-amplitude bursts of activity, to a more continuous pattern toward the term age (Lamblin et al., 1999; Wallois, 2010). Cortical evoked responses to sensory inputs such as sounds begin to appear in early preterm period, when thalamic afferents are relocating from the transient subplate zone to the cortical plate (Graziani et al., 1974). Myelination of fibers further decreases the latency of these sensory cortical evoked responses from the late preterm period toward infancy (Dubois et al., 2008; McCulloch, Orbach, & Skarf, 1999), referring to **increasing efficiency** of communication pathways.

Concurrent with these changes, fluctuations in the spontaneous neural activity of distant brain regions within a network also become more synchronized, and **functional connectivity** between these brain regions emerges. In infants, functional connectivity is often assessed during sleep with functional MRI. The first finger prints of emerging functional connectivity are found already during preterm period, highlighting regions and **resting state networks** that overlap with that of post-term period and partially with that of adults (Doria et al., 2010; Smyser et al., 2010; Thomason et al., 2014). Toward the term age, interhemispheric connectivity increases and different functional networks begin to get established (Doria et al., 2010; Fransson et al., 2009; Smyser et al., 2010; van den Heuvel et al., 2015). Yet, network measures suggest that cortical hubs, i.e. the key cortical regions interacting with many other regions and facilitating the functional integration across networks, may remain restricted to primary and sensory-motor cortices, suggesting that the functional architecture better supports basic perceptive and motor behaviors at this early stage (Fransson, Aden, Blennow, & Lagercrantz, 2010). The postnatal maturation of resting-state

functional networks continues asynchronously, showing a gradient from the primary sensorimotor/auditory networks, to the visual, default-mode and executive control networks (Gao et al., 2014; Gao et al., 2009).

In sum, several studies have highlighted the micro- and macro structural as well as the functional aspects of maturation in the infant brain that occur asynchronously across different regions and networks. What remains less investigated, is the **link between the structural and functional aspects of maturation**. We were interested in this question.

We intended to study the link between microstructural maturation of white matter pathways and functional efficiency of evoked responses for two brain networks with different developmental trajectories. We build on the rationality of a previous study in 1 to 4 months old infants, showing that the conduction speed of visual evoked responses was related more to the optic radiations (projection pathways) maturation than to the infants' age (Dubois et al., 2008). We aimed at replicating this result for projection pathways and extending them to cortico-cortical callosal pathways in the visual network and to similar pathways of the auditory network, in chapters 2 and 3 respectively.

1.1.3. Early hemispheric asymmetries and functional lateralization in the developing brain

In the previous sections, we described several regional asynchronies of cortical and connectivity development and maturation, e.g. earlier and faster maturation of primary and sensory areas relative to associative ones. However, we did not point that these **asynchronies** also exist **between the left and right** hemispheres, better known as asymmetries. Here, we highlight a few examples of asymmetries to draw the reader's attention to their presence in early developmental period, but we will discuss more examples and in more details when focusing on the language and face processing networks in the rest of this chapter.

Early asymmetries are especially highlighted in the perisylvian regions. For example, cortical sulci in the temporal areas appears about 2 weeks earlier in the right than the left hemisphere in the fetal period (Figure 1.6)(Chi et al., 1977; Dubois et al., 2008), and *planum temporale* is larger in the left, while superior temporal sulcus is deeper in the right hemisphere during the first postnatal months (Glasel et al., 2011; Leroy et al., 2011). Asymmetries also exist at **micro-structural** level and in the **maturational tempos** of cortical regions and white matter pathways, e.g. superior temporal and inferior frontal regions and arcuate fasciculus, in the first months of infancy (Leroy et al., 2011).

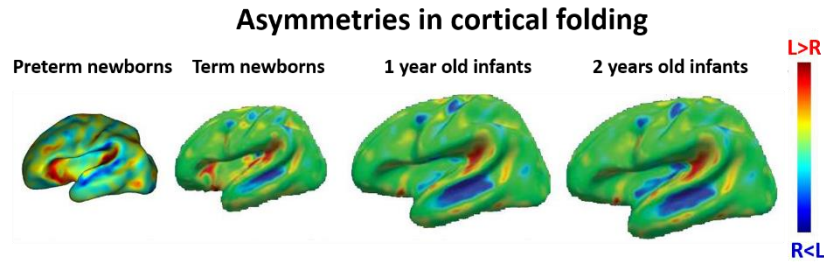


Figure 1.6. Structural imaging of asymmetrical cortical folding. Asymmetries in cortical folding in preterm and post-term periods (Adapted from Dubois & Dehaene-Lambertz., 2015).

What gives rise to early structural asymmetries is still debated but a number of mechanisms are suggested to cause or interact with their emergence. **Genetic factors**, differential expression of genes, e.g. LMO4, in the two cerebral hemispheres could be one candidate (Sun et al., 2005). Random events like fluctuations in gene expressions might interfere with the pattern of brain development and make the impact of genetic factors more probabilistic (Raj & van Oudenaarden, 2008). **Non-genetic factors** like the position of the fetus *in utero*, exposing one side of the body more outward and thus channeling the environmental inputs more toward one hemisphere, may also result in differential development of the two hemispheres (Previc, 1991). The early regional asymmetries could also be the outcome of the interaction between these factors.

Asymmetries are not limited to structure and are present at the functional level too. For example, fMRI activations in response to speech in the perisylvian regions have shown to be stronger in the left than the right hemisphere in the first months of infancy (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Dehaene-Lambertz et al., 2010; Shultz, Vouloumanos, Bennett, & Pelphrey, 2014). How the structural asymmetries impact the functional architecture of the infant brain is still not clear. They might affect the dynamics of functional networks, at the time that these networks are gradually stabilizing, and result in different computational properties and responsiveness of the left and right networks of brain regions (Dehaene-Lambertz & Spelke, 2015). These differences might further give advantage to certain regions to process frequent stimuli in the environment (e.g. speech and faces) and therefore become better attuned for processing it (de Schonen, de Diaz, & Mathivet, 1986; Dehaene-Lambertz & Spelke, 2015). For example, the left hemisphere is known to be more sensitive to fast temporal changes embedded in the speech signal.

In sections 1.2 and 1.3, we will describe more specifically the lateralization of language and face processing networks and focus on their development.

1.2. Neural bases of language

1.2.1. Language network and its lateralization in the adult brain

In the adult brain, linguistic processing is performed through a dedicated network of brain regions that extend around the sylvian fissure (Figure 1.7). The two key regions in this network are the inferior frontal gyrus (Broca's area) and the posterior part of the superior temporal gyrus (Wernicke's region) that are connected by two main roads: dorsally by the arcuate fasciculus (AF) and parts of the superior longitudinal fasciculus (SLF) and ventrally by the inferior fronto-occipital fasciculus (IFOF), extreme capsule (EmC) and external capsules (EC) and uncinate fasciculus (UF) (Axe, Klingner, & Prescher, 2013).

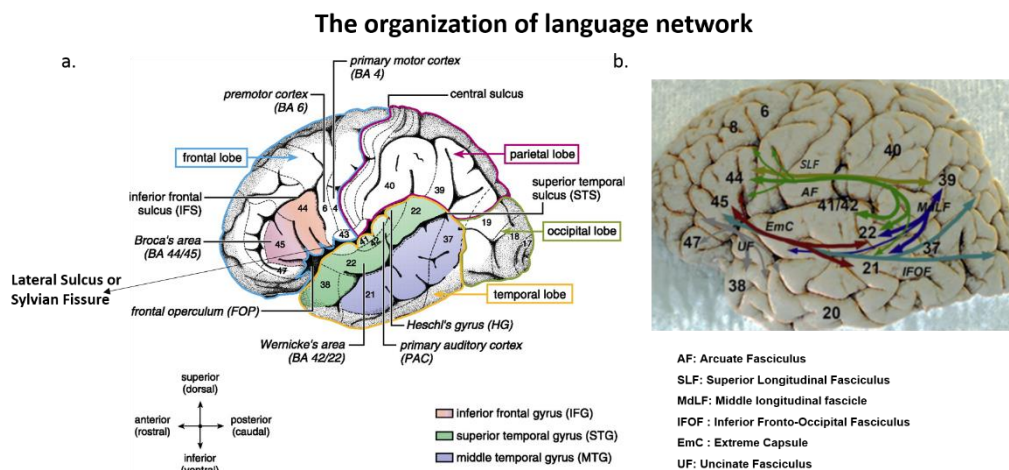


Figure 1.7. Network of brain regions implicated in linguistic processes. a) These regions are extended around the Sylvian fissure. Two main anatomical landmarks are Broca's and Wernicke's area (Adapted from Friederici., 2011). b) Connectivity of human language-related areas : including the fascicles of dorsal and ventral pathways (Adapted from Axe et al., 2013).

The **perisylvian region** is not symmetric in the two hemispheres. Macroscopic differences include elongated sylvian fissure and larger *planum temporale* (Geschwind & Levitsky, 1968), larger white matter volume underneath the Heschl's gyrus and primary auditory cortices in the left compared to the right hemisphere (Penhune, Zatorre, MacDonald, & Evans, 1996). The arcuate fasciculus is also larger and more compact in the left than in the right hemisphere (de Schotten et al., 2011; Parker et al., 2005). Microscopically, the pyramidal neurons of the left auditory cortices are larger (Hutsler, 2003) and the white matter below the posterior superior temporal cortices has more thickly myelinated axons in the left than in the right (Anderson, Southern, & Powers, 1999). The size of the neuronal columns and the distance

between them is larger in the left superior temporal lobe (Seldon, 1981). Receptor density profiles of distant perisylvian regions (Broca's area and Wernicke's region) are similar in the left but not right hemisphere (Zilles et al., 2015), in agreement with their common specialization for language processing.

Functional characteristics of the language network can be identified by localizing the brain activity when adult subjects listen to linguistic stimuli such as sentences and words. These activations appear around the perisylvian regions and are stronger in the left hemisphere, when subjects listen to their native language compared to non-native language (Mazoyer et al., 1993; Pallier et al., 2003). These observations suggest that the left perisylvian regions are responsive to features of speech specific to the native language. Yet, attributing a specific role to each of these regions is debated, as language is a complex hierarchical system that can be described at the level of phonology, syntax and semantics. Two main views exist about what aspects of language are better processed by the left hemisphere network. One view attributes this lateralization to speech and describes that spectro-temporal feature of the speech, notably the fast temporal transitions embedded in speech stimuli, are better processed by the structural properties of the auditory network in the left hemisphere (Boemio, Fromm, Braun, & Poeppel, 2005; Zatorre & Belin, 2001). This view is supported by evidence showing that brain oscillations at speech-relevant frequencies best correlate with activations in the left auditory cortices (Giraud et al., 2007). The second view relates the **leftward superiority of language network** to the communicative feature of language. This view is supported by evidence showing that leftward activation asymmetries are more pronounced for familiar versus unfamiliar (non-communicative) language (Pallier et al., 2003), evidence from deaf subjects showing similar leftward activations for communicative gestures of sign language (Sakai et al., 2005).

Human **adults have extensive experience** with language. Therefore, from adult studies alone it cannot be understood whether the described asymmetries of activations and anatomical properties are the **causes** for the speech (and language) to be lateralized or if they are a **consequence of the exposure** to linguistic stimuli with certain spectro-temporal properties. One way to approach this question is to study the ontogeny of these functional lateralizations early in life, when infants have limited knowledge of linguistic structures compared to experienced adults. This allows tackling when the functional and structural asymmetries are emerging, and how one may precede the other, to eventually shed light on their underlying mechanisms. In the following section, we describe early language acquisition and its neural bases and the emergence of their lateralizations.

1.2.2. The first stages of language acquisition in infants

Much before infants start to produce speech, their linguistic abilities start developing and their perceptual system is tuned to several aspects of speech stimuli. Newborns and young infants **prefer speech** stimuli over other auditory stimuli with similar acoustic features (Colombo & Bundy, 1981; Vouloumanos & Werker, 2007). They are able to discriminate two languages on the basis of different prosodies (Mehler et al., 1988; Nazzi, Bertoncini, & Mehler, 1998). **Perceiving phonetic contrasts** is yet another piece of information that is required for speech processing and infants are capable of this, very early on. Neonates and even preterm infants of 6 months gestation perceive the difference between phonetic contrasts that rely on voicing differences (e.g. /ba/ vs. /pa/) or place of articulation (e.g. /ba/ vs. /ga/) (Bertoncini et al., 1987; Eimas, Siqueland, Jusczyk, & Vigorito, 1971; Mahmoudzadeh et al., 2013).

These initial preferences and discrimination abilities further develop with experience and are **narrowed down** to more precise processing for native language, while losing some of the sensitivity to non-native language. For example, throughout the first year of postnatal life and with more exposure to native language, infants improve in perceiving the phonetic contrasts of their native language, while they degrade in perceiving similar phonetic contrasts for non-native language (Kuhl et al., 2006; Werker & Tees, 1984). Many other linguistic abilities emerge during the first year of postnatal life. From 4 months on, infants are able to associate artificial words with visual items (Ozturk et al., 2013; Kabdebon., 2016). Around 6 months of age, they start building up their lexicon and know words like mommy and daddy (Tincoff & Jusczyk, 1999). They begin to understand the communicative role of speech by expecting speech to be addressed to humans rather than objects (Legerstee, Barna, & DiAdamo, 2000). Parallel to all these linguistic abilities, infants are sensitive to non-linguistic spectral cues as well. Newborns show a preference for mother's voice, to which they had unique exposure during prenatal life (DeCasper & Spence, 1986). Even preterm infants, perceive pitch contrasts such as the difference between female and male voice (Mahmoudzadeh et al., 2013).

The presence and fast improvement of these abilities, despite the distance till the mature state, suggest that infants brain give them the ability to understand and learn many aspects of language in a biologically efficient way. In the next section, we present an overview of the neural bases that allow language learning in the developing infant brain.

1.2.3. Neural bases of language development in infants

Structural development of language network: Concurrent with the progressive linguistic achievements, the neural architecture of perisylvian regions develops and matures progressively. It starts already from the preterm period, with a gradient in cortical folding, primary auditory cortices preceding the associative ones (Dubois, Benders, et al., 2008). At birth, auditory cortices are still immature and their laminar organization continues to mature till childhood (Moore & Guan, 2001). **Cortical microstructure** continues to change in several regions of the language network along development. In early postnatal months, a gradient of maturational stages is observed across regions, with superior temporal sulcus having the least mature microstructure relative to the inferior frontal region, and further to *planum temporale* and Heschl's gyrus (Leroy et al., 2011).

In the **white matter**, both the primary and long associative pathways are already established in the preterm period but their microstructural properties change toward childhood. Dorsal pathways lag behind the ventral pathways in terms of their microstructural maturation properties (Brauer, Anwander, Perani, & Friederici, 2013; Dubois et al., 2016), but that they have faster maturation rates between 1 to 6 months of infancy (Dubois et al., 2016). Myelination of axons also occurs at different times and with different rates for different pathways. In acoustic radiations (between thalamus and primary auditory cortices), myelination goes on from preterm period through the first postnatal year, and in cortico-cortical association fibers of language network (e.g: fronto-occipital, uncinate and arcuate fasciculus, and external capsule) it is extended from the first postnatal year toward childhood (Brody et al., 1987; Dubois et al., 2014; Yakovlev & Lecours., 1967). These examples emphasize the progressive maturation of the regions within the language network, similar to progressive emergence and improvement of language abilities in infants and children.

Functional development of language network: Understanding the development of language network also requires evaluating the **responsiveness of this early neural architecture**. Brain responses to linguistic stimuli can be recorded and localized in order to characterize the functional counterparts of the previously described anatomical substrates. Functional correlates of categorical phonetic discrimination abilities have been studied throughout the first postnatal year, by inspecting brain responses recorded with EEG when infants were listening to a series of repeated syllables (e.g: /ba/ /ba/ ba/ /ba/) with occasional changes in the series (e.g: /ba/ /ba/ ba/ /ga/). The so-called mismatch response, raised over the fronto-temporal brain areas, highlights the responsiveness of the developing network to a change in the synthetic speech stimuli

(Dehaene-Lambertz & Baillet, 1998; Dehaene-Lambertz & Dehaene, 1994; Kushnerenko et al., 2002; Pang et al., 1998). This mismatch response to phoneme contrasts have different spatial distribution over the scalp and timing than those raised to pitch contrasts (change of voice of the speaker), suggesting an early pre-specialization for phonetic processing that is different from other more general auditory abilities (Bristow et al., 2009). These EEG studies reveal the functionality of the early language network and its sensitivity for speech processing, but they do not provide information about the sources of the responses due to the low spatial resolution of EEG.

fMRI studies have succeeded to better localize these responses in neonates and young infants when listening to short periods of speech, demonstrating **activations around the perisylvian regions** (*planum temporale*, superior temporal, angular and inferior frontal gyri) (Dehaene-Lambertz et al., 2002; Dehaene-Lambertz et al., 2006; Perani et al., 2011; Shultz et al., 2014). These activation patterns showing several overlaps with those of adults, reveals sensitivity of these regions speech stimuli much before infants produce speech. In 3-months-olds, these responses were located around the angular gyrus when contrasted with responses to backward speech (speech stream played in reverse order, disturbing prosodic cues of natural language), suggesting that these regions are involved in processing language prosody (Dehaene-Lambertz et al., 2002). Figure 1.8 illustrates the localization of these activation patterns in infants and adults.

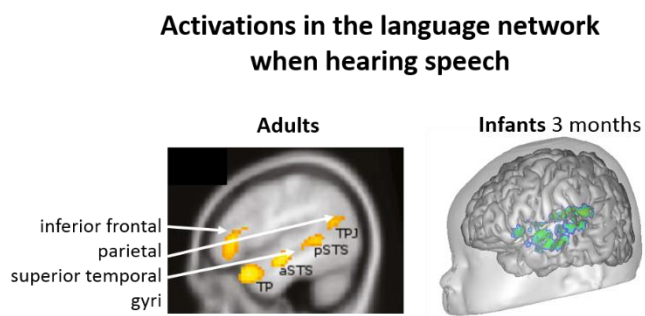


Figure 1.8. Hemodynamic response to speech. The activations in the peri-sylvian regions, when listening to speech stimuli in adults and 3-month old infants. Activation patterns are very similar between the two populations (adapted from Pallier et al., 2011 and Dehaene-Lambertz et al., 2002).

These activation patterns follow a temporal order in 3-months-olds, phase-lagged when moving from primary auditory cortices to superior temporal gyrus, temporal pole and inferior frontal gyrus, suggesting a hierarchical organization of the perisylvian regions at this age (Dehaene-Lambertz et al., 2006). Evidence from NIRS studies have also contributed to our understanding of the development of language network, revealing activation patterns for different levels of language processing that overlap with the

described characteristics of responses evidenced by EEG and fMRI. Preterm infants of 6 months of gestational age, the time when neurons are still migrating to the final location, demonstrate discrimination responses for a change in phoneme or voice that are distributed over the fronto-temporal regions (Mahmoudzadeh et al., 2013). In neonates, the detection of patterned speech structures (such as “mubaba”, with immediate repetition of syllables) among nonpatterned structures (such as “mubage”) evokes activations over similar fronto-temporal areas (Gervain et al., 2008), and in 3-months-olds processing of speech streams involves large-scale increased connectivity of fronto-temporal networks (Homae, Watanabe, Nakano, & Taga, 2011).

Overall, these studies demonstrate the functional architecture of perisylvian regions is able to perform **basic linguistic processings**. Next, we focus on the functional and structural lateralization of the early language network.

1.2.4. Is the early language network asymmetric?

Insights on the lateralization of the language network in infants come from indirect behavioral measures as well as direct measures of functional lateralization of the responses to linguistic stimuli and structural asymmetries. In the following, we describe the evidence that mainly support the presence of a asymmetric network in early development.

Dichotic listening evidence:

One of the early views on the emergence of lateralization was put forward by Lenneberg in 1967, proposing that lateralization is a consequence of language learning (Lenneberg, 1967). This view was soon contradicted by studies reporting lateralization of speech processing in infants before they learn a language. Some of these studies were based on observing the sucking behavior of infants for simultaneous presentation of two syllables in the two ears, for judging their reaction to similar and dissimilar pairs of syllables. Neonates and infants demonstrated better detection of dissimilar pairs of syllables (dichotic syllables), among a series of similar pairs, when the dissimilar syllable was presented to the right ear (Bertoncini et al., 1989; Entus, 1977). This observation suggested that syllabic discrimination was performed better in the left hemisphere, that receives the right-ear input through stronger contralateral pathways. However, these effects remained indirect and sometimes doubted, especially due to the inconsistencies that were found in similar studies using different behavioral assessments (Glanville, Best, & Levenson, 1977; Vargha-Khadem & Corballis, 1979). Later supports came from neuroimaging studies that were able to decipher structural and functional differences between the two hemispheres, confirming the

presence of an early asymmetrical language network. We describe these neural bases and their asymmetries in the next part.

Brain imaging evidence:

Structural asymmetries: Regarding the cortex, earliest structural asymmetries are observed during the fetal and preterm periods over the cortical gyri, and in favor of right hemisphere, with Heschl's gyrus, superior frontal and temporal gyrus folding 1-2 weeks earlier in the right hemisphere (Dubois, Benders, et al., 2008; Kasprian et al., 2010). Asymmetries continue to emerge and become more evident in the perisylvian regions along the preterm period and early postnatal months, with thicker Heschl's gyrus and more elongated *planum temporale*, and advanced growth of anterior region of the Sylvian fissure in the left relative to the right hemisphere, but deeper superior temporal sulcus in the right compared to the left hemisphere (Dubois et al., 2009; Hill et al., 2010; Glasel et al. 2011; Li et al., 2014; Smith et al., 2011; Leroy et al., 2011; Dubois & Dehaene-Lambertz., 2015). Apart from morphological differences, microstructural properties of the left and right perisylvian regions also differ. Inferior frontal sulcus (Broca's area) is more mature on the left, whereas posterior superior temporal sulcus is more mature on the right hemisphere (Leroy et al., 2011). Figure 1.9. a. & b. illustrates these inter-hemispheric asymmetries for example regions of *planum temporale* and superior temporal sulcus.

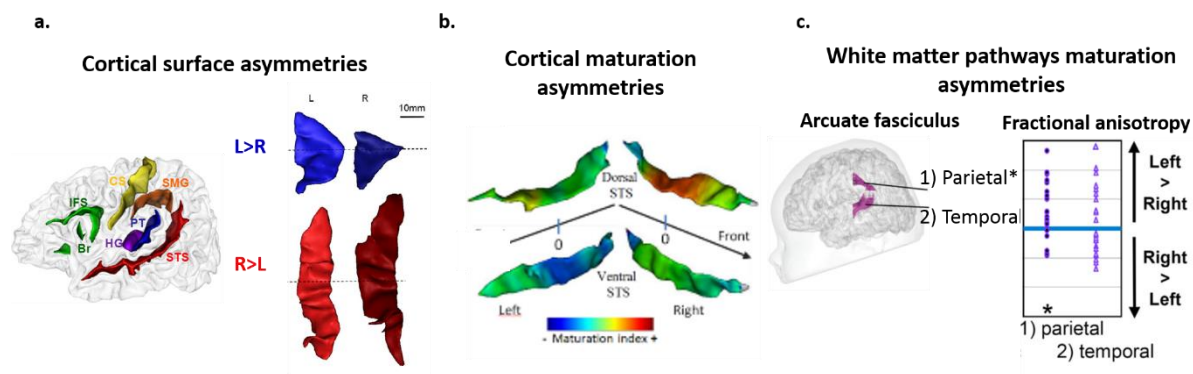


Figure 1.9. Structural asymmetries in the language network in infancy. a) Cortical surface asymmetries in Planum temporale (PT) and Superior Temporal Sulcus (STS), example of a 14 weeks old infant: PT is bigger in the left hemisphere, while STS is deeper in the right hemisphere (adapted from Glasel et al., 2011). b) Cortical maturation asymmetries in temporal areas in infants between 1-4 months of age: STS is more mature in the right hemisphere (adapted from Leroy et al., 2011). c) Maturation asymmetries in the parietal segment of Arcuate fasciculus in infants between 1-4 months of postnatal age, assessed with fractional anisotropy (Adapted from Dubois et al., 2009).

Regarding white matter, the most well-known asymmetry reported to exist at term and early postnatal months, is a leftward asymmetry of microstructure for arcuate fasciculus, similar to adults (Dubois et al., 2008; Dubois et al., 2016; Liu et al., 2010). A similar leftward asymmetry is also reported for

other bundles of dorsal linguistic pathway, i.e. superior and middle longitudinal fascicles, in the first semester of life (Dubois et al., 2016). It is suggested that asymmetries of maturation in the parietal portion of arcuate fasciculus (Figure 1.9. c) might be interdependent with the asymmetry of the perisylvian regions described in the previous section. For example, the asymmetrical calendar of maturation in inferior frontal regions, in the posterior superior temporal sulcus and in the parietal segment of the arcuate fasciculus are correlated between 1 and 4 months of age (Leroy et al., 2011).

A thorough understanding of early asymmetries and their interaction requires studying more pathways, from the brain stem and subcortical structures to thalamo-cortical pathways and short pathways connecting adjacent gyri. They can be particularly important to understand whether the early linguistic lateralizations observed in infants might result from more sensory and domain-general asymmetries or from asymmetries in more linguistic regions. It is technically challenging to study some of these pathways *in vivo*, due to the limitations of classical tractography methods for dissecting bundles that cross other bundles along their path and have different maturational stages (Dubois et al., 2016). For example, in the thalamus, acoustic radiations are obscured by the optic radiations and asymmetry of this pathway in infants has not been assessed so far. As discussed in the appendix on methodology, more advanced diffusion models and tractography methods could help to overcome these issues. Using these approaches, we studied potential asymmetry of acoustic radiations in chapter 3.

Functional asymmetries: The findings of EEG studies for lateralization of language processing are less clear. Mismatch responses to phonetic contrasts were stronger over left fronto-temporal areas in newborns and 2-3-month-old infants (Dehaene-Lambertz & Dehaene, 1994; Dehaene-Lambertz & Gliga, 2004; Bristow et al., 2009), while there were not found to be left-lateralized in 3-months-olds (Dehaene-Lambertz & Baillet, 1998), 8-months-olds (Pang et al., 1998) and 9- and 12-months old infants (Pena, Werker, & Dehaene-Lambertz, 2012). These inconsistencies might be related to the poor spatial localization of EEG, mixing the responses raised from different sources.

Functional lateralization has been **more consistently observed in fNIRS and fMRI studies** with an overall trend for a left-ward bias for phonological processing and right-ward bias for pitch processing, similar to adults. Yet it is worth mentioning that contrary to structural lateralizations, evidence for functional lateralizations are scarcer. fNIRS studies of preterm infants as young as 6 months of gestational age have highlighted stronger discrimination responses in the left hemisphere for a change of phoneme but not voice (Mahmoudzadeh et al., 2013). In neonates, responses are stronger in the left temporal areas for infant directed speech compared to backward speech or silence, when assessed with optical

tomography (Pena et al., 2003). In 2- and 3-month-old infants, fMRI activations are more pronounced in the left angular gyrus for normal vs. backward speech (Dehaene-Lambertz et al., 2002), and in the left posterior temporal regions (around planum temporal) for speech relative to music and for mother's speech relative to that of a stranger (Figure 1.10) (Dehaene-Lambertz et al., 2010).

Functional asymmetries in the language network in infancy

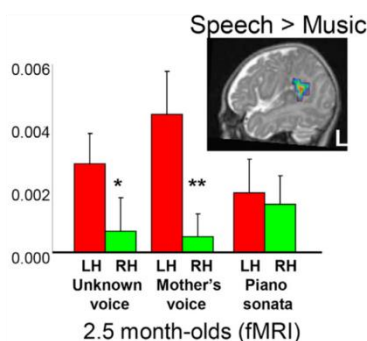


Figure 1.10. Functional asymmetries in the language network in infancy. fMRI activation by speech is higher in the left than right planum temporale, whereas it is symmetric for music (adapted from Dehaene-Lambertz et al., 2010).

These studies suggest a pre-specialization of the left perisylvian regions early on for speech stimuli that is perhaps initially tuned for perceiving the speech, through the mother's voice. The left-lateralized responses tend to become more selective to speech, and less responsive to biological non-speech sounds between 1 and 4 months of age (Shultz et al., 2014). In contrast to these fMRI studies reporting a dominant left hemisphere for speech processing in early months of infancy, one fMRI study of newborns indicated activations extended bilaterally and more predominant in the right Heschl's gyrus for sentences with expressive child-directed intonations compared to silence period (Perani et al., 2011). Yet, the whole-brain analysis in the same study showed mainly bilateral activations and even left activations when hummed and flattened speech were compared (supplementary information, Perani et al., 2011).

In sum, studies on functional lateralization of the language network support the presence of a leftward lateralization in early infancy, mostly when employing techniques with higher spatial resolution (fNIRS and fMRI). Although asymmetries of activations seen in language network, seem to overlap with the regions of structural asymmetries such as *planum temporale* (Dehaene-Lambertz et al., 2002, Dehaene-Lambertz et al., 2010), no direct structure-function relationships between the observed asymmetries have been made so far. The presence of macro-, micro-structural and maturational asymmetries early on, of genetic or non-genetic origin, might aid in biasing one hemisphere for processing the prevalent stimuli in the environment of infants (speech) and for language learning (Dehaene-Lambertz & Spelke, 2015). More

studies are also needed to determine whether other early auditory asymmetries, e.g. at the level of cochlea (Sininger & Cone-Wesson, 2004), also contribute to the development of lateralization for speech and language.

We aimed to assess whether hemispheric differences for perceiving speech stimuli can be observed with techniques other than fMRI and fNIRS. We use EEG in infants between 1 and 6 months of age, and in order to better separate hemispheric responses, we use paradigms with monaural presentation of speech stimuli. We will later ask, if hemispheric differences interact with interhemispheric communications. We further assess microstructural asymmetries of early auditory pathways.

1.2.5. Development of asymmetries vs. plasticity for language learning

Throughout development, language network is progressively tuned to the perceptual features of the native language. This tuning follows a precise calendar, reproducible across languages. The different stages seem to have precise windows of opportunity during which learning is easier, i.e. **critical periods** exist for the different learnings. For example, learning the phonology repertoire or the syntax of a language is easier in infants than in adults, for a review see (Werker & Hensch, 2015). Several biological mechanisms (e.g. excitatory-inhibitory circuit maturation, synapse pruning, molecular brakes) and environmental factors (e.g. auditory input, diet, bilingual experience) play a role in triggering, mediating, re-opening and manipulating these critical periods (Werker & Hensch., 2015). In the previous sections, we described the evidence supporting the presence of lateralized language network in early development, that are relatively selective for the features of the native language. One may wonder whether, and to what extent, the **plasticity mechanisms** can act on the lateralized language network, to re-use the left-hemisphere resources for learning a second language or use the right-hemisphere counterparts in case of a disruption to the left-hemisphere resources.

In a study comparing Korean-born adult subjects adopted by French families in France at the age of 3-8 years and native French speakers, Pallier et al. (2003) reported leftward brain activations in adopted subjects when listening to French relative to Korean sentences, much like the control French-born group. Interestingly, these subjects did not show any leftward activations to Korean language, suggesting that the leftward resources lost sensitivity to their first language and were reused to adapt to the linguistic environment they experience after adoption. In another view, in the case of left hemisphere lesions or hemispherotomy in infants and children, the right-perisylvian areas are shown to take over the role of the left counterparts for linguistic processings (Hertz-Panier et al., 2002; Dehaene-Lambertz et al., 2004). Yet,

the extent to which the right hemisphere compensates for the initially left (Dehaene-Lambertz, Pena, Christophe & Landrieu, 2004; Hertz-Pannier et al., 2002) lateralized processes seem to depend on the developmental stage at the time of acquiring lesion. When comparing patients with early (before 5 years) and late (after 20 years) acquired left lesions, the latter group tend to show reduced left lateralization activations, while the former group demonstrates reversed lateralization patterns when listening to sentences (Rothermel et al., 1999). These examples suggest that the **left-lateralized language network is not crystalized** after becoming attuned to the initial linguistic environment. It can rather be re-used to adapt to and master a second language, even though the critical period for initial tuning of the underlying neural substrates for several linguistic particularities is closed. However, it is important to note that the initial linguistic input (even in another linguistic environment) within the early critical period, seems necessary for the language network to become specialized, and to further allow the plasticity mechanisms to act on this network.

1.3. Neural bases of face processing

Faces are among the most frequent stimuli in infants' environment after birth. Infants and children rely on several facial cues to make social bonding, perceive emotions and eventually use them for learning. Adults perceive faces in the visual scenes in a few hundred milliseconds. This rapid perception and recognition of faces rely on neural bases that are dedicated to process facial information. In this section, we introduce these neural bases and their development during infancy, with a focus on the emergence of hemispheric lateralizations.

1.3.1. Face processing network and its lateralization in the adult brain

In the adult brain, visual recognition relies on several brain regions extended mainly over the occipital, temporal and parietal regions. These visual areas consist of regions that are both retinotopically organized (i.e. point to point mapping between retinal (or visual field) and cortical regions) and areas that are functionally selective to deal with higher-level aspects of visual input (Grill-Spector & Malach, 2004; Wandell, Brewer, & Dougherty, 2005). Two main processing streams are described for dealing with a different aspect of visual information: 1. the ventral stream or the "what stream", starting from V1 and extending ventrally to the occipito-temporal areas, processes the information regarding object and visual categorization and recognition. 2. the dorsal stream or the "where stream", begins in V1 and extends up to the occipito-parietal areas, and processes the information regarding the location and motion of objects in space and further guiding action. Recognizing a face as a face or its identity relies on the ventral stream.

Face-selective regions in the ventral stream have been identified by their stronger activation to faces compared to other types of objects. These regions include the **fusiform face area (FFA)** located in the fusiform gyrus, regions of the inferior occipital gyrus (sometimes referred as OFA) as well as the posterior part of the STS, building up together the functional architecture that is implicated in the processing and perception of faces (Figure 1.11) (Grill-Spector, Knouf, & Kanwisher, 2004; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997). This functional architecture relies and is constrained by the structural architecture of the brain, notably the connectivity patterns (Saygin et al., 2012).

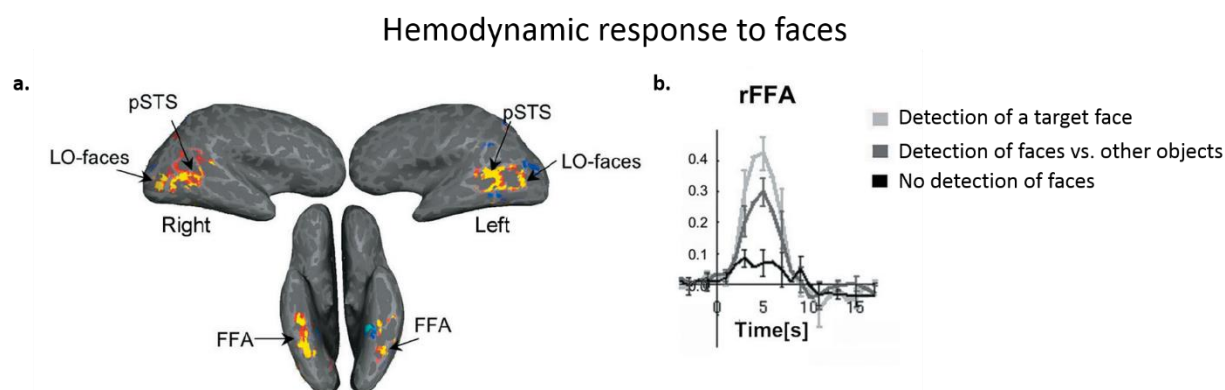


Figure 1.11. Hemodynamic response to faces: a) Face-selective regions in one representative subject. Face-selective regions (yellow) were defined as regions that respond more strongly to faces than houses, cars and novel objects at the voxel level. Blue voxels indicate voxels that passed the opposite contrast at a given statistical threshold. The activations extend over posterior part of the superior temporal sulcus (pSTS), fusiform area (rFFA), and lateral occipital cortex (LO). b) The amplitude of hemodynamic responses in the right fusiform area (rFFA) for detection of a target face (light gray), detection of any face (dark gray), no detection of faces (black). rFFA responds most strongly when detecting a face. (Adapted from Grill-Spector et al., 2004)

Compared to the language network, **microstructural characteristics** of the face-processing network is less well-established. One difficulty in identifying the microstructural characteristic of the face-selective regions is their small size and relatively less-precise location. A recent study has described four cyto-architecturally dissociable regions within the fusiform gyrus, that were associated with specific functional domains: notably FG2, FG3 and FG4 comprising face, place and word specific areas (Kevin S Weiner et al., 2017). The microstructural changes in the posterior fusiform gyrus (approximate location of FG2) between children and adults, as it is reflected in T1 MRI *in vivo*, has been recently suggested to relate to the increasing face-selectivity of responses in this region (Gomez et al., 2017). Reports on structural asymmetries of face-selective regions are similarly scarcer and findings are more variable across studies. Some studies have reported that the left fusiform gyrus has a larger volume (Goldberg et al., 2013; McDonald et al., 2000; Watkins et al., 2001), wider mini-columns and more density of pyramidal neurons (Chance et al., 2013) compared to the right fusiform. However, these asymmetries are not observed in all

studies and their presence and further relation to face processing need to be cautiously interpreted especially because they might relate to other functions nested in fusiform gyrus.

Regarding the **functional lateralization** of these regions, **FFA** is generally found to be more activated in the right compared to the left hemisphere in response to faces in fMRI studies (Haxby, Hoffman, & Gobbini, 2000; Kanwisher et al., 1997; McCarthy et al., 1997). Recognizing between individual faces compared to other objects of the same category also elicits activation in FFA that tend to be stronger in the right hemisphere (Grill-Spector et al., 2004). The hemispheric lateralization for processing faces has also been investigated using hemifield presentation of faces, demonstrating a left hemifield superiority, and thus a right hemisphere advantage, for face perception relative to the right hemifield. This hemifield asymmetry is shown to correlate with the right lateralization of FFA responses to faces across subjects (Galit Yovel, Arielle Tambini, & Tali Brandman, 2008).

ERP recordings of brain activity have also identified a **face-sensitive response (N170)**, a negative deflection appearing over visual cortices (occipito-temporal areas) reaching its maximum around 170 ms following the presentation of a face (Bentin et al., 1996), that has specific characteristics when raised by face relative to non-face stimuli: It is larger in amplitude and peaks a few milliseconds earlier for faces compared to other familiar objects and is stronger on the right compared to the left occipito-temporal areas (Rossion & Jacques, 2011). MEG studies, have identified a similar M170 component, sensitive to face perception and discrimination (Halgren, Raji, Marinkovic, Jousmäki, & Hari, 2000; F. Liu, Harris, & Kanwisher, 2002), but this component has not always shown a rightward asymmetry (but see (Kloth et al., 2006)), which might relate to different sensitivity of EEG and MEG to cortical sources. Apart from evoked response components, face-selective responses have been identified using different EEG approaches, namely frequency tagging. Using rapid presentation of faces at a given frequency among a pool of other objects, brain's oscillatory activity is entrained at the same frequency. The so called "frequency-tagged" responses are shown to be stronger over the right occipital areas (see Figure 1.12 for more details when same approach was applied to infants) (Rossion et al., 2015). The right-lateralization of face-selective responses is also supported by clinical studies of patients with prosopagnosia, exhibiting lesions in the right posterior fusiform gyrus (De Renzi, 1986; Landis et al., 1986).

In sum, all these findings point to the existence of a face processing network in **occipito-temporal areas** in the adult brain that show more sensitivity to faces in the right hemisphere. What aspect of faces recognition induces face-selective activations (and particularly in the right hemisphere) is still debated and several facial features are described to drive these activations. For example, the N170 has been shown to

be particularly sensitive to eyes (Eimer, 1998; Itier, Alain, Sedore, & McIntosh, 2007), or the right hemisphere face network is shown to be more involved in processing faces as a whole (facial features with respect to each other) and left hemisphere network seem to be better at processing facial features (parts of faces)(Rossion et al., 2000).

The **expertise adults have with faces**, makes it difficult to disentangle whether the face processing neural substrates are tuned to faces because of their biological relevance for the species or if they are the product of extensive experience, and thus expertise, with faces. One may also wonder if the lateralization of responses raised from occipito-temporal regions is a consequence of experience with faces over years or if the anatomical and functional properties of these regions favor face processing to be lateralized. In this debate, focusing on the **ontogeny of face perception** in early developmental period, when infants still have little experience with faces, might shed light on the origins of the selectivity of the face processing network and its underlying mechanisms. It will further allow asking whether right lateralization of this network is present already early on.

1.3.2. Early face processing abilities

Several studies on early developmental period favor the existence of predispositions to faces and face-like patterns. Head turns or gaze orientations have been used to assess the early face processing abilities. Human fetuses have shown to preferentially react to face-like patterns relative to non-face patterns, when the stimuli are projected over the maternal abdomen and the head-turn behavior is observed (Reid et al., 2017). Neonates with little experience to faces preferentially orient to faces compared to non-face stimuli (Morton & Johnson, 1991). Infant monkeys, with no exposure to faces after birth, show a preference for faces compared to non-face stimuli, and can discriminate between human and monkey faces (Sugita, 2008). These evidences refer to little role of experience for the initial face processing abilities and thus innate **biases for face detection** and discrimination.

Yet, whether these biases are specific to faces or if they hold for more general properties found in faces and some non-faces patterns is debated. Evidence in support of face-specific biases come from newborn studies showing their sensitivity to facial features like direct gaze compared to averted gaze (Farroni, Csibra, Simion, & Johnson, 2002). Other studies in support of more general biases of the early visual system, have described some properties for visual stimuli, also found in other objects, that are better processed by the functional properties of the immature visual system of newborns and infants (Simion, Macchi Cassia, Turati, & Valenza, 2001; Turati, 2004). These biases include the ability to deal with low-

spatial-frequency patterns (de Heering et al., 2008) and preference for **top-heavy patterns**, i.e. patterns with more elements in the upper visual field (Simion et al., 2002), as well as patterns with congruent shape contours and the spatial disposition of inner features they encompass (Macchi Cassia, Valenza, Simion, & Leo, 2008).

The early predispositions of the neonate's visual system further allow **processing configural and featural information of face patterns** accordingly, with a superiority of global-level configural information relative to the local-level featural information (Cassia, Simion, Milani, & Umiltà, 2002; Simion & Di Giorgio, 2015). These early perceptual abilities for perceiving face-like patterns, further develop and enable infants to recognize between individual faces, e.g. mother's vs. strangers's faces (Bushnell, Sai & Mullin, 1989; Pascalis et al., 1995), or familiarized face of a stranger vs. a novel face (Pascalis & de Schonen, 1994). In the first few months after birth, the individual face recognition ability is further attuned to conspecific faces (Pascalis, de Haan, & Nelson, 2002; Simpson et al., 2017), faces of own race (Kelly et al., 2005) or more represented gender in the environment (Quinn et al., 2002; Righi et al., 2014), indicating the role of learning and experience in face processing abilities beyond the initial predispositions.

Over all, the early existence and progressive improvement of face recognition abilities suggest the existence of a relatively performant brain network for processing face-related information, that we will describe in the following section.

1.3.3. Neural bases of face processing in infants

At the brain level, these early face processing abilities (being domain general or face specific), have been described to rely on subcortical structures, while progressively interacting and integrating cortical structures, when cortical circuitries develop and become mature (Acerra, Burnod, & Schonen, 2002; Johnson, Senju, & Tomalski, 2015). Subcortical structures are known to be more responsive to low-spatial-frequency patterns, like that of faces, thus making them candidate neural bases for initial face-preference abilities. In support of this view, evidence from newborns have shown that their face recognition abilities rely more on low- than high-spatial-frequencies (de Heering et al., 2007). The top-heavy pattern preference in neonates, most likely relies on upper visual field advantage of the visual system, that relies on superior colliculus (Sprague et al., 1973). However, relying only on subcortical substrates for processing low spatial frequency facial information cannot account for newborns preferences for direct vs. averted gaze (Farroni et al., 2002) and recognizing individual faces (Pascalis & de Schonen, 1994). More recent evidence from fNIRS have allowed recording cortical responses to faces in newborns (Farroni et al., 2013), confirming that

both subcortical and cortical accounts participate in the early face processing system (Accera et al., 2002; Johnson, Senju, & Tomalski, 2015). In the following, we try to describe the neural correlates of the developing face processing network, particularly in the first postnatal year.

Structural development of face processing network

The current knowledge on the structural maturational of face processing networks in the infant brain mainly relies on postmortem studies. *In vivo* studies are particularly challenging for evaluating the maturation of cortical areas, due to low MRI signal contrast between gray and white matter in the occipital areas at this age. However, for white matter pathways diffusion MRI has been used to study the maturation of early visual pathways. Postmortem studies suggest that **maturation of visual cortices** expands from infancy to childhood (Murphy et al., 2005). Projection pathways (connecting thalamus and primary visual cortices) and cortico-cortical callosal pathways (connecting visual cortices inter-hemispherically) already develop before birth (Dubois et al., 2014), but short-range cortico-cortical connectivity (e.g. connecting V1 and V2) continue to develop throughout the first postnatal year (Burkhalter, 1993). **Myelination of white matter pathways** start at birth for optic radiations and continues intensely over the first six postnatal months. For visual callosal fibers and associative fibers, myelination starts at 3 months and continues more slowly through childhood. For short-range cortico-cortical connections, this process is possibly starting later (Yakovlev & Lecours., 1967).

Yet, little is known about the structural maturation of face-sensitive cortical regions in the early postnatal months. In a recent study of children and adults, it has been shown that microstructural changes in the posterior fusiform gyrus (approximate location of FFA), reflected in T1 MRI signal, extends from childhood to adulthood (Gomez et al., 2017). The authors suggested that the microstructural changes might partially reflect continued proliferation toward adulthood.

Functional development of face processing network

To assess the responsiveness of the face processing network during development, several studies have used EEG, NIRS and fMRI techniques to unravel the temporal and spatial extents of brain responses to faces. EEG studies have identified two components in **infants' ERP** recorded over occipito-temporal regions, that show similar sensitivity to faces as adult' N170 shows. These two components appearing as a negative deflection followed by a positivity (**N290 and P400** respectively), are shown to be **sensitive to face inversion** (de Haan, Johnson, & Halit, 2003; Halit, de Haan, & Johnson, 2003), or gaze direction (Farroni et

al. 2002), face distortion (Gliga & Dehaene-Lambertz, 2005), conspecific faces (Scott, Shannon, & Nelson, 2006) and gender (Righi et al. 2014) and individual face recognition (Scott & Nelson, 2006); Peykarjou et al., 2015) between 3-to-12 months of postnatal age. Face-sensitive responses are also recorded in 4-6 months old infants, using **EEG** and the same **frequency-tagging approach** that demonstrated face-specific responses in adults. These responses that appeared over the right occipital regions, were related to recognizing the category of faces among a pool of other objects (de Heering & Rossion, 2015) (Figure 1.12).

Right lateralized EEG responses to faces in infancy

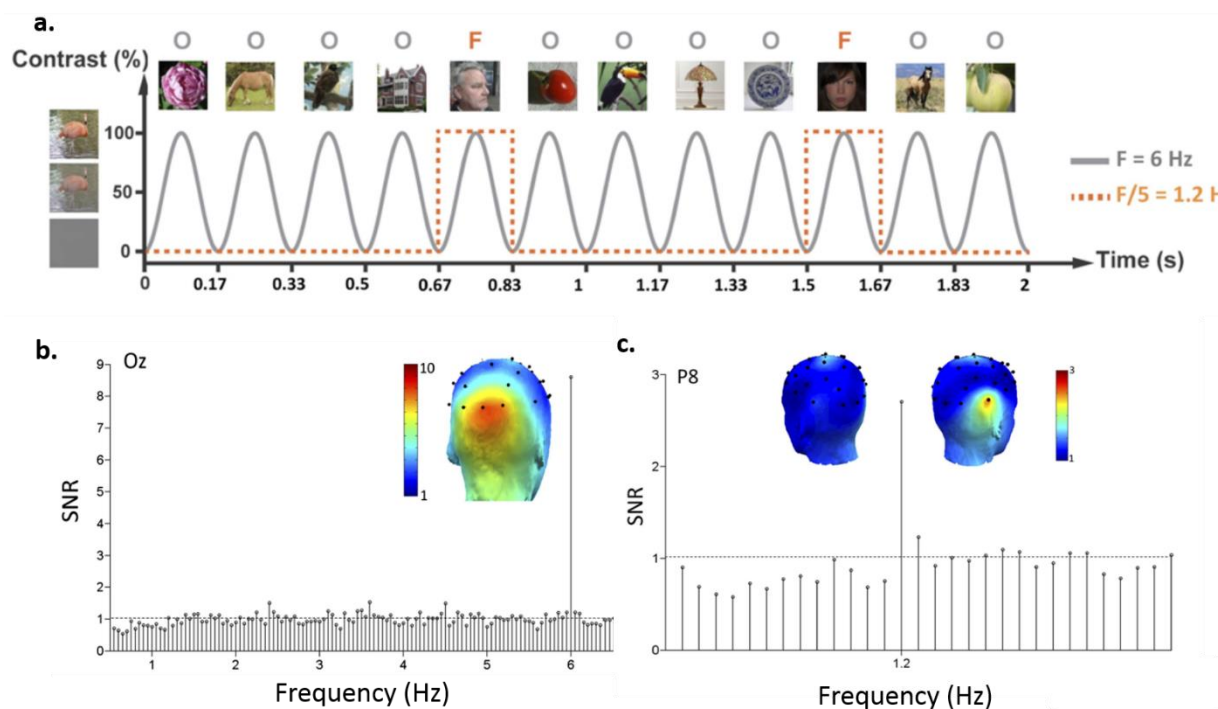


Figure 1.12. Right lateralized EEG responses to faces in infancy. Using rapid presentation of images, brain's oscillatory activity was entrained at the frequency of image presentation in 4- to 6-month-old infants. a) Visual stimulation sequence contains various non-face objects among which faces (with various identities and viewpoints) are inserted periodically (i.e. every 5 image). Six images were presented per second with a sinusoidal contrast modulation. b) EEG signal-to-noise ratio (SNR) spectrum showing a peak of activation at 6 Hz located on the medial occipital regions, reflecting generic visual stimuli perception. c) EEG SNR spectrum showing a peak of activation at 1.2 Hz (frequency of face presentation) located on the right occipito-temporal areas, reflecting generic face perception (Adapted from de Heering and Rossion.,2015).

Functional NIRS studies recording brain hemodynamic responses over **temporal areas**, have shown increased activity to faces compared to human arm in neonates (Farroni et al., 2013) and relative to blank or pictures of vegetables in 5 to 8-months-olds (Carlsson et al., 2008; Nakato et al., 2009; Otsuka et al., 2007), indicating selectivity of these areas to faces compared to the control stimuli. **PET** and **fMRI** studies of 2 to 8 months old infants have also underscored activations in a network of brain regions including

fusiform area (Deen et al., 2017; Tzourio-Mazoyer et al., 2002), but the specificity of these activations to faces are less clear in these studies, since same regions were activated for objects as well (Deen et al., 2017).

Over all, these studies support that the occipital-temporal regions are performant for perceiving faces as a category and also discriminating between them in early infancy. Next, we address the lateralization of face processing and asymmetries of these regions.

1.3.4. Is face processing lateralized in infants?

Evidence from behavioral studies:

A number of behavioral studies have addressed the question of lateralization of face processing early on, using **divided visual field presentation**. Four-month-old infants oriented faster to their mother's face than to a stranger's presented in the left hemifield relative to when presented in the right hemifield (De Schonen, De Diaz, & Mathivet, 1986). In a follow-up study, 4-to-9 months old infants were shown to succeed better in discriminating between faces and associating them to a reward location over a screen, when they were presented in the left compared to the right visual field (de Schonen & Mathivet, 1990). The hemifield differences were subsequently interpreted as **hemispheric differences** and therefore an outperforming right hemisphere for face discrimination. Although with the indirectness of measures, some questions remained to be investigated. For example, from the latter study it is not clear whether the left hemifield, and right hemisphere, advantage was only due to better discrimination abilities or better ability to associate faces to the position of rewards, as no clue existed about the localization of cerebral responses. Follow-up experiments using similar paradigms also asked what facial features were better processed in each hemifield and thus hemisphere, demonstrating outperformance of the right hemisphere for processing configural facial information and a left hemisphere advantage for processing local facial features (Deruelle & de Schonen, 1991, 1998), similar to adults (Sergent, 1984).

Evidence from brain imaging:

Regarding structural asymmetries of face processing network, the question has remained largely uninvestigated in infants. As for functional lateralization, **ERP studies remain less conclusive**, either not showing any lateralization (de Haan et al., 2002; Righi et al. 2014; Peykarjou et al., 2015), or weakly and inconsistently present across studies (Gliga & Dehaene-Lambertz., 2005; Scott et al., 2006). Contrary to the ERP studies, the previously described **EEG** study of de Heering & Rossion (2015) in 4-5 months olds, found

that while the frequency-tagged responses for the pool of several objects were bilaterally distributed over occipital areas, responses to the frequency of face presentations appeared over right occipital regions. **fNIRS studies** showed that responses to the category of up-right faces were **stronger in the right** than the left hemisphere in 5-8 months old infants (Otsuka et al., 2007; Nakato et al., 2009), but no evidence of lateralization was found for discriminating between faces (Kobayashi et al., 2011; Nakato et al., 2011). A more recent fNIRS study, has shown the superiority of right lateral occipital regions to objects shape discrimination (Emberson, Crosswhite, Richards, & Aslin, 2017), suggesting that the right-lateralization for faces in early infancy might account for patterns beyond faces as well. Lateralization of fusiform area responses was only found in PET study of 2-months-olds, when contrasting faces with light stimuli (Tzourio-Mazoyer et al., 2002), but not in fMRI study of 4-6 months old infants, when contrasting faces with objects (Deen et al., 2017). In sum, right-lateralization of face-category information seem to be present starting from 2 months through 8 months of age, occipito-temporal cortex beyond fusiform area and its specificity could incorporate more patterns than faces at this age.

We aim to investigate hemispheric differences for face discrimination abilities when faces are presented in a single hemifield, similar to the described behavioral studies, but with a focus on the neural correlates using ERP. Compared to the previous neuroimaging studies, we target individual face discrimination rather than face categorization. We further evaluate how the neural correlates of such abilities change with age. From a structural perspective, we also evaluate possible microstructural asymmetries of early visual pathways.

1.3.5. Development of lateralization vs. plasticity for face processing

In the previous section, we reported the evidence supporting the presence of a right lateralized face processing network in early developmental period. Here, we describe an example study addressing how a disruption to the development of these lateralized networks early on, impacts the relevant processing abilities in a longer run. In a study by Le Grand et al. (2003), individuals with a unilateral congenital cataract, who had a treatment for removing the cataract and fitting contact lens over the first two postnatal years, were tested after several years to evaluate their face processing abilities. In early infancy, the nasal visual hemifield, and thus the temporal hemi-retina, is relatively immature compared to the temporal hemifield and nasal hemi-retina (Lewis & Maurer, 1992). Thus, the unilateral cataract was assumed to mainly disrupt the input going from nasal hemi-retina of each eye to the contralateral hemisphere: the left and right eye cataracts affected the input to the right and the left hemispheres, respectively. Comparison between patients with restricted visual input to left and right hemispheres,

demonstrated that only the latter group showed difficulty in perceiving a change in the spacing between eyes as well as between the eyes and the mouth when judging the similarity of face pictures. None of the left or right cataract patients in this study showed difficulty in perceiving changes related to the shape of internal features or the external contour of faces. This observation suggested that deprivation of the right hemisphere could affect proper development of face processing abilities, especially for discriminating between individual faces using configural facial information, that could last till adulthood (Le Grand, Mondloch, Maurer, & Brent, 2003). It might further suggest that critical periods exist at least for certain aspects of face processing, i.e. configural processing, that once missed, will not be completely compensated by the plasticity mechanisms.

What neural mechanisms create these long-lasting effects is still under investigation. Some insights from patients with congenital prosopagnosia who show particular deficit of configural face processing, suggest that the changes in the neural architecture of extrastriate cortices and their connectivity pattern might play a role in the face processing deficits of these patients. These changes include increased volume of anterior and posterior middle temporal gyrus as well as significantly smaller anterior fusiform gyrus (Behrmann, Avidan, Gao, & Black, 2007), or decreased connectivity between early visual cortices and regions of ventral stream (FFA and posterior STS) (Lohse et al., 2016), in congenital prosopagnosia compared to controls. Although the comparison between patients with congenital cataract and congenital prosopagnosia should be cautiously done, these studies might converge on the point that **disruption of right hemisphere network** during development can have long lasting effects at the behavioral and neural level.

1.4. Lateralization versus. interhemispheric connectivity

Corpus callosum is the major communication pathway between the cerebral hemispheres. It consists of neuronal fibers that connect different regions across the two hemispheres, mostly homotopic but also heterotopic regions (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). Depending on the regions that these fibers connect, they participate in different functional networks and therefore play a different role. Fibers of the anterior portion of corpus callosum (genu) connect the prefrontal cortices, while fibers of the middle portions (body) in the anterior part connect the somatosensory and motor cortices and in the posterior part connect the parietal areas. In the most posterior portion of corpus callosum (splenium), fibers connect occipito-temporal cortices (Figure 1.13). Axons connecting primary visual, auditory, motor and somatosensory areas, have bigger diameters and are more myelinated, whereas axons connecting the frontal and parietal areas are thinner and less myelinated (Aboitiz et al., 1992).

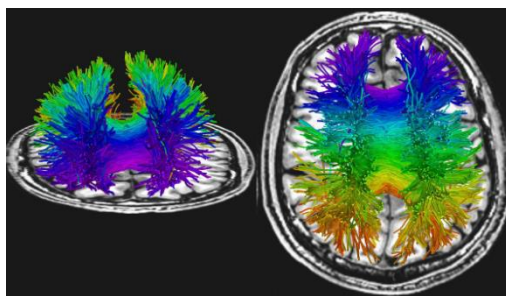


Figure 1.13. Callosal fiber connections reconstructed with tractography (Adapted from Fillard et al., 2009)

The increased size of the human brain in primate evolution, co-occurring with the emergence of structural asymmetries and functional lateralizations has incited the idea that **interhemispheric connectivity** might modulate **hemispheric lateralization** (Ringo, Doty, Demeter, & Simard, 1994). The initial view underlined the relatively long length of the callosal pathways as a constraining factor for the interhemispheric communications and their timing efficiency, that may increase functional lateralizations (Ringo et al., 1994). However, the larger brain size and the consequent larger interhemispheric distances might have been compensated by an acceleration of the callosal transmissions thanks to more abundant larger diameter, myelinated and thus faster axons in the human brain (G. M. Innocenti, Aggoun-Zouaoui, & Lehmann, 1995; Wang et al., 2008). Thus, the lateralized functional architecture of the human brain might result from a trade-off between the several requirements and consequences of an increased brain size and scaled speed of interhemispheric connections (Caminiti et al., 2009).

Two main roles have been described for the callosal fibers: an **inhibitory role**, through which an activated region in one hemisphere inhibits a region in the opposite-side hemisphere, and an **excitatory role**, through which an activated region in one hemisphere, activates a region in the opposite-side hemisphere (Bloom & Hynd, 2005). It has been suggested that lateralizations might interact with interhemispheric connectivity through these roles. Through inhibition, the specialized hemisphere might inhibit the non-specialized hemisphere and therefore increase the functional asymmetry between hemispheres (Cook, 1984), whereas through excitation the specialized hemisphere may activate the non-specialized hemisphere and allow integration of information across the hemispheres (Galaburda, Rosen, & Sherman, 1990; Yazgan, Wexler, Kinsbourne, Peterson, & Leckman, 1995). It is important to note that the excitatory/inhibitory functional effects from one hemisphere to another is relatively distinct from the excitatory/inhibitory synaptic connections of callosal fibers, as interneurons could interfere within the cascade of synaptic events.

Early insights on the role of corpus callosum in the organization of functional networks, come from **split-brain patients**, who underwent commissurotomy to treat chronic epileptic seizures. Despite normal functioning in several aspects, these patients show signs of disconnected behaviors such as difficulty in comparing sensory information presented to the two hemispheres, or recovering information presented to one hemisphere on the opposite side (for a review see (Gazzaniga, 2000)). The question about the role of callosal fibers was not directly addressed in these studies. Yet, data on split-brain patients do not favor the inhibitory role of callosal connections, mainly showing that interhemispheric transmission of information was impacted but the asymmetries did not seem to be affected after commissurotomy.

Lesion studies have provided information on the role of portions of callosal fibers, by assessing the change in laterality with respect to the lesions location. Pollman et al (2002) demonstrated that laterality in dichotic syllables perception task increased with lesions to the posterior, but not other parts of the corpus callosum (splenium, where the auditory callosal fibers cross) (Pollmann, Maertens, von Cramon, Lepsien, & Hugdahl, 2002). This finding referred to the role of the splenium fibers in transferring auditory information across hemispheres, in particular toward the left hemisphere, by showing an increased laterality when the pathway was disrupted.

Other evidence on the role of interhemispheric connectivity, comes from studies focusing on the relationship between the **size of the corpus callosum and behavioral laterality scores** (e.g. language comprehension, sensory motor integration). These studies hypothesized that if the callosal fibers exert an inhibitory effect, bigger size of the corpus callosum would increase the lateralization, whereas if the callosal fibers play an excitatory role, the reverse should be true (Yazgan et al., 1995). However, several inconsistencies exist across the findings of these studies, regarding the inhibitory and excitatory role of corpus callosum, casting doubt on the robustness of the measures of interhemispheric connectivity. These studies commonly used “rough” measures of midsagittal area of the corpus callosum or its relatively big sub-regions, in order to relate them to the lateralization scores in different tasks. Such measures might be inappropriate, considering the wide range of callosal fibers participating in different functional networks. More appropriate measures can be obtained with tractography in order to dissect and assess the strength of callosal fibers specifically associated to a network, and to relate them to the laterality score in the related task. Westerhausen et al (2009) used tractography to dissect the callosal fibers connecting the temporal areas and related their midsagittal area to a laterality index in a dichotic syllables perception task, indirectly underlying the excitatory role of callosal fibers in accessing the left hemisphere resource (Westerhausen et al., 2008). The measure of callosal size is also not informative on the microstructural properties of the

callosal fibers (such as axon diameter and myelination) that can impact the functional responses and their laterality. Combining tractography and DTI measures sensitive to the microstructural properties of white matter, Wahl et al. (2000) reported that the integrity of the motor callosal fibers connecting the primary motor cortices is related to the magnitude of interhemispheric inhibition across these regions, as measured with Transcranial Magnetic Stimulation (TMS) and functional connectivity (Wahl et al., 2007). In the following, we focus on the visual and auditory callosal connectivity.

1.4.1. Interhemispheric connectivity in the visual and auditory networks

Visual network: The callosal fibers connecting the primary visual areas mostly connect areas with similar columnar and retinotopic receptive fields (similar orientation preferences), especially around the vertical meridian of the visual field (Innocenti et al., 1995). Such pattern of connectivity may explain the role of the callosal fibers in midline fusion to create a **uniform visual field representation**. More abundant thickly myelinated fibers connecting primary visual areas A17, A18 perhaps serve for facilitating this fusion (Aboitiz & Montiel, 2003). In earlier studies, **transfer of visual information** across hemispheres were assessed through simultaneous half visual-field presentation of two items and a task of similarity judgment that requires exchange of information across hemispheres (Davis & Schmitz, 1973; Hellige, 1990). Later, recordings of visual evoked potentials in response to unilateral hemifield presentation of stimuli enabled tracking the transfer of evoked responses across hemispheres and assessing the corresponding delays. These interhemispheric transfer delays have been reported to be sometimes shorter in the right to the left hemisphere direction (Brown, Larson, & Jeeves, 1994; Moes, Brown, & Minnema, 2007), while reverse pattern has been found in other cases even for similar stimuli (Assaf Horowitz et al., 2015; Nowicka, Grabowska, & Fersten, 1996; Whitford et al., 2011). The underlying phenomena for these controversial findings remain unclear despite efforts in this direction. Yet, these studies suggest that functional asymmetries might exist for callosal transmissions. On the anatomical level, the current structural neuroimaging approaches (e.g. diffusion imaging combined with tractography) cannot dissociate the direction of effective connectivity, leaving the question open for potential future technological improvements.

Auditory network: The callosal fibers connecting the primary auditory cortices, mostly connect areas with predominantly similar binaural interactions, i.e. areas with cells responding more strongly to binaural input and some responding more strongly to the dominant ear input and some that only respond to monaural input (Imig & Adria, 1977; Ojima, 2011). These areas of predominantly similar binaural preferences, might interact with the interhemispheric callosal fibers for cortical **sound localization** (Aboitiz

& Montiel, 2003; Bamiou, Sisodiya, Musiek, & Luxon, 2007). Beyond sound localization, auditory callosal fibers may modulate **speech lateralization**. Using dichotic listening paradigm, the role of the callosal fibers has been studied with the hypothesis that they provide the relay for accessing the dominant left hemisphere resources (Hugdahl & Westerhausen, 2016; Kimura, 1961). In support of this view, it has been shown that the strength of interhemispheric connections between superior temporal regions is related with the accuracy of reports from the left ear (but not the right) in a dichotic paradigm (Westerhausen et al., 2009). This finding suggests that callosal route is asymmetrically employed for transmitting information across hemispheres in order to perceive syllables, i.e. providing a path for left-ear syllables (right hemisphere) to cross and reach the dominant left hemisphere. Some recent evidence from unilateral TMS stimulation of auditory cortices at rest suggests that this asymmetry of interhemispheric auditory communications might be more generally valid. When applying TMS to the right auditory cortex, but not the left, functional connectivity decreases within the auditory network and the greater the structural interhemispheric connectivity (measured with the number of streamlines and FA volume in the tract), the larger the decrease in functional connectivity after stimulation was (Andoh, Matsushita, & Zatorre, 2015). The asymmetry in activity propagation might suggest a facilitated transfer of activation in the right-to-left direction.

Overall, interhemispheric connectivity in the visual and auditory networks might primarily serve primary functions of each network like midline fusion and binaural interactions. In addition, asymmetry of interhemispheric connectivity might also affect the functional lateralization within each network. Compared to adults, little is known about the role of interhemispheric connectivity and its asymmetry in early development. This question is particularly important to understand functional lateralization in the developing brain. Given that regions of the left and right hemispheres have different calendars of development and thus might be differently affected by the environment, one may wonder about the role of this major interhemispheric tract in maintaining brain functional unity despite structural and functional heterogeneity. Moreover, interhemispheric connections mature slowly and might impose long delays on interhemispheric transmissions during infancy, whose consequences are not known. Identifying these delays is thus crucial for understanding the extent to which the efficiency of neuronal networks might be limited over the course of development. In the following, we briefly describe the development of corpus callosum and functional interhemispheric connectivity. We further present a model that might be suited for studying the role of interhemispheric connectivity in early developmental period.

1.4.2. Development of interhemispheric connectivity

The development of the corpus callosum starts during the second trimester of pregnancy (Ren et al., 2006). All callosal connection have grown toward the end of the gestation. The adult pattern of interhemispheric connectivity emerges through further refinements of connectivity patterns caused by pruning and myelination of axons (Innocenti and Price et al., 2005). These phenomena start from the end of the gestation (Dubois et al., 2015) and continue until adolescence (Brody et al., 1987) with the posterior fibers in the splenium developing first and the anterior fibers in the genu catching up later. In rhesus monkeys, up to 70% percent of callosal fibers are eliminated through pruning in the first 4 postnatal months. In humans, this process occurs throughout the first postnatal year and possibly later (Dubois et al., 2015; Kostović & Jovanov-Milošević, 2006). In cats, bilateral eye deprivation in early postnatal days, significantly decreases the number of callosal neurons and alters their distribution areas (Innocenti & Frost, 1980), suggesting that pruning might also depend on the visual experience. Myelination also occurs for the fibers that are eliminated, starting at 3 months of age in the splenium, and at 6 months in the genu of corpus callosum and continues with different rates up to adulthood (Yakovlev & Lecours., 1967; Baumann and Pham-Dinh, 2001)

The **functional maturational course** of the **interhemispheric connectivity** is less studied. Functional MRI studies have highlighted the presence of **bilateral** resting state networks already from the preterm period that resemble those of adults (Fransson et al. 2007; Doria et al. 2010; Smyser et al.2010). These symmetrical networks can be due to thalamic synchronization rather than callosal connections given the relative immaturity of corpus callosum in neonates. The correspondence between the functional and the underlying structural connectivity requires more investigations on the contribution of subcortical and cortico-cortical callosal connectivity to the observed patterns. EEG studies have also highlighted the appearance of interhemispherically synchronized networks from the term age (Omidvarnia, Fransson, Metsäranta, & Vanhatalo, 2013; Tokariev, Videman, Palva, & Vanhatalo, 2016). However, the underlying neurophysiological processes driving the **EEG synchronized networks** and **fMRI resting state networks** are distinct from each other. EEG connectivity measures in neonatal period are mostly sensitive to transient bursts of neural activity that begin to synchronize in the two hemispheres toward the term age. The different neurophysiological sensitivity of the two techniques in addition to their differential spatio-temporal sensitivity might thus explain the different developmental timelines of the fMRI resting state networks and EEG synchronized network (Cusack, Ball, Smyser, & Dehaene-Lambertz, 2016). FNIRS recordings of brain hemodynamic activity during sleep, have shown that the interhemispheric connectivity

increases between the homologous regions of the occipital, temporal and parietal but not frontal regions from birth to 3-months and 6-months of infancy (Homae et al., 2010).

Interhemispheric transfer of information during infancy has been previously studied for transfer of visual information using **behavioral assessments**. To test interhemispheric transfer, de Schonen & Bry (1987), de Schonen & Mathivet (1990) and Deruelle & de Schonen (1998) used a paradigm in which stimuli were presented in a hemi-field when infants' attention was focused the center of the display (de Schonen & Mathivet, 1990; S. de Schonen & Bry, 1987; Deruelle & de Schonen, 1998). They first trained one single hemisphere to distinguish between two visual patterns and counted the number of trials it took infants to reach the learning criterion, i.e. infants had to orient to a toy, either above the display for one pattern or under the display for the other pattern. Next, by switching the side of the presentation of patterns, they tested how long it took for the unexposed hemisphere to reach the same learning criterion. The economy in the number of trials between the first and second hemisphere was considered as an index of interhemispheric transfer of information. According to this index, de Schonen & Bry. (1987) reported that transfer of information occurred at 5 months of age, but not before, when face like and non-face patterns were used. However, this discrimination might have relied on subcortical pathways. When testing for discrimination between face-like patterns, the transfer did not occur before 10 months of age (de Schonen & Mathivet, 1990; Deruelle & de Schonen 1998). Using a slightly different paradigm, Liégeois et al. (2000) investigated whether infants were able to make similarity judgments between the eyes shape of a face-like pattern when it was presented in a single hemifield or across the two visual hemifields (bilateral presentation), with one eye of the stimulus on each hemifield (Liégeois, Bentejac, & de Schonen, 2000). The infants had to associate the same/different conditions to different reward locations. With this paradigm, the authors demonstrated that integration of information from the two visual hemi-fields emerged only around 24 months of age. The relatively late onset of efficient interhemispheric communications, compared to the much earlier onset of myelination in callosal fibers (around 3 months) raises questions about the efficiency of early callosal connectivity. However, in the above-mentioned studies, discrimination between patterns were based on the ability of infants to assign each pattern to a rewarded location, a complex task that depends on several processes beyond discriminating the visual patterns.

1.4.3. Agenesis of corpus callosum: A model to study the role of interhemispheric connectivity in the development of visual and auditory networks

Agenesis of corpus callosum (AgCC) is an interesting model for studying how the absence of callosal fibers may change the organization of different networks. AgCC is a brain developmental pathology where callosal fibers fail to cross the midline and instead run intra-hemispherically, giving rise to Probst bundles and partly modifying the organization of white matter connectivity (Bénézit et al., 2015; Owen et al., 2013; Probst, 1901). The **interhemispheric synchronization** of EEG recordings is decreased in asleep AgCC infants, children and adults compared to typical subjects (Koeda et al., 1995; Kuks, Vos, & O'Brien, 1987; Nielsen, Montplaisir, & Lassonde, 1993). This decrease is particularly noticeable for slow EEG oscillations (Kuks, Vos, & O'Brien, 1987). Apart from the decreased interhemispheric synchrony, it is suggested that AgCC interferes with lateralized functions and **reduces the structural and functional asymmetries** and functional lateralization in the brain. However, some studies disagree with bilateral representation of lateralized functions in callosal agenesis patients, and on the contrary, have reported hemispheric lateralizations to be present in AgCCs (Ettlinger, Blakemore, Milner, & Wilson, 1972; Pelletier et al., 2011). Yet, these studies do not rule out the view that callosal connections might facilitate the satisfactory performance of lateralized functions. In the case of language, fairly good performance of AgCC subjects in linguistic tasks pushes forward the view that lateralized language network remains intact (Chiarello, 1980). However, their difficulties in certain aspects of linguistic abilities such as phonological and rhyming processing, and also in syntax and linguistic pragmatics (Sanders, 1989; Temple & Ilesleya, 1993; Temple, Jeeves, & Vilarroya, 1989) might suggest alterations in the lateralized language network.

More recent evidence from neuroimaging techniques support the role of callosal fibers in development of lateralization in the language network. FMRI study of an AgCC subject, has shown bilateral activations over superior temporal and inferior frontal gyri for speech perception and production (Riecker et al., 2007). Using MEG to compare typical adults and adults with AgCC, Hinkley et al. (2016) demonstrated that oscillatory power in (12–30 Hz) band decreases bilaterally in AgCC but left-laterally in controls during picture naming and verb generation, indicating reduced language lateralization in AgCC subjects (Hinkley et al., 2016).

Most of the knowledge on AgCC come from adults and children studies, especially because in many cases isolated AgCC remains undiagnosed until adulthood when MRI exams are asked for other reasons. However, the adult brain might have undergone several plasticity mechanisms over years to compensate

for the disconnection caused by AgCC. Lack of data in early developmental period has kept the question on the **role of callosal fibers in the development of brain networks** open.

We assess the maturation of interhemispheric callosal connectivity during infancy from structural and functional points of view. We address the role of callosal pathway in transferring visual and auditory information across hemispheres when callosal fibers are relatively immature, and further ask whether they interact with functional lateralization early on. We also integrate insights from infants with callosal agenesis to better characterize the role of interhemispheric connectivity in the auditory network.

1.4.4. Plasticity for the establishment of interhemispheric connectivity patterns

In the previous sections, we reported some evidence suggesting that interhemispheric connectivity might interact with hemispheric lateralization. One might wonder how this interaction will be limited when callosal connections are interrupted. Here, we describe a few evidence showing that plasticity mechanisms might recover interhemispheric communications to some extent in case of an early elimination of these pathways. In AgCC, the early absence of callosal fibers might allow alternative interhemispheric pathways (commissural/subcortical) to maintain several aspects of efficient interhemispheric communications. Plasticity mechanisms might further facilitate these communications. This can be also extrapolated from the studies showing that contrary to adults, children show smaller deficits after callosotomy (Lassonde, Sauerwein, Chicoine, & Geoffroy, 1991), suggesting that callosal pathways share common functions with alternative pathways early on. Thus, plasticity mechanisms may compensate the lack of callosal connections through these pathways.

Some animal studies also suggest that reorganization of the cortical circuits and their interhemispheric connectivity might be more limited when networks are more stabilized. In cats with sectioning of the posterior part of the corpus callosum before and after complete maturity of these pathways, only cats with early callosal transection showed a capacity for the interhemispheric transfer of pattern discriminations (Ptito & Lepore, 1983). These results indicate that with maturation of callosal fibers, other alternative pathways become less accessible with age and that early postnatal months might be an important period for the establishment of adult-like interhemispheric connectivity pattern. In the particular case of visual system, elimination of callosal fibers is significantly related to the early visual experience (Innocenti & Frost., 1980), preventing the plasticity mechanisms to compensate for restituting the normal-range number of callosal fibers, once visual input is deprived from early on. However, if deprivation occurs

after an initial short period of normal vision, normal interhemispheric connectivity pattern could be relatively restituted (Innocenti, Frost, & Illes, 1985).

1.5. Outline

We aimed to investigate the neural correlates of visual and auditory development in the infant brain with a focus on the ontogeny of two lateralized functions: face and speech processing. First, we studied how the neural substrates of early visual and auditory perception change over the first semester after birth, at the functional and structural levels. Using EEG and diffusion MRI, we evaluated how age changed the latency of auditory/visual evoked responses and the microstructural properties of white matter pathways that conducted these responses. In each network, we assessed whether the functional and structural changes were related to each other, beyond their dependency on age. Next, we tackled whether the neural substrates of face and speech processing were lateralized and if their lateralization interacted with interhemispheric connectivity in early infancy. We approach these questions in chapters 2 to 4.

In chapter 2, we present a study on the neural correlates of visual development and face processing lateralization in infants between 1 and 6 months of age. Using a paradigm with hemifield presentation of faces, we study hemispheric responses that were further transferred interhemispherically. We characterize the developmental changes in the latency of these responses and relate their speed to the structural properties of the underlying pathways. We address hemispheric lateralization of early face processing abilities by assessing each hemisphere's capability in a face discrimination task. We further evaluate the efficiency of interhemispheric transfer of visual information, asking whether face-relevant information stored in one hemisphere can be accessed on the opposite hemisphere.

In chapter 3, we present an ongoing study on the neural correlates of auditory development in infants between 1 and 6 months of age. Building up on the rationality of study in chapter 2, we use paradigms with monaural and binaural presentation of syllables and study how auditory responses change with age. In an attempt to We further studied the structural maturation of auditory white matter pathways and attempted to relate them to the functional maturation of auditory responses. We discuss how relating the functional and structural measures of development in the auditory network requires further investigations on the contribution of different pathways and callosal fibers to the measured auditory responses. To follow up on this issue with respect to the role of interhemispheric callosal connectivity in the auditory network, we performed the study in chapter 4. We further compare hemispheric differences in syllabic perception.

In chapter 4, we focus on the role of callosal fibers in the auditory network, by comparing infants with agenesis of corpus callosum and typical infants at 3-4 months of age. Using an auditory paradigm and EEG, we evaluated the brain responses to auditory stimuli and compared them between the two groups. This allowed us to assess the role of corpus callosum in the early organization of the auditory network.

In chapter 5, we discuss the position of the findings of these studies among the previous literature and highlight some perspectives. In the appendix on methodology, we describe the challenges of applying diffusion MRI and EEG methods to infants, and discuss the methodological limitations of our studies.

Chapter 2

The right hemisphere, but not the left, discriminates faces in infants

Preface:

The study in chapter 2 mainly addresses the question of face processing lateralization in infancy with the help of neuroimaging techniques. Lateralized presentation of stimuli (faces in one hemifield) are used to recover responses over each hemisphere and to further track their interhemispheric transfer. In parallel, the structural and functional correlates of visual development are investigated, by studying maturation of visual responses and white matter pathways. Another attempt was toward relating the structural and functional aspects of visual development.

A follow up control experiment is also presented in the appendix of this chapter, aiming to assess the specificity of the right-lateralized responses that we observed for faces in the original study. This experiment is still ongoing, but the preliminary data and results are presented in the appendix.

2. Early lateralized face processing

2.1. Abstract

Several cognitive functions, such as language processing, handedness, and face recognition, are strongly lateralized in the adult human brain. The ontogeny of these functional asymmetries is still poorly understood. Are they a consequence of differential development based on competition mechanisms, or are they constitutive of the human brain architecture from the start? Here, using structural MRI and a face discrimination EEG paradigm with lateralized presentation of faces, we studied visual development in 40 infants between 6 to 24 weeks of postnatal life. We showed that the corpus callosum is sufficiently mature to transfer visual information from one hemisphere to the other. The inter-hemispheric transfer-time of early visual responses (P1), with no left-right asymmetries, is related to fiber myelination of the splenium of the corpus callosum, evaluated with diffusion imaging. Looking at later face-specific responses (N290 and P400), we revealed that only the right hemisphere shows evidence for face discrimination when presented in the left visual hemifield. This capability improved throughout the first semester of life in the right hemisphere with no evidence of discrimination in the left hemisphere. The right-hemisphere advantage for face processing is thus a characteristic of the human infant's extra-striate visual cortex, highlighting the differential left-right organization of the human brain already established in infancy.

Keywords: Face processing, Brain Development, Infancy, EEG, MRI, Diffusion imaging, Hemispheric Lateralization, Myelination

2.2.Introduction

The adult human brain is parcellated into multiple functional regions which are remarkably similar across individuals despite differences in cultural, linguistic, or socio-economic background. Even for culturally learned skills such as reading, similarly-localized activations are observed across writing systems and ages of acquisition (Stanislas Dehaene, 2009) revealing the weight of structural constraints on functional architecture. Despite a growing body of evidence on the existence of specialized functional modules in the adult brain, the developmental course of such functional specialization is still poorly understood. Hemispheric functional asymmetries represent a radical example of functional specialization since *a-priori* similar cortical areas end up with different functional specificities.

Here, we aimed to understand the origin of the right-hemispheric advantage for face processing. Two main hypotheses can be proposed. First, structural differences between hemispheres result in a better efficiency of the right hemisphere to process faces from the start. These structural differences might be determined early on during gestation based on cortical “protomaps” (Rakic, 1988). They might also be driven or amplified by maturational asymmetries in gray matter or white matter pathways, which would give rise to a transitory advantage in one hemisphere when infants are exposed to frequent and expected stimuli such as speech and faces (de Schonen & Mathivet, 1989; Dehaene-Lambertz & Spelke, 2015). In line with this first hypothesis, asymmetries in cortical maturation (Leroy et al., 2011) and in bundle myelination (Dubois, Dehaene-Lambertz, et al., 2008; Dubois et al., 2016) have already been reported in the language network during the first semester of life. The second hypothesis postulates that both hemispheres are equally competent at the onset of development and responses to faces become restricted to the right hemisphere as infants and children enlarge their visual world and learn new visual categories (Johnson, 2001). The organization of the final mosaic of specialized regions in the adult brain is determined through competition possibly weighted by inherent structural connectivity advantages (Saygin et al., 2016). For example, visual word-specific activation is left-lateralized in order to reduce the path length toward the oral language network, resulting in a competition between words and faces to occupy the same territory in the left hemisphere (Dundas, Plaut, & Behrmann, 2013). This idea is supported by evidence of more right lateralized responses to faces in normal readers compared to dyslexic children (Monzalvo et al., 2012) and illiterate adults (Dehaene et al., 2010). In both hypotheses, connectivity, maturation, and exposure have an influence on the brain’s final organization; however, these hypotheses diverge on the initial organization of the brain. The former promotes initial neural specificities of genetic origin, which constrain the processing of the visual environment, whereas the latter emphasizes the role of the environment in

determining the organization of the brain. This debate is not purely theoretical as plasticity might be reduced in areas committed to specific functions, explaining long-term effects of early sensory deprivation (Le Grand et al., 2003) and, more generally, inadequate early stimulation.

Faces are the first and most frequent visual stimulus to which infants are exposed, and face recognition is crucial to establish social bonding. Face perception is hypothesized to rely on both innate biases for orienting one's gaze to face-like stimuli and personal experience in discriminating faces of one's entourage (Acerra et al., 2002; Gauthier & Nelson, 2001; Morton & Johnson, 1991). From birth on, neonates discriminate their mother's face from a stranger's initially using predominantly the hairline and outer contour of the head (Bushnell, Sai, & Mullin, 1989; Pascalis et al., 1995). They tolerate only a slight deviation from the frontal view in recognizing the same face (Turati, Bulf, & Simion, 2008). During the first months of life, they rapidly progress in recognizing novel faces, even when presented in different orientations (Cohen & Strauss, 1979), and perform better for ethnic faces with which they are most familiar (Kelly et al., 2005) and the gender that is most represented around them (Quinn et al., 2008; Quinn et al., 2002; Righi et al., 2014).

What are the neural bases of this rapid and efficient learning? Is there already a right hemisphere advantage to process faces in infants? Electro-encephalography (EEG) is the easiest technique to study the infant brain. Two evoked-related responses (ERPs) components, the N290 and P400, have been reported to be modulated by face perception (de Haan, Pascalis, & Johnson, 2002; Gliga & Dehaene-Lambertz, 2005; Gliga & Dehaene-Lambertz, 2007; Halit, de Haan, & Johnson, 2003), and face discrimination (Key & Stone, 2012; Peykarjou, Pauen, & Hoehl, 2016; Righi et al., 2014; Scott, 2006). Although a larger right response has been reported in some studies (Gliga & G. Dehaene-Lambertz, 2005; Scott, Shannon & Nelson, 2006), these components are commonly measured bilaterally. Recently, 4-6 month-old infants were shown to recognize faces in different orientations in natural scenes, and the face-selective responses highlighted by a frequency-tagging approach appeared to be strongly right-lateralized (de Heering & Rossion, 2015), in agreement with hemispheric asymmetries described in adults using the same method (Rossion, Torfs, Jacques, & Liu-Shuang, 2015).

Near-infra-red spectroscopy (NIRS) studies confirm an early right hemispheric superiority. Using a recording patch over the temporal areas in 5 to 8-month-old infants, Kakigi and collaborators reported a bilateral response to canonical upright faces relative to a baseline of vegetable pictures (Honda et al., 2010; Nakato et al., 2011; Otsuka et al., 2007), but a right hemispheric advantage emerged when canonical vs. scrambled faces (Honda et al., 2010) and upright vs. inverted faces (Otsuka et al., 2007) were contrasted.

The response in the right hemisphere progressively enlarged along the third trimester of life, notably for other views of a face (Nakato et al., 2009). PET and fMRI studies in young children are surprisingly less conclusive. Responses to faces have been localized to the fusiform regions in infants (Deen et al., 2017; Tzourio-Mazoyer et al., 2002) but might be less specific to such stimuli than later in life, as these regions were similarly activated by faces and objects in 3 to 8-month-old infants contrary to adults (Deen et al., 2017). The reported fusiform activations were either not lateralized (Deen et al., 2017) or weakly right lateralized (Tzourio-Mazoyer et al., 2002). Note that in NIRS studies, measures from a large temporal recording patch were merged. This might increase the sensitivity to small but consistent differences in each voxel from the ventral temporal areas but also sum up activity from different regions involved in face perception – i.e., the fusiform gyrus, the occipital face area and the posterior superior temporal region – which were reported but not merged for analyses in the MRI and PET studies. Face-specific activations measured with fMRI in the ventral visual areas remain weak over a long period. Hardly observed in young children at 5-8 years of age (Scherf, Behrmann, Humphreys, & Luna, 2007), but see (Cantlon, Pinel, Dehaene, & Pelphrey, 2011), face-selective responses in the fusiform gyrus progressively enlarge throughout childhood, with a stronger right-lateralization in adults than in children (Gathers et al., 2004; Golarai et al., 2007; Peelen, Glaser, Vuilleumier, & Eliez, 2009). A longer period of gray matter microstructural changes in the posterior fusiform gyrus than in neighboring areas might support this long functional development (Gomez et al., 2017).

Another way to establish each hemisphere's specificities is to exploit visual hemifield presentation: due to the organization of the visual pathway, only the contra-lateral hemisphere is informed on the stimulus until inter-hemispheric transfer occurs. In adults, reaction times for recognizing faces are faster when presented in the left hemifield (right hemisphere) than in the right hemifield while opposite results are obtained for word reading (Rizzolatti, Umiltà, & Berlucchi, 1971). A left hemifield alexia reported in a patient with a lesion of the splenium (Cohen et al., 2000) and the requirement of a left hemifield presentation to encode face identity across different orientations (Verosky & Turk-Browne, 2012) are some of the examples which establish that in adults, word and face identification is restricted to a specific hemisphere and that information presented to the other hemisphere needs to be transferred to the specialized hemisphere to be correctly processed.

In infants, a left hemifield (i.e. right hemisphere) superiority was observed in three-month-olds, who oriented faster to familiar faces presented in the left hemifield than in the right (de Schonen & Mathivet, 1990; De Schonen et al., 1986). A robust left hemifield superiority was also reported when the

two faces were differing in eye size and eye orientation but a reverse effect (left hemifield-right hemisphere advantage) was observed when differing for by their eye shape in 4 to 10 month-old infants (Deruelle & de Schonen, 1998). However, behavioral experiments cannot disentangle the following hypotheses: (1) both hemispheres perform the task but the left hemisphere is slower than the right, or (2) only the right hemisphere performs the task, revealing a radical dissociation as reported in adults.

Furthermore, if both hemispheres have different competencies, what is the role of the corpus callosum in amplifying or reducing these differences? This large pathway is completed during gestation (Kostovic & Jovanov-Milosevic, 2006), but its myelination continues until adolescence. Concerning the splenium fibers which connect visual regions, their myelination begins after the third postnatal month and rapidly progresses until the end of the first year (Brody et al., 1987; Yakovlev & Lecours., 1967) and possibly later on (Nakagawa et al., 1998). We may thus wonder whether this rapid maturation has a role in the development of left-right functional asymmetries allowing the most competent hemisphere to inhibit the other (Levitan & Reggia, 2000) or whether the callosal fibers only follow the maturational calendar of the connected visual areas.

Exploring the question of inter-hemispheric transfer, de Schonen and collaborators used a conditional learning paradigm in which infants learned to orient to an upper toy for one image and to a lower toy for another image. The images were first presented in one hemifield, then the authors measured whether the number of trials to reach the learning criterion was reduced for the same images secondarily presented in the other hemifield. A transfer was observed at 6 months when a face and a scrambled face were presented (de Schonen & Bry, 1987) but no inter-hemispheric transfer was observed before 24 months of age when two faces were used (de Schonen & Mathivet, 1990; Deruelle & de Schonen, 1998; Liégeois et al., 2000). Therefore, reconsidering the first study, Liégeois et al. (2000) hypothesized that face categorization was probably conveyed through subcortical pathways to both hemispheres and that face identity encoding required the corpus callosum, which was not fully functional before the second year of life. By contrast, Sann and Streri (2007) showed that neonates were able to transfer tactile and haptic information from one hand to the other (Sann & Streri, 2007). The discrepancy between these results might be related to a different experimental sensitivity but more probably to the fibers connecting perioral regions being consistently more mature than splenium fibers from gestation on (Flechsig, 1920).

We thus aimed to reconsider these questions thanks to the opportunities offered by coupling structural and functional brain imaging techniques. We used diffusion imaging and high-density (128 channels) electro-encephalography (EEG) in a group of 40 infants aged between 1 to 5 months, 13 of them

completing both diffusion imaging and EEG tests. We first assessed the influence of connectivity on the infant's visual responses by correlating the speed of visual ERPs with diffusion tensor imaging (DTI) measures of white matter maturation obtained in the same infants. DTI can be used to follow white matter myelination throughout infancy due to its sensitivity to water molecule diffusion (Dubois et al., 2014; Dubois et al., 2008; Neil, Miller, Mukherjee, & Huppi, 2002; Song et al., 2003; Song et al., 2005). Water diffusion becomes preferentially channeled along axons with the progressive myelination of the fibers, resulting in a decrease in transverse diffusivity. In parallel, myelination accelerates the conduction of neural responses, which can be captured on the scalp through decreases in the latencies of the ERP components. For central stimuli, for instance, the latency of the first visual evoked component (P1) shifts from around 300 ms at birth to about 120 ms after 12 weeks of age (McCulloch et al., 1999). In a previous study, we related this acceleration to the myelination of the optic radiation and, notably, to a decrease in transverse diffusivity (Dubois, et al., 2008). In the present study, we compared the P1 latency for central and lateralized stimuli and correlated the latency of the P1 response appearing on the contralateral hemisphere to the transverse diffusivity of the optic radiation. We also measured the inter-hemispheric transfer-time (IHTT) as the difference between the contra- and ipsi-lateral P1 and correlated it with the transverse diffusivity in the splenium fibers that connect the visual areas. In adults, a shorter IHTT has been shown to correlate with lower mean diffusivity (Westerhausen et al., 2006), higher fractional anisotropy (Whitford et al., 2011), and higher axon diameter (Horowitz et al., 2015) in the posterior part of the corpus callosum.

Second, we evaluated each hemisphere's competency in discriminating lateralized faces. Are both hemispheres or is only the right hemisphere reacting to a new face? How is information on face identity exchanged between hemispheres? Infants were thus exposed to two streams of faces in the left and right hemifield (Figure 2.1). One face was assigned to one hemifield and was presented frequently (standard image). Occasionally deviant faces, defined as either a new face (new-deviant image) or the standard face of the other side (known-deviant image), were presented. The new-deviant condition was used to separately study each hemisphere's response to change and thus to compare their efficiency. Contrarily, the known-deviant condition was used to study the functional efficiency of the corpus callosum at this age. We hypothesized that if the corpus callosum is already efficient at this age, the ipsi-lateral face ("known-deviant" image) should be considered as familiar as the contra-lateral face (standard image), whereas if there is no inter-hemispheric transfer, it should be considered as novel as the "new-deviant" face.

2.3. Materials and Methods:

We report results obtained in two groups. A first group of infants was studied with both EEG and diffusion MRI to study the functional maturation of visual responses for lateralized stimuli in relation to the structural maturation of white matter pathways. A second group of infants was tested only with EEG to complete our initial analyses on face discrimination using lateralized stimuli and also to study responses for central faces.

2.3.1. Subjects

The first group consisted of 24 healthy full-term infants aged between 5.8 to 22.4 weeks (mean 14 ± 5.9 weeks, 11 girls). They were first scanned with MRI and then underwent EEG recordings within a week. Two infants had artifacted MRI images, 3 were not tested with EEG because their parents were unable to return in the predetermined delay, and 4 were rejected due to excessive movement during EEG. Thus, 22 infants were included in the structural analyses (mean age: 13.8 ± 4.2 weeks), 15 infants in the ERPs analyses (mean age: 15 ± 4.1 weeks), and 13 infants provided good MRI and EEG data to analyze the correlations between DTI parameters and ERPs latencies (mean age: 14 ± 4.3 weeks).

The second group of 25 healthy full-term infants (from 5.6 to 23.6 weeks old, mean age: 13.9 ± 5 weeks, 14 girls) was only tested with EEG. Twelve additional infants were excluded due to insufficient data quality. These 25 infants were merged with the 15 infants described above for a total of 40 infants in whom we studied electrophysiological responses to lateralized face presentations. Out of the 25 infants of the second group, 23 of them were presented with additional centered faces during the experiment.

The study was approved by the ethical committee for biomedical research. All of the infants' parents were informed about the content of the experiment as well as its goals and gave written informed consent before starting the experiment.

2.3.2. MRI acquisition and post-processing of diffusion MRI images

Acquisitions were performed during spontaneous sleep in a 3T MRI system (Tim Trio, Siemens Healthcare, Erlangen, Germany), equipped with a whole-body gradient (40mT/m, 200T/m/s) and a 32-channel head coil. T2-weighted (T2w) images were acquired in infants using a 2D turbo spin echo sequence (spatial resolution = $1 \times 1 \times 1.1 \text{ mm}^3$) (Kabdebon et al., 2014). A diffusion-weighted spin-echo EPI sequence was used with 30 orientations of the diffusion gradients applied with $b=700 \text{ s.mm}^{-2}$. Fifty interleaved axial

slices covering the whole brain were acquired with a 1.8mm isotropic spatial resolution, leading to a total acquisition time of 5min40s which is reasonably short for unsedated infants (Dubois et al., 2016).

After correction for motion artifacts with Connectomist software (Dubois et al., 2014; Duclap et al., 2012), probabilistic tractography was performed based on a 2-crossing-fiber diffusion model over individual brain masks with FSL software (Behrens et al., 2007). Using individual seed regions, several tracts were dissected: left and right optic radiations and visual callosal fibers from the visual network as well as acoustic radiations and auditory callosal fibers from the auditory network for comparative purposes. Seeds were localized at the level of Lateral Geniculate Nucleus (LGN) and occipital regions for optic radiations and at the level of Medial Geniculate Nucleus (MGN) and auditory regions for acoustic radiations. Seeds for callosal fibers were located in left and right primary visual/auditory areas and fibers connecting these primary areas should pass through the corpus callosum splenium. Following the estimation of the diffusion tensor, DTI maps (fractional anisotropy FA, mean $\langle D \rangle$, transverse λ_{\perp} and longitudinal λ_{\parallel} diffusivities) were computed for each subject. Averaged parameter X was calculated for each tract by taking into account fiber density on the tract probability map (Hua et al., 2008):

$$\bar{X} = \frac{\sum^i Pr_i \times X_i}{\sum^i Pr_i},$$

where i denotes the tract voxels, Pr_i is the fiber density at voxel i , and X_i is the value of the DTI parameter at voxel i . In white matter, DTI parameters are affected by axonal organization, compactness and myelination. We focused on transverse diffusivity which has been shown to be the best DTI marker of myelination (Dubois et al., 2008; Song et al., 2003; Song et al., 2005).

2.3.3. EEG protocol

2.3.3.1. Experimental paradigm

Colored front faces of four female and four male adults with neutral expressions were used as visual stimuli. Six of these images were used for lateralized presentation and two for centered presentation. The image presentation was driven by E-Prime (Psychological Software Products, Harrisburg, PA). The infants' eyes were attracted to the center of the screen by a rotating colored bull's-eye which remained at the center of the screen during the whole experiment (Figure 2.1).

Lateralized paradigm: Two streams of face images were presented at the left and right side of the rotating bull's-eye (Figure 2.1. b-c). The center of the image was at ~7.5 degrees of eccentricity from the

infants' center of view, its inner/outer edges at $\sim 3.1/12.5$ degrees of eccentricity for an infant sitting at about 60 cm from the screen. Each image was presented for 250 ms. The left and right images were presented asynchronously in an alternating fashion with a variable delay between images (550 to 950 ms post-offset of the image with a 50 ms step) to avoid anticipatory looks to the sides. Each stream included three types of images: a side-assigned face image (standard), a novel face (new-deviant), or the face commonly assigned to the other side (known-deviant). Inside a block, the faces were either all female or all male. Two similar paradigms but with different trial organizations were used for the two groups of infants.

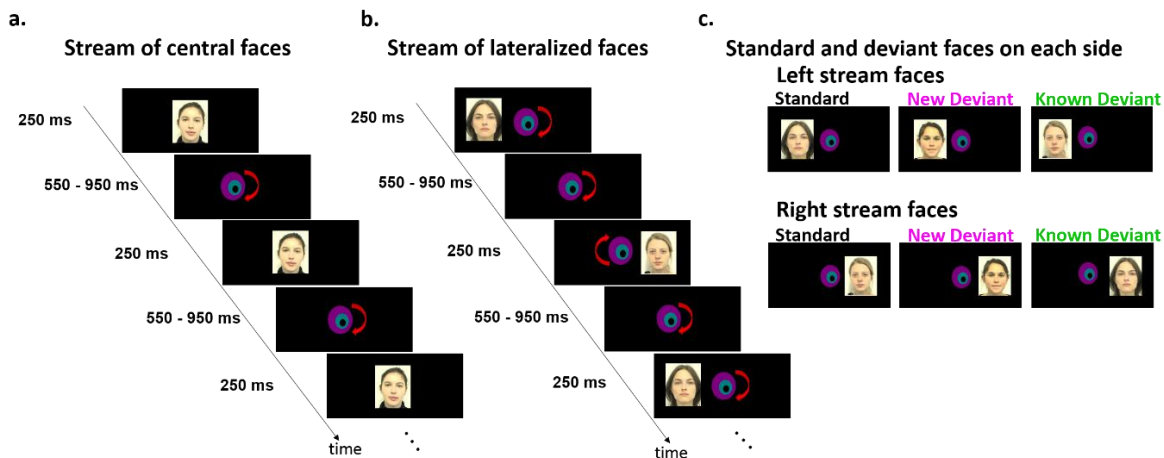


Figure 2.1. EEG experimental paradigms: a) Centralized presentation: A stream of female (or male) face images was presented at the center of the screen. Each face was presented during 250 ms, separated by a random interval of 550 to 950 ms during which a rotating and colored bull's-eye was presented at the center of the screen. b) Lateralized presentation: Two streams of face images were presented in the left and right visual hemifields in an alternating fashion. The colored bull's-eye was always rotating at the center of the screen to attract the infants' gaze toward the center of the screen and to avoid saccades to the periphery. In each block of the experimental design, one face image was attributed to each side and was presented for 250 ms followed by a post-stimulus random interval of 550 to 950 ms. Each block consisted of only female or only male images. c) The different conditions of the lateralized paradigm: For each block, one standard face was attributed to one side and presented in $\sim 80\%$ of trials. In $\sim 10\%$ of trials, known-deviant faces corresponded to the standard faces on the incorrect side whereas new deviant faces were rare faces with no attributed side ($\sim 10\%$ of trials).

First group (15 infants): To familiarize infants with the experimental paradigm and for them to learn the face-side assignment, 8 standard trials with side-assigned faces were first presented on each side (habituation phase). Then in a test phase, 54 trials were presented on each side, with a succession of 18 3-trial structures: 2 standard trials and the third trial being randomized chosen among either a standard, new- or known-deviant condition (Figure 2.1. c). Over the 54 trials, 42 (77.8 %) were thus standard trials, and 6 (11.1%) were new- or known-deviant trials. Each block included 124 trials (2 sides x (8 habituation + 54 test) trials), out of which 80.6 % were standard, 9.7 % new-deviant and 9.7 % known deviant. The whole experiment comprised 4 blocks alternating between female and male faces (9 mins).

Second group (25 infants): In the first group, the side of the first block image was not counterbalanced across infants, implying that the critical third image of the 3-trial structure (standard vs new- vs known-deviant faces) was always presented on the left side before the right side. In the second group, we controlled for trial order, such that: 1. Deviant trials were preceded by a similar number of standard trials on both left and right sides. 2. No two successive deviant faces at the same or opposite sides were allowed. Infants were presented with 4 blocks of 80 trials at each side (60 standard, 10 new-deviant, 10 known-deviant). As for the first group, 8 standard trials were presented at the beginning of each block in each hemifield, leading to 176 trials per block (2 sides x (8 habituation + 80 test) trials), out of which 77.3 % were standard, 11.4 % new-deviant and 11.4 % known-deviant.

Central paradigm (23 infants): We took advantage of this second group to test infants' responses to centered stimuli (Figure 2.1.a). 4 additional blocks of 30 trials (2 images with female and 2 with male faces) were presented after the blocks with lateralized stimuli. One female and one male face, not used during the lateralized paradigm, were presented at the center of the screen for 250 ms, spaced by a random interval of 250-550 ms during which the colored bull's-eye was presented (Figure 2.1. a). The total duration of the second experiment (lateralized + centered paradigms) was at most 15 min.

2.3.3.2. EEG data acquisition

An EEG recording net comprising 128 electrodes (EGI, Eugene, USA) with a reference on the vertex was placed on the infants' heads relative to anatomical markers. Infants were seated on their parents' laps in front of the screen in a shielded EEG room. Music was continuously played behind the screen to attract the infants' attention toward the screen. If an infant was distracted, the experiment was briefly interrupted and the experimenter focused her/his attention back toward the screen. If it was not possible, the experiment was prematurely terminated. A camera placed above the screen recorded the infants' position and looking direction throughout the experiment. EEG was continuously digitized at a sampling rate of 250 Hz during the whole experiment (net amp 200 system EGI, Eugene, USA).

2.3.4. EEG processing and ERP analyses

2.3.4.1. EEG pre-processing

EEG recordings were band-pass filtered between 0.5 and 20 Hz on the EGI recording station, then exported to be processed using MATLAB toolboxes: EEGLAB (Delorme & Makeig, 2004) and Brainstorm (Tadel et al., 2011). The signal was segmented into epochs of 1700 ms, [-200, +1500] ms relative to the onset of each face presentation. Channels contaminated by movement or eye artifacts were automatically

rejected on a trial by trial basis based on amplitude variations inside an epoch: each channel epoch was rejected when the fast average amplitude exceeded 250 μV , or when deviation between fast and slow running averages exceeded 150 μV . Electrodes were rejected if they were marked as bad in more than 70% of the epochs, and trials were rejected if more than 50% of the electrodes were marked bad. Recordings were then re-referenced by subtracting the average activity of all channels over the brain to obtain average-reference recordings, then baseline-corrected by the 200ms preceding the onset of the image presentation. On average, we obtained 171/170 correct trials respectively for the left/right hemifield faces in the first group of infants, and 72/71/37 for the left/right/center location in the second group. For each infant, trials were first averaged by stimulus side (i.e., left/right/center) in order to evaluate the early visual ERP responses (i.e. P1). Then trials were averaged by condition (standard faces, new- or known-deviant faces in the left and right hemifield) to study face discrimination.

2.3.4.2. Early visual perception

P1 latencies: For left/right hemifield presentation, we evaluated the latency of the contralateral and ipsilateral P1 across the two groups (15+25=40 infants). On the grand average topography, we identified two symmetrical clusters of five electrodes around O1 and O2 where early visual responses were observed independent of infants' ages. We averaged the time-series across the electrode clusters in each infant and measured the latencies of the following components (Figure 2.2. b): P1 as the first positive peak in the hemisphere contralateral to the image, and P1 ipsi as the first positive peak appearing after P1 in the hemisphere ipsilateral to the stimulation. The inter-hemispheric transfer time (IHTT) was defined as the latency difference between these two peaks ($IHTT = Latency_{P1\ ipsi} - Latency_{P1}$). For central faces, P1 latency was identified in each infant as the first positive peak over a cluster of 6 medial occipital electrodes surrounding Oz (Figure 2.2. a).

Effect of age on P1 latencies and transverse diffusivity: We first assessed the effect of age on functional and structural measures: i.e. contralateral P1, IHTT and central P1 on one hand, and on transverse diffusivity in optic/auditory radiations and visual/auditory callosal fibers on the other hand. To evaluate domain-specific maturational patterns beyond a general effect of age, we computed partial correlations between transverse diffusivity measures (controlling for age) for the 4 pairs of tracts. We used a False Discovery Rate (FDR) approach to correct for the number of comparisons. Finally, we tested hemispheric asymmetries in the optic and acoustic radiations with paired t-tests on the transverse diffusivity in the left and right tracts.

Relationships between P1 latencies and tract-specific transverse diffusivity: We proceeded by examining the relationship between functional and structural measures of maturation. Because ERP latencies depend on the distance the neural signal has to travel in addition to the myelination of pathways, we computed conduction speeds of ERP responses (distance/latency) using anatomical distances in the brain. For contralateral P1 latency, we approximated the length of the optic radiations as the distance between the eyes and the occipital poles measured on each individual infant's T2w images as in our previous study (Dubois et al., 2008) and computed the conduction speed of P1 ($Speed_{P1}$). For inter-hemispheric transfer time, we measured the length of the callosal fibers obtained by tractography and computed the speed of inter-hemispheric transfer ($Speed_{IHTT}$). To confirm the specificity of these results to the visual domain, we performed the same analysis but considering the acoustic radiations and auditory callosal fibers as surrogate tracts for $Speed_{P1}$ and $Speed_{IHTT}$, respectively. We used a False Discovery Rate (FDR) approach to correct for the four comparisons.

2.3.4.3. Discrimination of lateralized presented faces

To study face discrimination responses, we considered only the standard and deviant trials which were at the same position in the block structure. For the first group for which faces were presented in a 3-trial structure, we considered the third face of the structure which was either a standard, known-deviant or new-deviant face. In the second group to mimic the constraints imposed on deviant trials in the first paradigm, we selected the standard faces following at least 2 standard faces on the same or opposite side. The numbers of trials considered in each condition was therefore balanced. On average, we obtained 11/10/14 trials per subject for the new-deviant/ known-deviant/ standard conditions at each side. Epochs were averaged for each condition and side of presentation in each infant. As results were similar in the two groups, the data were merged.

In the literature, two face specific components, the N290 and the P400 recorded over the lower temporal regions, have been reported in infants (de Haan et al., 2002). We thus selected two clusters of 10 electrodes in the left and right inferior temporal regions extending from O1 to T5 electrodes on the 10-20 international system (as in Kouider et al., 2013). For each experimental condition, we averaged the voltage over these electrodes and over a 100 ms time-window centered on each component's peak in each infant. The peaks were determined on the grand-average from merging all conditions and infants. Therefore, we analyzed the three visual components (P1, N290 and P400) on the following time-windows [150-250] ms for the P1, [300-400] ms for N290 and [450-550] ms for P400 (Figure 2.4). The time-windows are slightly delayed compared to the classical timing of N290 and P400 components as latencies are delayed for

lateralized stimuli relative to central stimuli and also because our infant cohort is younger than those most commonly tested.

The voltage values were entered in three independent analyses of variance, each comprising three within-subject factors: condition (standard, known-deviant and new-deviant), electrodes (left and right cluster), and side of stimulation (left and right hemifield). We examined two effects of interest in pots-hoc analyses using paired t-tests: 1. Whether the new-deviant condition was significantly different from the standard condition in order to demonstrate face discrimination capabilities. 2. Whether the known-deviant condition was significantly different from the new-deviant condition or from the standard condition in order to evaluate the efficiency of the inter-hemispheric transfer. Finally, we evaluated whether the face discrimination response was correlated with age using robust regression. We report significant effects with a p-value below 0.05, once corrected for multiple comparisons using FDR correction.

2.4.Results:

2.4.1.An efficient inter-hemispheric transfer of early visual responses in infants

ERPs responses: Brain visual responses to faces were recorded with a high-density EEG system (128 channels) in infants aged between 5.6 to 23.6 weeks. 23 were tested with central faces (Figure 2. 1). The P1 latency measured over medio-occipital areas decreased with age from 185 to 121 ms ($R^2 = 0.41$, $p < 0.001$ in 23 infants, Figure 2. 2. a., c) and reached a plateau around 12 weeks of age (Figure 2. 2. c). This decrease in P1 latency was better fitted with a 3rd degree polynomial ($R^2 = 0.72$, $p < 0.001$) than a linear model (Akaike's information criterion (Akaike, 2011): AIC polynomial model = 179; AIC linear model = 189).

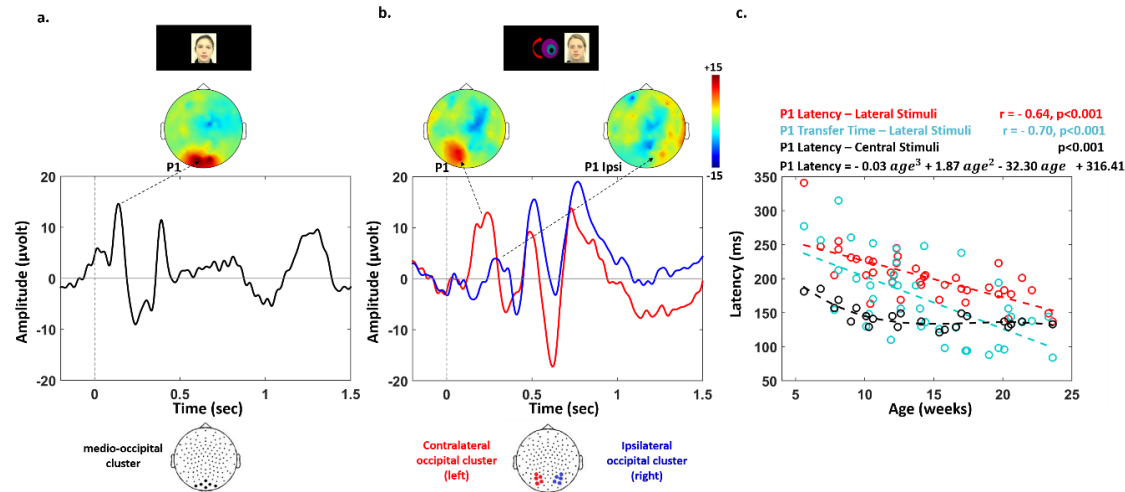


Figure 2.2. Examples of visual event-related responses in one infant: a) Voltage time course in response to central stimuli averaged over a cluster of electrodes covering the mid-occipital region in one infant. Time zero marks the onset of the face stimuli. b) Responses to faces presented in the right hemifield averaged across the left and right occipital clusters of electrodes (red and blue curves respectively) in one infant. The contralateral P1 appears over the left hemisphere and then propagates toward the ipsilateral hemisphere. c) Relation between P1 latencies and age: P1 for central stimuli (black curve), contralateral P1 for lateralized stimuli (red curve), and inter-hemispheric transfer-time (blue curve). P1 latencies were faster for central than for lateralized stimuli and reached a plateau after 12 weeks of age, whereas the decrease was linear for the contralateral P1 and the inter-hemispheric transfer times.

Lateralized faces were used in 40 infants (comprising the 23 infants mentioned above). An initial response over the contralateral hemisphere was identified followed by a response on the ipsi-lateral hemisphere (Figure 2. 2. b.). The P1 latency for contralateral responses to lateralized faces was slower than the responses for central faces ($t(1,22) = 9.3$, $p = 0.004$) and linearly decreased with age (from 341 to 137 ms, $R^2 = 0.51$, $p < 0.001$ in 40 infants; Figure 2. 2.c). The IHTT similarly decreased from 315 to 84 ms ($R^2 = 0.39$, $p < 0.001$, Figure 2. 2. c). The age-related slopes did not differ between the contralateral P1 latency and IHTT ($t(1,39) = 1.5$, $p > 0.1$). Finally, P1 latencies and IHTT were similar for faces in the left and right hemifield (P1: $t(1,39) < 1$, $p > 0.1$; IHTT: $t(1,39) = -1.5$, $p > 0.1$).

DTI measures: The maturation of the optic radiations and commissural fibers was studied in 22 infants imaged with diffusion MRI and compared to the equivalent tracts in the auditory domain to control for general vs domain-specific maturation. We dissected the optic and acoustic radiations (OR, AR), the visual and auditory callosal fibers (vCC, aCC) with probabilistic tractography (Figure 2. 3. a.). In all tracts, DTI transverse diffusivity significantly decreased with age (Figure 2. 3. b, $-0.87 < r < -0.68$, $p < 0.001$).

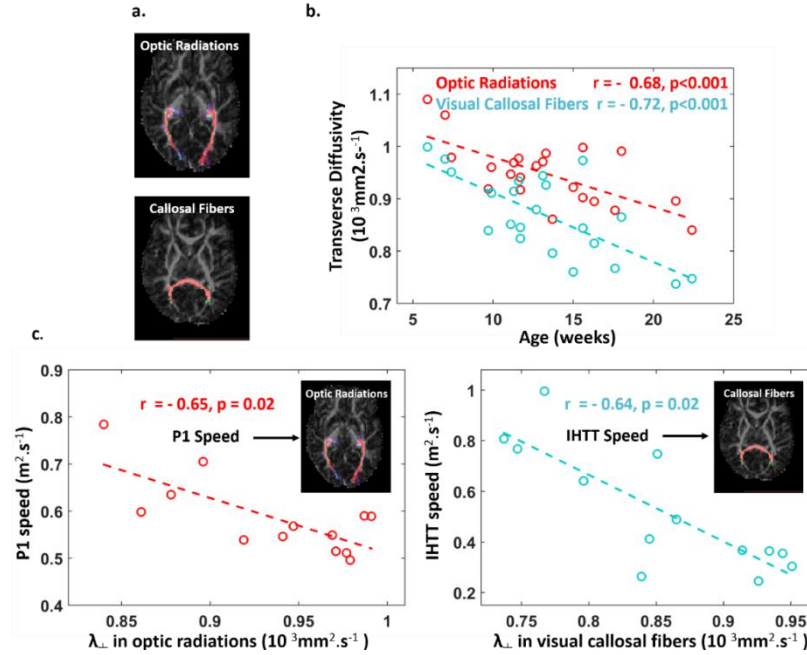


Figure 2.3. Structure-function relationships: a) Reconstructed bundles of the visual network: optic radiations, extending from the lateral geniculate nucleus to occipital regions (top) and callosal fibers connecting the occipital regions and passing through the splenium (bottom). b) Relation between transverse diffusivity and age in the two bundles. c) Partial-correlations show that P1 speed is related to the transverse diffusivity in the optic radiations (left) and the inter-hemispheric transfer speed is related to transverse diffusivity in the visual callosal fibers (right), independent of age.

Using partial correlations to remove global effects of the infants' ages (Table 2.1), we observed significantly correlated maturational patterns for the microstructural properties of optic radiations and visual callosal fibers (r (OR-vCC | age) = 0.78, $p < 0.001$) and for the visual and auditory callosal fibers (r (vCC-aCC | age) = 0.74, $p < 0.001$). These results suggest that bundles belonging to the visual network mature in synchrony as do callosal fibers connecting visual and auditory regions in the splenium. Finally, transverse diffusivity was lower in the left relative to the right hemisphere in both optic radiations ($t(1,21) = -5.3$, $p < 0.001$) and auditory radiations ($t(1,21) = -5.1$, $p = 0.001$), suggesting an advanced maturation in the left hemisphere tracts.

Table 2. 1. Maturational synchrony across bundles: Partial-correlations were computed for transverse diffusivity in the different pairs of bundles, while controlling for the age. P-values are FDR corrected for multiple comparisons.

	Optic Radiations	Visual Callosal Fibers	Acoustic Radiations	Auditory Callosal Fibers
Optic Radiations		$r = 0.78, p < 0.001$	$r = 0.63, p = 0.004$	$r = 0.55, p = 0.014$
Visual Callosal Fibers			$r = 0.35, p > 0.1$	$r = 0.74, p < 0.001$
Acoustic Radiations				$r = 0.42, p = 0.069$
Auditory Callosal Fibers				

In a subgroup of 13 infants studied with both the ERP lateralized paradigm and diffusion MRI, we investigated whether the conduction speed of visual evoked responses (i.e. distance/latency, see method) was related to the maturational properties of the underlying pathways. Using partial correlations to

account for infants' ages (table 2.2), we observed that the speed of the contralateral P1 was related to the maturation of optic radiations ($r(\text{speedP1} - \text{OR} \mid \text{age}) = -0.65, p = 0.021$, Figure 2.3.b), while the speed of inter-hemispheric transfer was related to the maturation of visual and auditory callosal fibers ($r(\text{speed}_{\text{IHTT}} - \text{vCC} \mid \text{age}) = -0.64, p = 0.025$, Figure 2. 3. c.; $r(\text{speed}_{\text{IHTT}} - \text{aCC} \mid \text{age}) = -0.65, p = 0.021$).

Table 2. 2. Structure-function relationships: Partial-correlations were computed between the speed of P1 or IHTT and transverse diffusivity in similar bundles of the visual and auditory networks, while controlling for age. P-values are FDR corrected for the number of comparisons.

	Partial Correlations
Speed P1 ~ Optic Radiations	$r = -0.65, p = 0.021$
Speed P1 ~ Acoustic Radiations	$r = -0.45, p > 0.1$
Speed IHTT ~ Visual Callosal Fibers	$r = -0.64, p = 0.025$
Speed IHTT ~ Auditory Callosal Fibers	$r = -0.65, p = 0.021$

Altogether, these results reveal that the inter-hemispheric transfer of early visual responses is already efficient during infancy and is strongly related to the maturation of the underlying callosal fibers.

2.4.2. An efficient discrimination of left-hemifield faces

In the second step of this study, we evaluated whether infants were able to discriminate faces that were presented either in the left or right hemifields (Figure 2. 1.c). Figure 2. 4 shows the grand average ERP on the ipsi- and contra-lateral clusters for each stimulated visual hemifield, all conditions merged (standard, new-deviant image and known-deviant faces). We focused our ERP analyses on the P1 to examine the effects of low-level features, and on the N290 and P400 components which are the classical components related to face perception in the infant literature (de Haan et al., 2002).

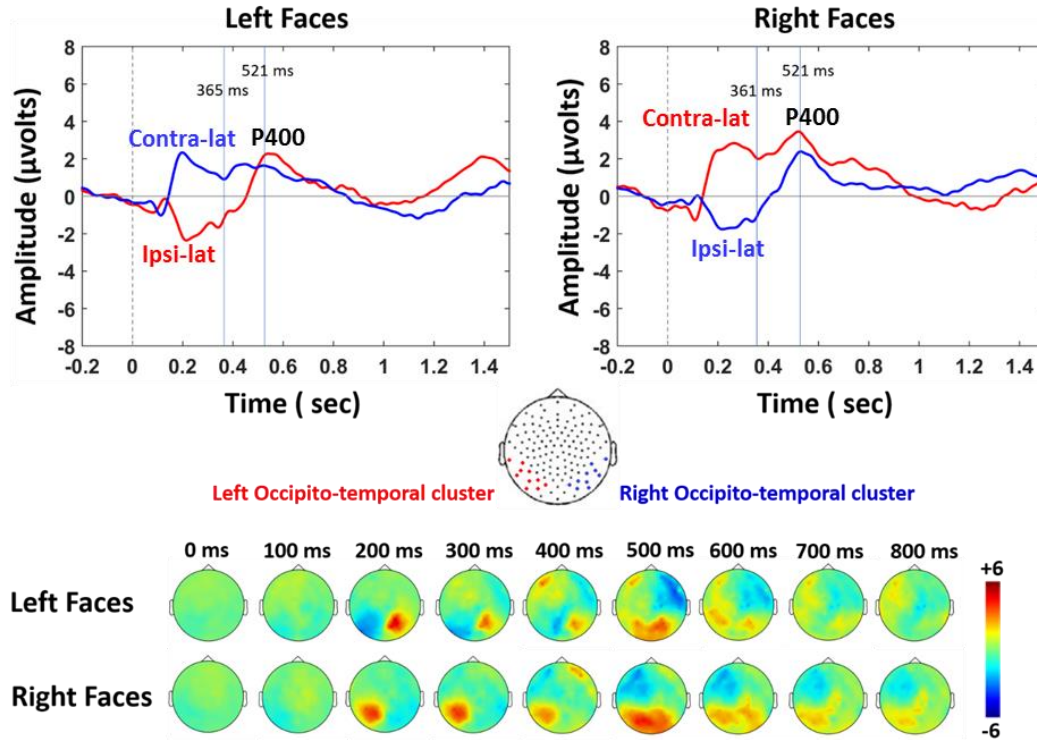


Figure 2. 4. ERP according to hemifield: Top row) Grand-averages were computed over the left (red line) and right (blue line) occipito-temporal clusters presented below the plots for faces presented in the left and right visual hemifields. The peaks of the N290 and P400 are indicated on the plots. Bottom row) 2D voltage topographies. The N290 interrupts the positivity on the contra-lateral cluster and the ascending slope on the ipsi-lateral cluster. We consider the following positivity as the P400 although latencies are delayed relative to what is reported for central faces

In each of the 40 infants tested with the lateralized paradigm, we averaged the voltage over three 100 ms time windows (P1: [150-250] ms; N290: [300-400 ms]; P400: [450-550 ms]) and over symmetrical left and right clusters of 10-electrodes in the occipito-temporal regions (Figures 2.4-6). We entered these values into separate analyses of variance (ANOVA) with condition (3-levels), hemifield (2-levels) and cluster (2-levels) as within-subject factors. Considering the P1, the ANOVA revealed a significant interaction hemifield by cluster ($F(1,39)=26.5$, $p<.001$) because, as expected for a lateralized stimulation, the contralateral response was larger than the ipsilateral response (for each hemifield, $p<.001$). A modest trend for an interaction condition by cluster was also present ($F(1,39)=2.6$, $p=.08$). Considering the N290, there was a main effect of condition ($F(1, 39) = 3.4$, $p\text{-value} = 0.039$), a marginally significant effect of cluster ($F(1,39) = 3.6$, $p = 0.065$), a significant interaction hemifield by cluster ($F(1, 39) = 15.1$, $p\text{-value} < 0.001$) and a marginally significant interaction between condition and cluster ($F(1,39) = 2.7$, $p = 0.074$). Considering the P400, only a main effect of hemifield was observed ($F(1,39) = 5.1$, $p = 0.030$). We then analyzed each hemifield separately.

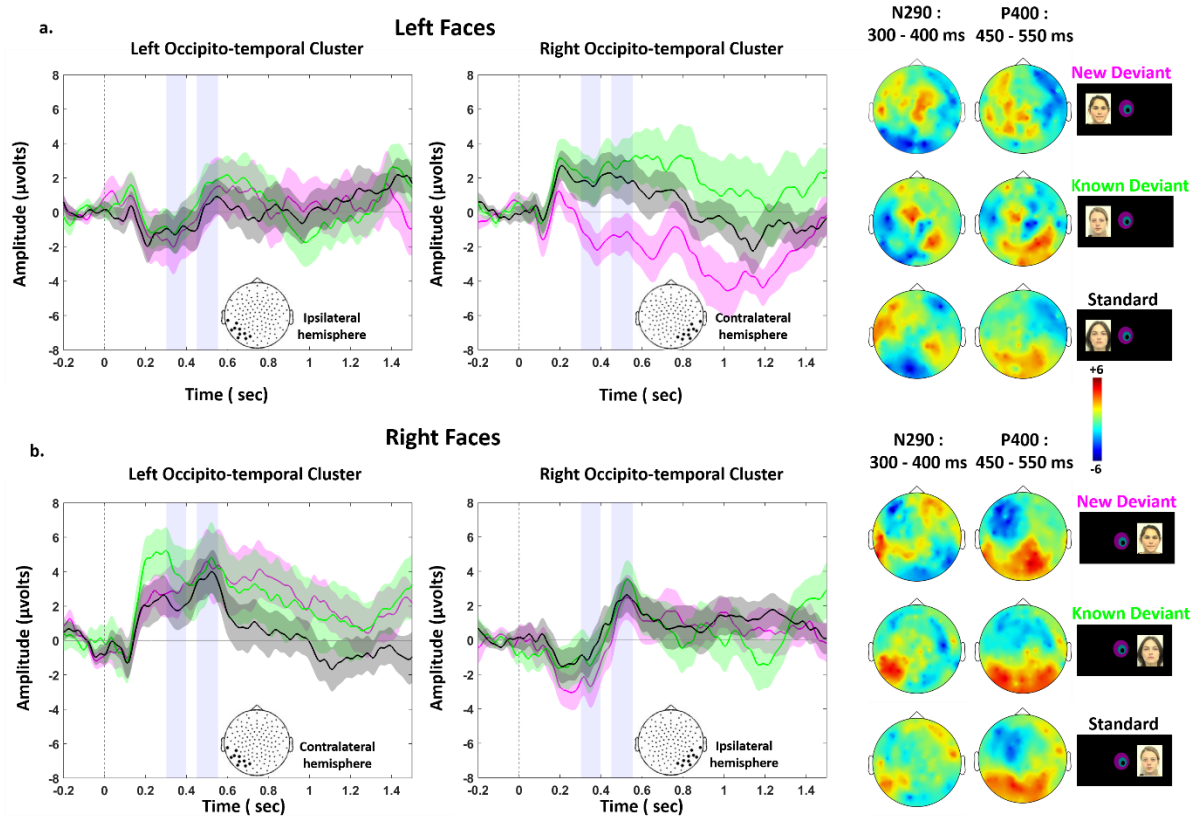


Figure 2.5. ERP according to the face conditions: Grand-averages were computed over the left and right occipito-temporal clusters (left and right plots respectively) for the new-deviant, known-deviant and standard faces presented in the left (a) and right (b) visual hemifields. Voltage topographies (right column) averaged over the [300-400] ms and [450-550] ms time-windows corresponding to the N290 and P400 respectively. There is a clear discrimination of new faces relative to the standard and known-deviant faces for the left hemifield faces over the contra-lateral right cluster, whereas no difference between conditions was observed for the right hemifield faces.

Responses to left hemifield faces. Considering the P1, there was no effect of condition on the contralateral ($F(1,39) = 2.4$, $p > 0.1$) and ipsilateral hemisphere ($F(1,39) < 1$). For the N290, an effect of condition was observed over the contralateral right cluster ($F(1,39) = 4.2$, $p = 0.016$) but not over the ipsilateral left cluster ($F(1,39) < 1$). Post-hoc t-test analyses for paired conditions indicated that the N290 amplitude was larger (i.e. more negative) for new-deviant faces than for standard and known-deviant faces (respectively: $t(1,39) = -2.2$, $p = 0.031$; $t(1,39) = -2.7$, $p = 0.014$) (Figure 2.5. a, Figure 2.6. a., table 2.3), whereas no difference was detected between standard and known-deviant faces ($t(1,39) < 1$). Thus, infants discriminated faces presented in their left hemifield, whereas standard faces from the other side (right hemifield) did not elicit a novelty response, demonstrating that face information had been transferred between hemispheres. The N290 amplitude difference between new and standard faces became larger with age ($r = -0.38$, $p = 0.047$, Figure 2.6. c.) due to an increase of the N290 absolute amplitude in response

to new-deviant faces. No age effect was observed for the difference between new- and known-deviant faces ($r = -0.16$, $p > 0.1$, Figure 2.6. c.).

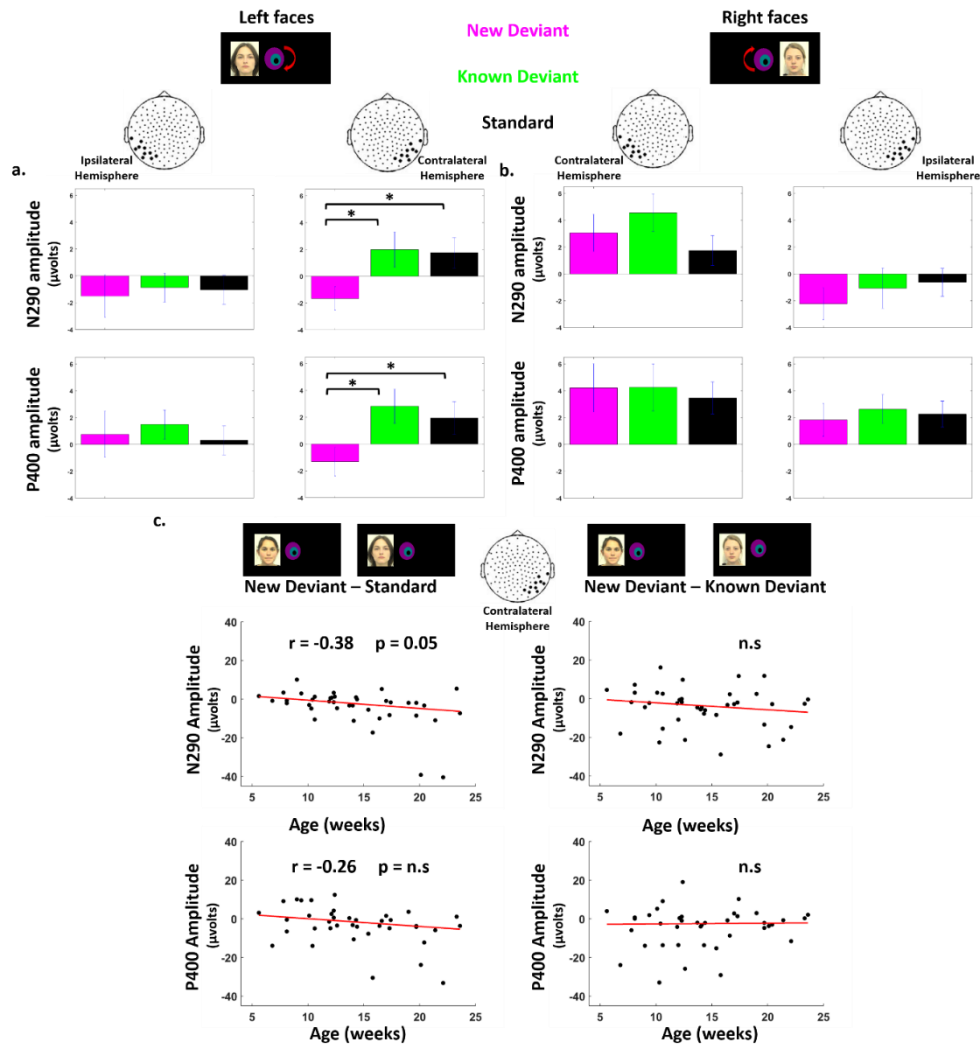


Figure 2. 6. Comparison of N290 and P400 components across face conditions: N290 (upper row) and P400 (lower row) amplitudes for faces presented in the left (a) and right (b) hemifield averaged over the left and right clusters (left and right plots respectively) in the different face conditions (new-deviant faces in pink, known-deviant faces in green, standard faces in black). The error bars represent the standard mean error across individuals. * highlights the significant differences between conditions after FDR correction for multiple comparisons (p -value < 0.05). In c) the differences between conditions for left hemifield faces averaged over the right cluster are plotted as a function of infant age. There was an increase of the discrimination ability for new-deviant vs standard faces (a significant trend for N290 and a non-significant trend for P400 in the left plots) but not vs know-deviant faces (right plots, $n.s.$ non-significant p -value > 0.1).

The same pattern was seen for the P400. An effect of condition was observed over the contralateral right cluster ($F(1,39) = 3.18$, p -value = 0.047) but not over the ipsilateral left cluster ($F(1,39) < 1$). The P400 was significantly weaker for new faces relative to standard faces ($t(1,39) = -2.3$, $p = 0.042$) and known-deviant faces ($t(1,39) = -2.7$, $p = 0.029$), whereas responses for standard and known-deviant faces did not differ ($t(1,39) < 1$) (Figure 2.5. a., Figure 2.6. a.). The difference between new and standard faces tended to

become larger with age despite not surviving multiple comparison corrections ($r = -0.26$, $p\text{-value} > 0.1$) (Figure 2.6. c.). No age effect was observed for the difference between new- and known-deviant faces ($r = 0.16$, $p\text{-value} > 0.1$, Figure 2.6. c.).

Responses to right hemifield faces. There was no significant effect of condition for the P1, N290 and P400 responses, either in the contralateral left or in the ipsilateral right clusters (Figure 2.5. b., Figure 2.6. b., Table 2.3). As we were surprised by this result, we looked for putatively delayed effects. By visually inspecting the time-series, we selected two later time-windows ($t1$: [750-850 ms], $t2$: [1050-1150 ms]). Again no effect of condition was found (on the contralateral left cluster: $t1$: $F(1,39) = 1.6$, $p > 0.1$; $t2$: $F(1,39) = 1.7$; $p > 0.1$; on the ipsilateral right cluster: $t1$: $F(1,39) < 1$; $t2$: $F(1,39) < 1$), although new-deviant faces tended to evoke more positive responses than standard faces on the contralateral left cluster ($t1$: $t(1,39) = 1.8$, $p = 0.071$; $t2$: $t(1,39) = 1.9$, $p = 0.065$) but not the ipsilateral right cluster ($t(1,39) < 1$, for both $t1$ and $t2$). Responses for known-deviant faces did not differ from the two other conditions ($p > 0.1$ for $t1$ and $t2$ on both contra- and ipsi-lateral clusters). Thus, no reliable difference between conditions was detected in the contra-lateral and ipsi-lateral hemisphere revealing that infants were not able to discriminate faces presented in their right hemifield either in the left or right hemisphere.

Table 2. 3. Comparison of N290 and P400 responses for the different face conditions: P1, N290 and P400 responses were compared for faces presented in the left (a) and right (b) hemifield. The main effects of experimental condition are reported before post-hoc analyses.

Left Faces		
	Left Occipito-temporal cluster	Right occipito-temporal cluster
P1	$F = 0.2, p > 0.1$	$F = 2.4, p = 0.101$
N290	$F = 0.1, p > 0.1$	$F = 5.1, p = 0.016$
		New vs. Standard: $t = -2.7, p = 0.014$
		Known vs. Standard: $t = 0.2, p > 0.1$
P400	$F = 0.2, p > 0.1$	New vs. Known: $t = -2.7, p = 0.014$
		$F = 3.9, p = 0.047$
		New vs. Standard: $t = -2.3, p = 0.042$
		Known vs. Standard: $t = 0.5, p > 0.1$
		New vs. Known: $t = -2.7, p = 0.029$
Right Faces		
	Left Occipito-temporal cluster	Right occipito-temporal cluster
P1	$F = 2.5, p = 0.090$	$F = 0.5, p > 0.1$
	New vs. Standard: $t = 0.1, p > 0.1$	
	Known vs. Standard: $t = 2.5, p = 0.042$	
	New vs. Known: $t = -1.7, p > 0.1$	
N290	$F = 1.5, p > 0.1$	$F = 0.6, p > 0.1$
P400	$F = 0.1, p > 0.1$	$F = 0.2, p > 0.1$

Finally, we studied whether the responses to standard faces presented in the right and left hemifield were different. The amplitudes of the P1, N290 and P400 were similar for the left and right hemifield, on the ipsi- and contra-lateral clusters ($ps > 0.1$) confirming not only that both hemispheres were processing the stimuli but also that responses to left standard faces were not reduced relatively to right standard faces.

2.5. Discussion:

By combining structural and functional measures using multi-modal imaging, we uncovered several aspects of visual development in human infants. We first confirmed the interdependency between DTI measures of white matter maturation and the speed of the neural responses, not only at the level of projection tracts, such as the optical radiations, but also at the level of cortico-cortical tracts, such as the corpus callosum. In particular, the myelination of the splenium fibers supports the progressive acceleration of information transfer between hemispheres during the first semester of life. Second, we revealed that the right hemisphere, but not the left, discriminates faces presented in the contralateral hemifield. The response to a new face enlarged and accelerated with age only in the right hemisphere revealing an improvement in the right hemisphere's processing ability whereas the left hemisphere remained

unresponsive to face differences. Third, new faces presented in the right hemifield did not evoke any discriminative response neither in the left nor in the “competent” right hemisphere highlighting the still poorly functional inter-hemispheric transfer at this age. Finally, we observed no evidence for an inhibitory role of the corpus callosum on the left responses as the P1 latencies, the IHTT and the N290/P400 amplitudes for standard faces did not differ for left and right hemifield presentations in either hemisphere.

2.5.1. Fiber-specific microstructural maturation correlates with the acceleration of evoked responses

Age-dependent acceleration of the P1 response has been repeatedly reported for central visual stimuli (Dubois et al., 2008; Lippe, Roy, Perchet, & Lassonde, 2007; McCulloch et al., 1999), reflecting the increasing efficiency of the visual pathway from the retina and LGN to the visual cortices. Here, lateralized stimuli evoked delayed P1 responses relative to central stimuli probably because of the micro-architectural differences between the fovea composed of very dense cones and the peripheral retina primarily containing rods (Allen, Tyler, & Norcia, 1996; Tachibanaki et al., 2005). P1 acceleration persisted after 12 weeks of age for lateralized stimuli whereas the adult latency was already reached for central stimuli at this age. The speed of the early visual responses for lateralized stimuli was related to the transverse diffusivity in the optic radiation independent of age, as we had previously demonstrated for central stimuli (Dubois et al., 2008). Thus, myelination of the optic fibers is one of the major factors improving visual efficiency during the first semester of postnatal life beyond the maturation of the peripheral paths and of V1.

The correlation between the structural and functional measures of development was also seen for callosal connections and the speed of inter-hemispheric transfer. We measured IHTT for the first time in infants and related its acceleration to the maturation of splenium callosal fibers connecting occipital regions. IHTT shortened from 300ms in the youngest to 84ms in our oldest infant. This delay is notwithstanding far longer than in adults: 7-13 ms in response to checkerboards (Saron & Davidson, 1989), 15 ms in response to white squares (Whitford et al., 2011), 30 ms in response to faces (2007), but is in the expected range for thin unmyelinated callosal fibers whose conduction delays are between 100 and 300 ms (Ringo et al., 1994). The maturation of visual callosal fibers was significantly correlated with the maturation in the optic but not the auditory radiations uncovering domain-related rather than a general maturation. Thus, diffusion imaging might be a practical tool for following the efficiency of white matter pathways during development and to reveal neural connectivity through correlated maturation in normal but also pathological populations.

2.5.2. Lateralized presentation reveals an incompetent left hemisphere to discriminate faces

Our main goal was to study each hemisphere's ability to process faces by using two streams of faces in the left and right visual hemifields. We are confident that almost all faces were seen in a lateralized hemifield based on several arguments. First, *at the experiment level*, the short duration of face presentations (250ms) was below the time delay for a saccadic eye movement at this age which is about 400ms in 4 month-old infants (Kulke, Atkinson, & Braddick, 2015). The randomized delay between faces prevented infants from predicting the exact stimulus onset and orienting their gaze to the corresponding hemifield. We further inspected the video recordings of the infants' behavior during the experiment to verify that they were continuously centered with respect to the screen and that they did not shift their gaze toward a side of the screen. Second, the identification of *contralateral P1 responses* to left and right faces confirmed that infants were focused on the central distractor at the onset of the lateralized stimulation (see Figures 2.2 and 2.4). This response was followed by *ipsilateral responses*, and the significant correlation between the IHTT and the maturation of the splenium callosal fibers validates that we were measuring a genuine transfer of information between hemispheres. Finally, the similar succession of components (P1, N290 and P400, Figure 2.4) observed over each hemisphere contralateral to the stimulation confirms that each hemisphere was perceiving and processing the contralateral face. These arguments support the reliability of our experimental paradigm to test each hemisphere separately in infants.

With this paradigm using lateralized stimuli, we were able to uncover striking differences between left and right hemisphere capabilities. We recorded discrimination responses only in the right hemisphere for new faces presented in the contralateral left hemifield, revealing *a contrario*, a surprisingly incompetent left hemisphere. If any evidence of face discrimination capacity for the left hemisphere existed in this task, it was a delayed, weak and hardly significant response around [750-850] and [1050-1150] ms post-stimulus, which contrasts with the earlier and robust N290 and P400 responses in the right hemisphere. It might be possible that the discrimination between our face images was done on low-level cues. However, if such were the case, we should have expected an early difference at the level of the P1 as shown by Rossion and Caharel (2011) in adults. This was indeed not the case (i.e. no effect of condition at the level of the P1), but further studies might verify this point by using scrambled images as controls as in de Heering and Rossion (2015).

In adults, the left visual hemifield superiority for faces is related to right-left FFA asymmetrical activation for face recognition (Yovel, Tambini, & Brandman, 2008). In infants, this hemispheric difference was first asserted by de Schonen and her collaborators based on behavioral studies in which they measured

the latency of gaze orientation toward faces presented in the left and right visual hemifield (de Schonen & Mathivet, 1990; de Schonen et al., 1986): four-month-old infants oriented faster to their mother's face than to a stranger's presented in the left hemifield. Furthermore, the same infants oriented faster toward their mother's face presented in the left rather than the right hemifield. In a second task, they had to associate the position of a rewarding toy (above or under the screen) with the identity of a face (mother or stranger) presented within the right or left hemifield. Infants succeeded only when the faces were presented in the left hemifield and thus processed by the contralateral right hemisphere (i.e. 72% vs 17% of infants reached the learning criterion for left vs right hemifield faces; percentages computed from table 4 in de Schonen and Mathivet, 1990). Our results confirm that infant's orienting failures for right-hemifield faces in this study were related to a genuine difficulty in discriminating the two faces in that hemifield rather than to subsequent difficulties in associating each face with the spatial position of the reward.

In NIRS studies, a right hemispheric superiority was robustly observed when configural perception was tested in 5 to 8-month-olds (i.e. upright vs inverted faces (Otsuka et al., 2007) and canonical vs scrambled faces (Honda et al., 2010)) with a progressive development of a response for other views of the face during the second semester of life (Nakato et al., 2009). Similarly, de Heering and Rossion (2015) who used a rapid presentation of faces in different sizes and view-points relative to various visual categories reported a strong right hemisphere advantage in 4-6 months. These results suggest that face categorization mainly relies on the right hemisphere from the first months of life on. However, discrimination between different faces measured with NIRS induced bilateral responses in 7 to 8-month-olds (Kobayashi et al., 2016; Kobayashi et al., 2011; Nakato et al., 2011). Here, our paradigm with rapid presentation of faces and divided attention between the two hemifields may have amplified the differences in face processing abilities of the left and right hemisphere much in the same way dichotic presentation reveals the superiority of the left hemisphere for speech. The left hemisphere has been shown to be sensitive to face features (Deruelle & de Schonen, 1998), which may require a foveal analysis and a longer time to be discriminated, whereas the fast presentation outside the fovea in our paradigm might have favored a rapid configural analysis performed by the right hemisphere (Deruelle & de Schonen, 1998). Furthermore, even if the left and right hemifield faces were never directly in competition but were successively presented with a random delay of 550 to 950 ms, attention might have amplified the spontaneous bias. In adults, this delay would be sufficient to reallocate attention from one side to the other but unlikely in infants because of their difficulties in rapidly disengaging and reengaging their attention.

The N290 amplitude increased with age in response to new faces compared to standard faces, whereas the P400 amplitude showed the opposite effect. This pattern suggests an acceleration of the discrimination response shifting from the P400 to the N290 time-range, and supports the hypothesis that both components are precursors of the adult face-specific N170 component (Halit et al., 2003). This acceleration is probably related to the more refined representations of faces in the infant's environment and of their distinctiveness (Kelly et al., 2005; Quinn et al., 2008; Quinn et al., 2002; Righi et al., 2014; Sangrigoli & de Schonen, 2004). It is noteworthy that the P1 for central stimuli reaches the adult values around 12 weeks of age (figure 2.2.c), at the same time infants start to become sensitive to second-order relations (Ramesh et al., 2005; Bhatt, Bertin, Hayden, & Reed, 2005). This better sensory encoding might help infants perceive more subtle differences.

Le Grand et al. (2003) reported that visual input to the right hemisphere during the first months of life was necessary for adults to perceive second-order relations: adults with an early left cataract were unable to perceive a change in the spacing between both eyes as well as between the eyes and the mouth in successive pictures of faces contrary to adults with an early right cataract. However, they were able to perceive changes in the contours of the face or internal face features (eyes and mouth) similarly to normal participants (Le Grand et al., 2003). Combined with our results in which only the right hemisphere benefited from a discrimination improvement during the first semester of life, these findings might point to a genuine left-hemispheric difficulty in processing these relations in a face space and thus to a different microstructural organization of the left and right fusiform regions, probably of genetic origins with a critical window of learning for the right fusiform face area (FFA). Within the fusiform gyrus, Weiner et al (2016) have described four regions cyto-architectonically dissociable, and associated with specific functional domains: FG2 and FG4 comprising face and word specific areas. As the MRI signal is sensitive to water, but also to iron and myelin, quantitative MRI can provide markers of maturation of the gray matter (Leroy et al., 2011). The maturational calendar of these regions and of the neighboring areas might reveal the microstructural differences that may underlie this functional asymmetry.

2.5.3. Efficiency of the inter-hemispheric transfer of visual information:

Right-lateralized faces were not discriminated by the left hemisphere. Does this result imply that infants do not process faces presented in their right visual hemifield at all? If such were the case, the right hemifield standard face should have been processed as a new face by the right hemisphere when occasionally presented in the left hemifield (known-deviant condition); however, this effect was not present in our study. On the contrary, we observed no difference between the left and right hemifield

standard faces regardless of presentation side or cluster, revealing that the transfer of information of face features was successful when a face was repeated. One could oppose this interpretation by suggesting that the infant may have shifted their gaze to the right hemifield and seen the standard face on this side; however such occurrences, if any, were rare given our visual controls and likely just as rare as the new-face condition. Thus, without inter-hemispheric transfer, the known-face should have elicited a similar response to that of a new face. However, if the inter-hemispheric transfer had been fully efficient, the new face perceived by the left hemisphere should have been transferred to the competent right hemisphere to be discriminated. Yet, we found no significant difference between conditions over the ipsilateral cluster, even at a later time-window for faces presented in the right hemifield. The long IHTT in our group, relative to adults, may have hindered a correct processing of a rare image, whereas the repeated image may have progressively succeeded in obtaining a robust representation in the right hemisphere. Inter-hemispheric transfer is thus imperfect at this time period and may remain so until the end of the second year of life, hereby explaining the behavioral results. Indeed, the cognitive tasks used in two previous behavioral studies investigating trans-callosal transfer were complex: one was based on similarity judgment between two visual items presented simultaneously in the two hemifields (Liégeois et al., 2000), and the second on the number of trials needed to learn to discriminate two visual items once the other hemisphere has already learned to discriminate them (de Schonen & Mathivet, 1990).

2.6.Conclusion:

Exploiting multimodal imaging, we have demonstrated that lateralized brain processes are not a property of the adult human brain but are observed from the first weeks on, likely due to structural specificities in the genetically specified left-right hemisphere architecture. We have also highlighted that an efficient transfer of visual information between hemispheres emerges before 6 months of infancy, but this transfer is still not fully efficient at this age and likely continues to improve over the course of several months, considering the extended maturation of the corpus callosum. Because our goal was to assess the functional improvements in relation with structural development, our age range extends over the first semester of life and we exploited the wide variation in the P1 latency. The N290 and P400 latencies are probably also accelerating, introducing inter-subject variability and possibly impinging upon statistical comparisons. Further studies should examine responses to right hemifield faces in a more homogeneous group but also at a later age in order to understand how the left hemisphere, and its abilities in featural analyses (Deruelle & de Schonen, 1998), becomes integrated in the face network. Identifying the anatomo-

functional substrates of early visual development is crucial to understanding possible deviations from this normal trajectory and long-term effects of early damage to the visual system.

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2.7. Appendix: Follow-up experiment

Here, we introduce a follow up experiment for the first study of this chapter and ask whether the right hemisphere advantage we previously observed, holds for discriminating between exemplars of another category of objects: car images. The two more probable hypotheses are :1. if the right hemisphere advantage holds for a car discrimination, then it might be inferred that the right hemisphere is better at extracting information and performing computations for within-category discrimination of stimuli beyond faces at least when a fast presentation is used. 2. if cars are not discriminated by the right hemisphere, it can imply that the right hemisphere advantage is relatively selective for processing facial information, probably through configural analyses. We are still running this experiment and it is a work in progress, but we describe the paradigm and the preliminary data we have acquired so far.

Procedure: This time we only tested older infants (4 to 5 months old), since they had larger discrimination responses in the first study. Our first attempt was to perform within infant comparison, to assess how the face discrimination and car discrimination responses differed. Therefore, we used the same paradigm as the second group of infants in the first study, but dividing the trials between face and car images. Infants were presented with 4 blocks of 80 trials at each side (60 standard, 10 new-deviant, 10 known-deviant images), in addition to the 8 habituation trials at each side at the beginning of each block. Each block contained only faces or only cars, changing from one block to the next. For the blocks with face images, we used only female faces. For the first 3 infants we tested, the experiment started with blocks of faces. However, doing so, infants quickly lost their interest in the experiment when the next block with car images appeared. Thus, for all the other infants we started the experiment with car images, to obtain more trials for them, as they were the important aspect of the new experiment. We obtained good data for 16 infants (mean age = 18.8 ± 2.1 , 9 girls).

Early responses: The number of achieved trials after preprocessing with the same pipeline were 18/17 trials for the left/right faces and 39/39 for left/right cars. Unfortunately, these numbers are lower than the first study inducing lower signal to noise ratio. Particularly, because several infants did not finish the experiment as they seemed less interested in car stimuli. Like the first study, the responses to lateralized stimuli (faces or cars) appeared over the contralateral hemisphere followed by a response on the ipsilateral hemisphere over the same lateralized cluster of electrodes as before (Figure 2.7). We have not yet determined the latency of P1 and ipsilateral P1 for each single infant, but the average response latencies are in the same range as before.

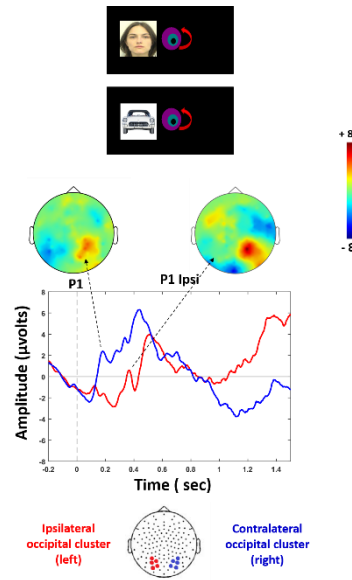


Figure 2. 7. Examples of visual event-related responses over the group of infants. Responses to images presented in the left hemifield averaged across the left and right occipital clusters of electrodes (red and blue curves respectively) over the infant group. The contralateral P1 appears over the right hemisphere and then propagates toward the ipsilateral hemisphere.

Discrimination responses: For faces, the number of deviant trials were unfortunately too low, 1 or 2 and 0 for some infants, making the data unexploitable for comparison between conditions. For cars, we obtained on average 4 trials for left/right new/known, and 9/8 trials for left/right standard conditions, respecting the selection criteria as the previous experiment, i.e. for the standard condition we only considered trials following at least 2 standard trials on the same or opposite side. Like before, we studied discrimination responses over the same N290: [300-400 ms]; P400: [450-550 ms]) time-windows and over symmetrical left and right clusters of 10-electrodes in the occipito-temporal regions (Figure 2.8). For each of the N290 and P400 average responses, we performed statistical analyses with condition (3-levels), hemifield (2-levels) and cluster (2-levels) as within-subject factors. Table 2.4 summarizes the anova results.

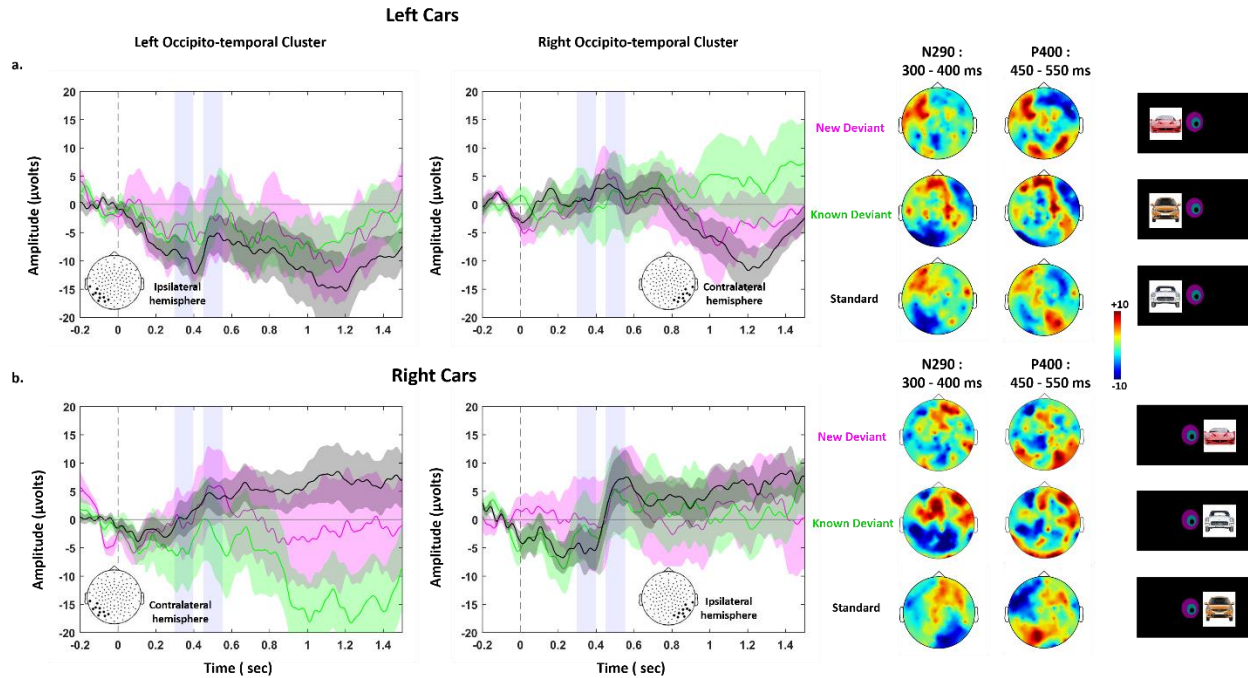


Figure 2.8. ERP according to the car conditions. Grand-averages were computed over the left and right occipito-temporal clusters (left and right plots respectively) for the new-deviant, known-deviant and standard cars presented in the left (a) and right (b) visual hemifields. Voltage topographies (right column) averaged over the [300-400] ms and [450-550] ms time-windows corresponding to the N290 and P400 respectively. No discrimination response for new cars relative to the standard and known-deviant cars are observed over these time-windows for the left or right hemifield cars over both clusters.

Contrary to the first study we did not find any discrimination response for any side of hemifield presentations or clusters of electrodes. However, given the insufficient number of trials and low signal to noise ratio, clearly visible in the time-course of ERPs and their large variance, the current findings need to be taken with great caution and definitely be validated with more infants. The low number of trials we achieved was partly due to the presence of both car and face blocks in the paradigm. Currently, we are running this experiment with only car images, to achieve the maximum number of trials possible. Although this approach will not allow us to perform within subject comparison between faces and cars, we can still perform between subject comparison with the data from the first study.

Table 2.4. Anova summary for N290 and P400 responses for the different car conditions. Amplitude of N290 and P400 were compared for the three type of car images presented in the left/right hemifield and for the left/ right clusters of electrode. No main effect or interaction was significant.

N290	Hemifield: $F(1,15) < 1$ Cluster: $F(1,15) < 1$ Condition: $F(1,15) < 1$ Hemifield x Cluster: $F(1,15) < 1$ Hemifield x Condition: $F(1,15) = 2.1, p = 0.161$ Cluster x Condition: $F(1,15) < 1$ Hemifield x Cluster x Condition: $F(1,15) < 1$
P400	Hemifield: $F(1,15) < 1$ Cluster: $F(1,15) < 1$ Condition: $F(1,15) < 1$ Hemifield x Cluster: $F(1,15) = 2.9, p = 0.111$ Hemifield x Condition: $F(1,15) < 1$ Cluster x Condition: $F(1,15) < 1$ Hemifield x Cluster x Condition: $F(1,15) = 2.1, p = 0.154$

Chapter 3:

Functional and structural correlates of auditory development throughout infancy

Preface:

The study in chapter 3 mainly addresses the structural and functional correlates of auditory development in infancy, with the aim of linking the two aspects. Similar to chapter 2, we used lateralized presentation of stimuli (syllables in one ear) to assess the hemispheric responses and characterize the transfer of auditory information across hemispheres. However, we faced difficulties in separating hemispheric responses from those responses that are transferred across hemispheres, and thus asked questions about the role of interhemispheric connectivity in auditory systems. This is why we moved to the study in chapter 4 before finalizing this work that is still in progress. Throughout this chapter we sometimes refer to the next chapter, where we assess the role of interhemispheric connectivity in the auditory network in early infancy.

3. Neural correlates of auditory development

3.1. Abstract:

Brain development is especially intense in the prenatal and the first post-natal years. Different brain regions and networks follow different maturational patterns and timelines. In white matter, myelination occurs rapidly in the postnatal period and changes the microstructural properties of tissue, reflected in Diffusion Tensor Imaging (DTI) parameters. In a previous study, we demonstrated that in the visual system, the latency of early visual responses and their interhemispheric transfer decreased with infants age over the first postnatal semester. The speed of these responses correlated to the microstructural changes in the corresponding white matter pathways, beyond age effects. Here, we investigated whether such findings can be extended to the development of auditory system. We used complementary Electroencephalography (EEG) and DTI information on the maturation of auditory responses and underlying white matter pathways. We recorded auditory evoked responses when 1-to-6 months old infants listened to syllables. Similar to the visual system, the latency of responses (auditory P2) decreased with infants age and DTI indices showed developmental patterns both in the projections and cortico-cortical pathways (acoustic radiations and auditory callosal fibers). However, we failed to show similar structure-function relationships as in the visual system, suggesting a few future directions. We further assessed hemispheric differences in terms of response amplitudes and latencies when syllables were presented binaurally and monaurally. For binaural syllables, we found a weak trend for stronger responses over the left than the right hemisphere, suggesting a left-hemisphere lateralization for syllabic perception. When syllables were presented monaurally, responses appeared bilaterally over the hemispheres contralateral and ipsilateral to the presentation ear, the former being stronger and faster than the latter. Ipsilateral responses were delayed in the left relative to the right hemisphere, suggesting an asymmetric interhemispheric transfer of information. We also assessed hemispheric asymmetries in terms of structural DTI parameters and observed a leftward asymmetry in acoustic radiations.

Key words: Speech asymmetries. Brain development. DTI, EEG, corpus callosum. Interhemispheric connectivity

3.2.Introduction:

In the human species, the brain continues to develop over a long period after birth. The multiple neural changes occurring during this period are still under investigation, but two main phenomena (synaptogenesis-pruning cycles in the gray matter and myelination of the white matter tracts) have been highlighted since the beginning of the 19th century by post-mortem examinations (Flechsig, 1920; Yakovlev. & Lecours., 1967). These studies have underscored the heterogeneous development of the human brain with different maturational patterns and timelines depending on the regions, networks and functional systems. With the rise of brain imaging, it is now possible to examine neural development in healthy infants and in larger groups, but the coarse image resolution still limits the information we have access to. Nevertheless, structural MRI studies have replicated and extended the former post-mortem studies, confirming the lengthy and heterogeneous changes occurring in the human brain during the first two decades. These studies have notably measured the age-related evolutions of cortical thickness (Li, Lin, Gilmore, & Shen, 2015; Sowell et al., 2003) and maturation (Leroy et al., 2011), as well as of white matter maturation (Dubois et al., 2014). In this tissue, as axons are progressively ensheathed by myelin, the increasing lipid content and fiber compactness constrain the diffusion of water molecules. This phenomenon can be measured indirectly with diffusion tensor imaging (DTI) that shows some decrease in transverse diffusivity and increase in fractional anisotropy in most of the tracts during infancy (Dubois et al., 2006; Hüppi et al., 1998). The combination of these different measures, eventually completed with other MRI markers, allows a refined description of the maturation timeline for the different white matter tracts (Kulikova et al., 2014).

Intense developmental changes are also occurring at the functional level, and can be measured with electro- or magneto-encephalography (EEG, MEG). The topography and latencies of event-related potentials (ERPs) are changing, especially during the first post-natal year. For instance, in the visual system, the first positive wave of response (P1) is measured around 300 ms at birth and reaches the adult value (~100-120 ms) around 3 months of age, indicating a drastic increase in the speed of visual responses in a few weeks (McCulloch et al., 1999). We might thus wonder how these structural and functional changes are related to each other. Since myelination accelerates the speed of neural transmission, we can expect the MRI indices of white matter maturation to correlate with the neural conduction speed reflected through the latencies of ERP components. Indeed, during early infancy, the increase in the speed of visual P1 is significantly related to the transverse diffusivity measured in the early visual projection pathways (optic radiations), independently of the effect of age (Dubois et al., 2008). This structure-function

relationship also holds for the maturation of cortico-cortical connections and later brain responses. Indeed, we recently showed that the speed of inter-hemispheric transfer (measured based on the latency difference between the contra- and ipsi-lateral responses to visual stimuli presented in one hemi-field) is related with the transverse diffusivity in the visual callosal fibers, again independently of age (Adibpour, Dubois, & Dehaene-Lambertz, under review). These two results suggest that at least during the first months of infancy and for the visual system, white matter maturation plays a key role in the acceleration of brain responses beyond the neural computations performed in the cortical gray matter, and that complementary neuroimaging measures based on MRI and EEG can be used to explore structural and functional connectivity in normal but also pathological development. However, it would be useful to test such relationships for another brain functional system, and investigate to which extent these results can be generalized (Dubois et al., 2016).

The auditory system has a different development than the visual system. Because of the noisy womb environment, the auditory cortex is already stimulated before birth, whereas the visual world is largely different *in-* and *ex-utero*. From the seminal work of Yakovlev and Lecours (Yakovlev & Lecours, 1967) on myelination of the different white matter tracts, it appears that for the acoustic radiations myelination starts shortly after birth and continues slowly throughout the first 3 years. For optic radiations, this process occurs much more rapidly over first postnatal semester, starting after the term birth and continuing very intensely up to 6 months of age. The auditory ERP latencies are also changing more slowly than the visual ERPs latencies. During the first months of infancy, the auditory ERPs consist of a broad positive peak (P2) followed by a broad negative peak (N2). The latencies of these components decrease from ~300 ms to ~150 ms (P2), and from ~530 ms to ~300ms (N2) throughout the first post-natal year (Barnet, Ohlrich, Weiss, & Shanks, 1975; Kushnerenko et al., 2002; Novak, Kurtzberg, Kreuzer, & Vaughan, 1989), for a review see (Wunderlich & Cone-Wesson, 2006), and keep decreasing more slowly toward childhood (Shafer, Yan, & Wagner, 2015). Earlier peaks (P1, N1) are barely identifiable before 4-5 years of age, when P1 latency starts to decrease from 90 ms to 50 ms toward adulthood (Lippé, Kovacevic, & McIntosh, 2009; Ponton, Eggermont, Kwong, & Don, 2000). In the auditory domain, structure-function relationships have only been studied from childhood to adolescence. DTI indices of maturation (anisotropy) in acoustic radiations were correlated with the M100 latency, evaluated through MEG recordings of cortical auditory responses (Roberts et al., 2009). However, both of these measures were also correlated with the children's age, and the DTI-MEG correlation did not survive when considering these common correlations to age.

Our main goal was to investigate the development of the auditory system in infants, based on complementary EEG and DTI information on the maturation of auditory responses and underlying white matter pathways. We focused on the first post-natal semester, when changes are stronger than later on, and when structure-function relationships have already been demonstrated in the visual domain. Regarding the ERP experiments, we used speech syllables (/pa/ and /ta/) to examine whether possible left-right asymmetries in white matter maturation might be related to functional differences. Previous functional MRI studies have reported hemispheric differences in the activations in response to speech stimuli. Dehaene-Lambertz et al (2010) reported larger activations in the left than in the right *planum temporale* for speech, whereas activations were symmetric for piano music in 2-3-month-old infants (Dehaene-Lambertz et al., 2010). By contrast Perani et al (2011) reported larger activations in a right than in a left sphere defined around Heschl's gyrus in neonates listening to normal speech. Yet, the whole-brain analysis presented in supplementary information showed mainly bilateral activations and even left activations when hummed and flattened speech were compared (Perani et al., 2011). Finally, Shultz et al (2014) observed an increase with age in the difference of activations for speech and for biological non-speech sounds, when summing the activations of all responding voxels in the left and right temporal lobes (Shultz et al., 2014). Altogether these results suggest that the left hemispheric bias for speech perception might increase during infancy, which can be possibly observed in ERP and/or DTI indices. To better target hemispheric brain responses and inter-hemispheric transfer in addition to early ERP responses, we further used a paradigm with monaural stimuli for one of the two infant groups, while binaural stimuli were used in the other group. Regarding structural development assessed with DTI, we examined both early projection and cortico-cortical connections (i.e. acoustics radiations and auditory callosal fibers). After analyzing how each functional and structural measure varied with the infants' age, the brain hemisphere and eventually the response side, we investigated to which extent these complementary measures of maturation are related in the auditory domain.

3.3. Material and Methods:

3.3.1. Subjects

First group: We tested a group of 23 infants aged between 5 and 21.4 weeks of postnatal age (10 girls and 13 boys) in a binaural auditory paradigm using only EEG.

Second group: We tested another group of 19 infants (6.7 to 28.7 weeks, 6 girls and 13 boys) in a monaural auditory paradigm with EEG, 16 of them came for MRI exam a few days before (5.9 to 22.4 weeks

old, 5 girls and 11 boys), out of a larger group of 22 infants for whom MRI data was acquired (5.9 to 22.4 weeks old, 9 girls and 13 boys).

The study was approved by the regional ethical committee for biomedical research. All parents were informed about the content of the experiments and their goals, and gave written informed consent.

3.3.2. EEG studies:

3.3.2.1. Experimental paradigms

Stimuli: Two consonant–vowel syllables (/pa/ and /ta/) with neutral intonation were produced by two female speakers and matched for intensity and total duration (200 ms).

Binaural Paradigm: In each trial syllables were presented by series of four, with an interval between the stimulus onset of 600 ms and 1s of silence following the fourth syllable onset and before the next trial (leading to a total duration of each trial of 2.8s). The syllable (/pa/ or /ta/, speaker) were randomly chosen among the four possibilities before the trial onset, and presented three times. The last syllable determined the type of trials: it was either similar to the first three (standard trials), or there was a change of phoneme (deviant phoneme trials) or a change of voice (deviant voice trials). A maximum of 192 trials were presented in 4 blocks of 48 trials, corresponding to 3 types of trials (standard, deviant phoneme, deviant voice) x 2 phonemes (/pa/ and /ta/) x 2 voices x 4 repetitions. Since all these factors were randomized within each block, the experimental conditions were balanced even if the infant stopped participating before the end of the experiment.

Monaural Paradigm: Small earphones were placed on the infant's ears and maintained in place by the EEG net. The paradigm was similar to the binaural paradigm except that the first three syllables were presented in a single ear, and the last syllable was either played in the same or in the other ear. The initial ear side was kept constant during each block. 192 trials were presented in 4 blocks (2 blocks per ear side) of 48 trials, corresponding to 2 sides for the last syllable (same- different side) x 3 types of trials x 2 phonemes x 2 voices x 2 repetitions.

3.3.2.2. EEG data acquisition:

An EEG net comprising 128 electrodes (EGI, Eugene, USA) with a reference located on the vertex was placed on infant's head relative to anatomical markers. EEG was continuously digitized at a sampling rate of 250 Hz during the whole experiment (net amp 200 system EGI, Eugene, USA). The infants were sitting on the parent's laps in a shielded room. They may have fallen asleep or remained awake during the

experiment. In the latter case, one experimenter was showing them interesting objects and cartoon images to keep them quiet. The experiment was stopped if infants became restless.

3.3.2.3. EEG pre-processing:

EEG recordings were band-pass filtered between 0.5 and 20 Hz using a zero-phase lag filter, and were further processed using MATLAB toolboxes: EEGLAB (Delorme & Makeig 2004) and Brainstorm (Tadel et al. 2011). The signal was segmented into epochs of 3700 ms for both paradigms, [-200, +3500] ms relative to the onset of the trial's first syllable. Channels contaminated by movement or eye artifacts were automatically rejected on a trial by trial basis, based on amplitude variations inside each epoch: For each channel, an epoch was rejected when the fast average amplitude exceeded 250 μV , or when deviation between fast and slow running averages exceeded 150 μV . Channels were rejected if they were marked as bad in more than 70% of the trials, and trials were rejected if more than 50% of electrodes were marked as bad. Recordings were then re-referenced by subtracting the average activity of all channels over the brain to obtain average-reference recordings, then baseline-corrected by [-200 0] ms time-window before the onset of the first syllable.

We computed auditory-evoked responses by averaging all correct trials. For the binaural experiment, we kept on average a total of 140 out of 192 trials. For the monaural experiment, we averaged all correct trials for each ear side independently, and kept on average a total of 68/69 out of 96 trials for the left/right ear respectively. Here, we focused on brain responses to the first syllable only, since it showed the highest and most reliable signal-to-noise ratio.

3.3.2.4. Auditory evoked potentials identification:

To measure the latency of auditory evoked responses to the first syllable, we identified two symmetrical clusters of electrodes in the left and right sides, where early auditory responses were observed independently of infants' age on the topography of the averaged response of all infants. For the binaural paradigm, we considered 27 electrodes in each side, covering the fronto-temporal areas and extending over T1-F7 (resp. T2-F8) for the left (resp. right) side respectively (Figure 3.1. a). For the monaural experiment, we identified two symmetrical clusters of 15 electrodes, around T7 (resp. T8) extending anteriorly up to F3 (resp. F4), and posteriorly down to P7 (resp. P8) (Figures 3.1. b & c.). For each infant, we averaged the activity over each cluster of electrodes, and identified P2 component as the first distinguishable positive peak, appearing between 150-350 ms in the time course of auditory evoked potentials. We focused on P2, because it is the most prominent response in the first semester after birth

(Wunderlich & Cone-Wesson., 2006). In each infant, we measured P2 latency at the peak, and computed its amplitude over a 50 ms time window centered on the peak.

3.3.3. MRI study

3.3.3.1. MRI acquisition:

Acquisitions were performed during spontaneous sleep in a 3T MRI scanner (Tim Trio, Siemens Healthcare, Erlangen, Germany), equipped with a whole-body gradient (40mT/m, 200T/m/s) and a 32-channel head coil. A diffusion-weighted (DW) spin-echo single-shot EPI sequence was used, with parallel imaging (GRAPPA reduction factor 2), partial Fourier sampling (factor 6/8) and monopolar gradients to minimize mechanical and acoustic vibrations. After the acquisition of the $b=0$ volume, diffusion gradients were applied along 30 orientations with $b=700\text{s.mm}^{-2}$. Fifty interleaved axial slices covering the whole brain were acquired with a 1.8mm isotropic spatial resolution (field of view = $230 \times 230 \text{ mm}^2$, matrix = 128×128 , slice thickness = 1.8mm, TE = 72ms, TR = 10s), leading to a total acquisition time of 5min40s which was reasonably short for unsedated infants. For anatomical landmarks, T2-weighted (T2w) images were acquired in infants using a 2D turbo spin echo sequence (spatial resolution = $1 \times 1 \times 1.1 \text{ mm}^3$), providing the best grey / white matter contrast at these ages (Dubois et al. 2014). To minimize specific absorption rate (SAR) and noise exposure, we used radio-frequency (RF) impulsions with “no SAR”, and “whisper” gradient mode. Infants’ ears were protected from the noise using headphones placed over their ears during the acquisition.

3.3.3.2. Pre-processing

Motion artifacts were corrected using Connectomist software (Dubois, Kulikova, et al., 2014; Duclap D., 2012).

3.3.3.3. Tractography

Probabilistic tractography was performed based on a 2-crossing-fiber diffusion model with FSL software (Behrens et al. 2007) over individual brain masks. Using individual seed regions, the following fiber tracts were identified from the auditory network: 1. left and right acoustic radiations (by locating seeds at the level of Medial Geniculate Nucleus (MGN) in thalamus, and temporal regions around Heschl Gyrus); 2. auditory callosal fibers (by locating the seeds in the left and right auditory regions) (see Figure 3.4.a).

3.3.3.4. Microstructure characterization

Following the estimation of the diffusion tensor, different DTI maps (fractional anisotropy FA, transverse λ_{\perp} and longitudinal λ_{\parallel} diffusivities) were quantified. For each subject and each tract, averaged index X was calculated by taking into account fiber density on the tract density map (Hua et al. 2008):

$$\bar{X} = \frac{\sum^i d_i \times X_i}{\sum^i d_i},$$

where i denotes the tract voxels, d_i is the fiber density at voxel i , and X_i is the value of the DTI index X at voxel i .

3.3.4. Statistical analyses

We first considered how age modulated the ERPs characteristics. We performed Analysis of Covariances (ANCOVA) on the P2 latencies and amplitudes for the binaural and monaural paradigms independently, with age as between-subjects factor and cluster side (left/right) as a within-subject factor. For the monaural paradigm, we entered a supplementary within-subject factor of response side (contralateral/ipsilateral side relatively to the ear of syllable presentation).

Second, we assessed how age correlated with DTI indices (FA, λ_{\perp} and λ_{\parallel}) in the identified tracts. We also tested the difference between the left and right acoustic radiations on the different DTI indices using paired t-test. We also evaluated the maturational relationships between the acoustic radiations and callosal fibers by computing partial correlations between DTI indices while controlling for infants age.

Third, we examined the relationships between functional and structural markers of maturation in infants who had both EEG (monaural paradigm) and DTI datasets. Aside from myelination, ERP latencies depend on the distance the neural signal travels, and this distance is expected to increase during the first semester after birth due to the fast growth of the brain. Indeed, myelination is supposed to impact directly the conduction speed rather than the latency. For that reason, we converted P2 latencies into response speeds (speed = distance/latency), by approximating the length of individual auditory pathways by the distance between the two ears, evaluated on each infant anatomical image. We further correlated this speed to the maturation of the acoustic radiations while controlling for age based on partial correlations. In these analyses, we focused on transverse diffusivity as the best DTI marker of myelination (Song et al. 2003; Song et al. 2005) and because we previously showed that in the visual system, the increase in the

responses speed throughout development is related to a decrease in transverse diffusivity in the corresponding pathways (Dubois et al. 2008, Adibpour, Dubois & Dehaene-Lambertz, under review).

From the study in chapter 4, comparing infants with callosal agenesis and typical infants, we suspected that P2 response already integrates some inter-hemispheric transfer of information via callosal fibers particularly for ipsilateral responses in the left hemisphere (Adibpour, Dubois, Moutard, & Dehaene-Lambertz, submitted). For this reason, we further considered to test the partial correlations between the speed of P2 responses and maturation of auditory callosal fibers, while controlling for age.

3.4.Results:

The ERP topographies are shown in Figure 3.1. The positive component extended more over the midline frontal regions in the case of binaural compared with monaural stimulation. Following monaural stimulation, we observed brain responses in both the contra- and ipsi-lateral sides, but the contra-lateral responses were larger and more extended than the ipsi-lateral ones, whatever the side of stimulation.

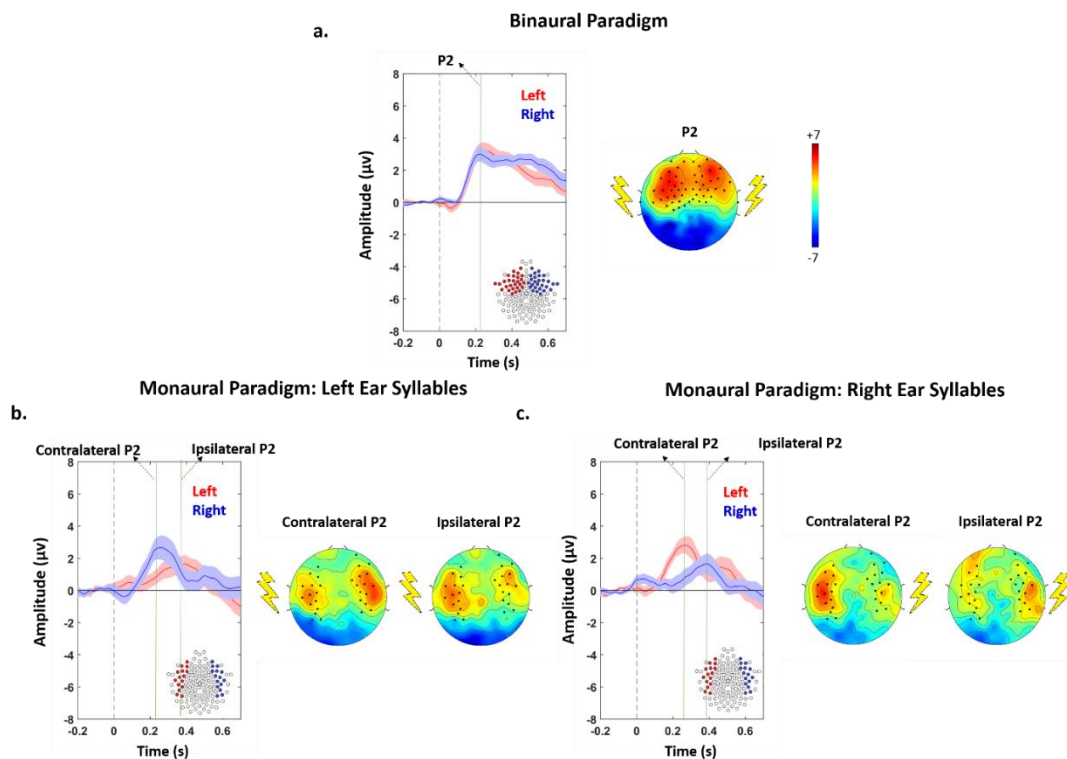


Figure 3.1: Time course of auditory evoked responses. Grand average ERPs in response to the series of four consecutive syllables presented: a) binaurally b) monaurally in the left ear and c) monaurally in the right ear. Average activity over the clusters of electrodes in left and right hemisphere (in red and blue respectively) are displayed on the left panel. Response topography at the maxima of P2 response is illustrated in the right panel. For monaural syllables, response topography at the time of both contralateral and ipsilateral P2 peaks are demonstrated. Time zero marks the onset the first syllables.

3.4.1. Development of P2 characteristics

Figure 3.2 shows variations in P2 latency as a function of age.

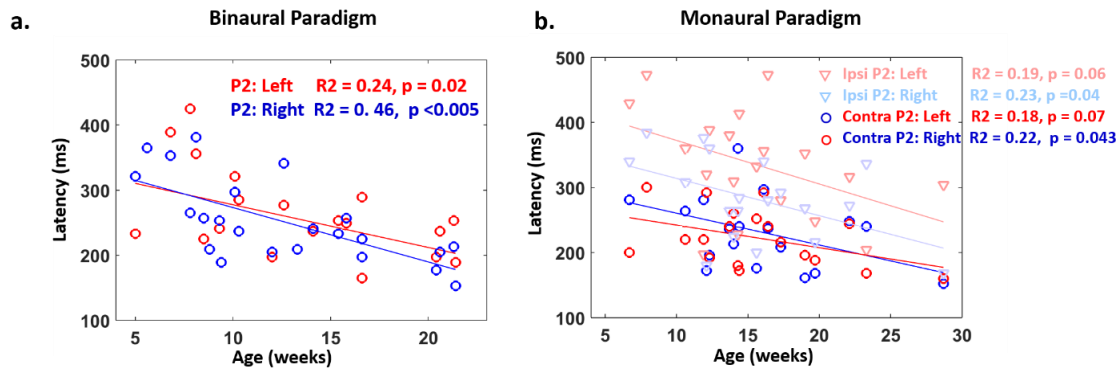


Figure 3.2: Decrease in P2 response latency with age. P2 response latency decreases as a function of age. a) For binaural syllables, P2 peak was identified over the left and right hemisphere (red and blue respectively). b) For monaural syllables, P2 peak was identified over the left and right hemisphere (red and blue respectively) for the contralateral (dark colors) and ipsilateral responses (light colors).

For binaural stimulation, ANCOVA analyses on P2 amplitude revealed a marginally significant effect of hemisphere ($F(1,22) = 3.1, p = 0.095$) due to larger amplitude in the left than in the right, but no effect of age ($F(1,22) < 1$) nor interaction between age and hemisphere ($F(1,22) < 1$). Regarding P2 latencies a main effect of age ($F(1,22) = 13.1, p < 0.005$) was shown, but no difference between hemispheres ($F(1,22) < 1$), nor interaction between age and hemisphere ($F(1,22) < 1$) (Figures 3.2. a and 3.3. a).

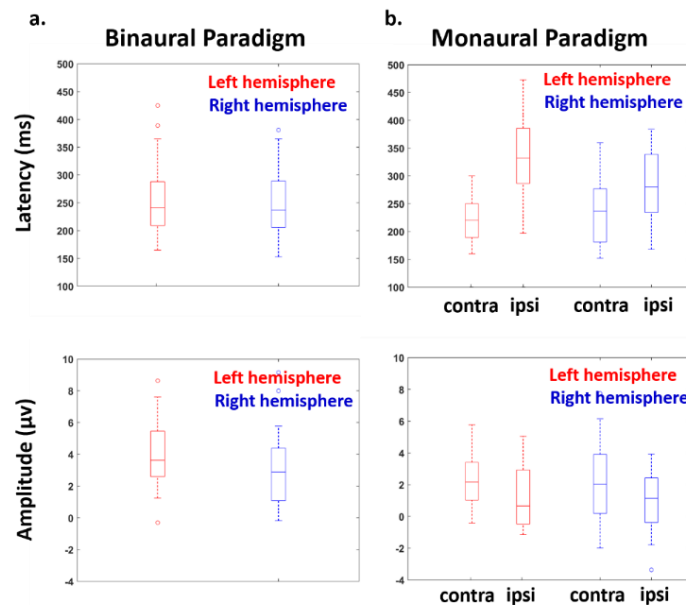


Figure 3.3: Hemispheric differences for P2 response latency and amplitude. Boxplots representing P2 latencies (top) and amplitudes (amplitude) averaged over the left (in red) and right (blue) hemispheres corresponding to both contralateral and ipsilateral responses, in response to: a) binaural syllables; b) monaural syllables.

For monaural stimulation, ANCOVA on P2 amplitudes only showed a marginally significant effect of response side ($F(1,18) = 3.4, p = 0.083$), due to larger amplitude in the contralateral than in the ipsilateral side. Regarding P2 latencies, we observed main effects of age ($F(1,18) = 15.16, p < 0.005$; Figures 3.2. b), and response side ($F(1,18) = 44.5, p < 0.005$), with an interaction between side and hemisphere ($F(1,18) = 10.7, p < 0.005$). Post-hoc analyses showed that the P2 latency is longer on the ipsi-lateral side than on the contra-lateral side whatever the hemisphere, and also for the left relative to the right ipsilateral responses ($t(1,18) = 2.5, p = 0.028$), whereas no difference was seen between contralateral responses (Figure 3.3. b, Table 3.1).

Table 3.1: Summary of ANCOVA analyses for P2 amplitude and latency in response to monaural syllables. P2 response amplitudes and latencies were entered in ANCOVA models as dependent variable, while age, hemisphere (left/right) and response side (contralateral/ipsilateral) were considered as independent variables.

Amplitude	Latency
age : $F = 1.6, p = 0.22$ hemisphere : $F < 1, p = 0.630$ response side : $F = 3.4, p = 0.083$	age : $F = 15.2, p < 0.005$ hemisphere : $F = 1.7, p = 0.210$ response side : $F = 44.5, p < 0.005$
age x hemisphere : $F < 1, p = 0.377$ age x response side : $F < 1, p = 0.923$ hemisphere x response side : $F < 1, p = 0.815$	age x hemisphere : $F < 1, p = 0.943$ age x response side : $F < 1, p = 0.393$ hemisphere x response side : $F = 10.7, p < 0.005$
	contra left vs contra right : $t < 1, p = 0.495$ contra left vs ipsi left : $t = -6.3, p < 0.005$ contra left vs ipsi right : $t = -3.4, p < 0.005$ contra right vs ipsi left : $t = -4.6, p < 0.005$ contra right vs ipsi right : $t = -4, p < 0.005$ ipsi left vs ipsi right : $t = 2.5, p = 0.028$
age x hemisphere x response side : $F < 1, p = 0.926$	age x hemisphere x response side : $F < 1, p = 0.530$

In summary, the infant's age clearly impacted the P2 latencies but not the P2 amplitude, which rather depended on the response side and hemisphere. Contra-lateral responses were faster and tended to be of higher amplitude than ipsi-lateral responses. Lastly, the left ipsi-lateral response was notably delayed compared with other responses.

3.4.2. Development of auditory pathways:

As expected from the literature, DTI indices highly changed with age in acoustic radiations and auditory callosal fibers, with increasing FA and decreasing transverse and parallel diffusivities (Figure 3.4). Transverse ($t(1,21) = -3.7, p < 0.005$) and parallel ($t(1,21) = -3.3, p < 0.005$) diffusivity were lower in the left than in the right acoustic radiations, suggesting more mature fibers in the left than in the right hemispheres.

Besides, partial correlations beyond age effects suggested some shared maturational patterns between the two bundles ($\text{FA: } R2(\text{AR} - \text{ACC} | \text{age}) = 0.38, p = 0.087$; λ_{\perp} : $R2(\text{AR} - \text{ACC} | \text{age}) = 0.4, p = 0.058$; λ_{\parallel} : $R2(\text{AR} - \text{ACC} | \text{age}) < 0.1, p = \text{n.s.}$).

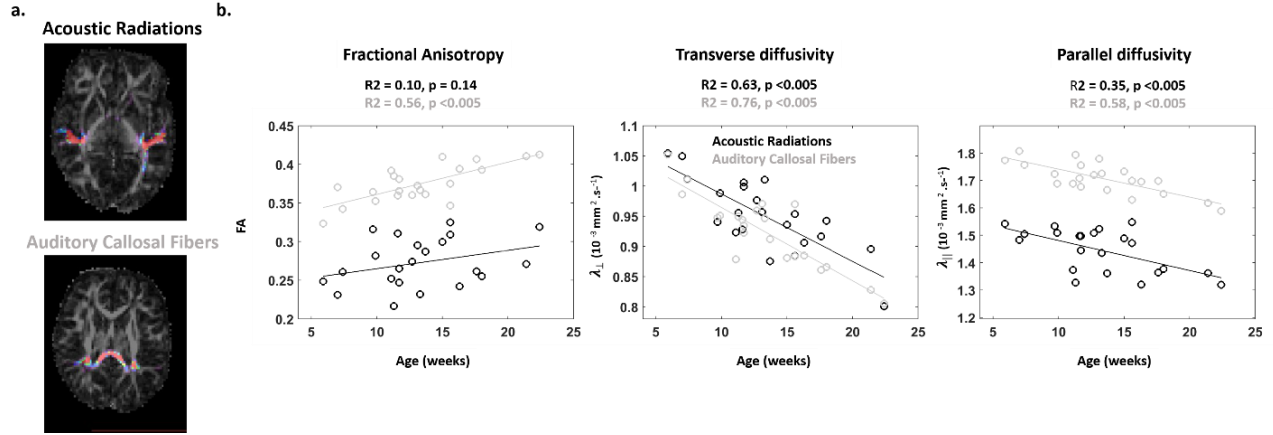


Figure 3.4: Maturation of auditory pathways quantified with DTI indices. Reconstructed bundles of the auditory network: acoustic radiations, extending from the medial geniculate nucleus to temporal regions and callosal fibers connecting the temporal regions and passing through the splenium. b) Age-related changes in DTI indices in auditory network tracts. FA increases with age, and transverse and parallel diffusivities decrease with age.

3.4.3. Correlations between auditory pathways maturation and P2 conduction velocities:

Partial correlations between P2 speed and transverse diffusivity in acoustic radiations, while controlling for the effect of age, were non-significant (Table 3.2). From the partial correlations relating P2 speed to the maturation of auditory callosal fibers, the only significant one was related to the ipsilateral P2 speed on the left cluster ($R2 = 0.28, F(1,15) = -2.3, p = 0.041$), suggesting a contribution of callosal pathways to these response (Table 3.2). This latter partial correlation is illustrated in Figure 3.5, where the variations in the residuals of P2 speed is plotted as a function of transverse diffusivity residuals in the auditory callosal fibers. Residuals are computed after regressing out the effect of age. This figure shows that the mentioned correlation is mainly driven by a few data sample, suggesting that they need to be considered with great caution.

Table 3.2: Partial correlations between P2 speed and maturation of acoustic radiations and auditory callosal fibers while controlling for age. Using partial correlations to control infants age, the maturation of acoustic radiations and auditory callosal fibers were related to P2 speed for the contralateral and ipsilateral responses appearing over the left and right hemispheres.

	Transverse diffusivity in acoustic radiations	Transverse diffusivity in auditory callosal fibers
Contralateral P2 speed-Left	$R2 = 0.02, p = 0.631, F < 1$	$R2 < 0.01, p = 0.804, F < 1$
Contralateral P2 speed-Right	$R2 < 0.01, p = 0.839, F < 1$	$R2 < 0.01, p = 0.983, F < 1$
Ipsilateral P2 speed-Left	$R2 < 0.01, p = 0.858, F < 1$	$R2 = 0.28, p = 0.041^*, F = -2.3$
Ipsilateral P2 speed-Right	$R2 = 0.03, p = 0.52, F < 1$	$R2 = 0.02, p = 0.618, F < 1$

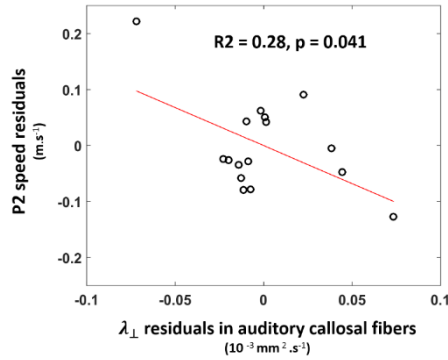


Figure 3.5: Partial correlation between P2 speed and auditory callosal fibers maturation while controlling for age. The plot represents the variations of P2 speed residuals for the left ipsilateral response as a function of transverse diffusivity residuals in the auditory callosal fibers. Residuals were obtained after regressing out the effect of age.

3.5.Discussion:

In this study, we showed that P2 auditory evoked responses during infancy are of higher amplitude in the left than right hemisphere following binaural presentation of syllables, and in the contra- than ipsilateral hemisphere following monaural presentation. We also observed longer latency for ipsi- than contralateral responses particularly in the left hemisphere, which might reflect an asymmetric inter-hemispheric transfer of responses. Besides, we demonstrated strong developmental changes in P2 latency and in the microstructure of auditory tracts, but no structure-function relationships when accounting for the infants' age.

3.5.1.Early markers of functional lateralization and structural asymmetries

We studied the lateralization of P2 responses in terms of both amplitude and latency. Regarding P2 amplitude, we observed a weak lateralization in favor of the left hemisphere following the binaural presentation of syllables, suggesting a dominance in processing CV syllables. This is relatively coherent with previous fMRI studies of young infants, where activations to speech stimuli were reported to be stronger in the left regions than the right perisylvian (Dehaene-Lambertz et al., 2002; Dehaene-Lambertz et al., 2010; Shultz et al., 2014). The specificity of this early lateralization still needs to be compared with responses to other types of stimuli, such as piano music that triggered no asymmetry in activations (Dehaene-Lambertz et al., 2010). In another view, some adult fMRI studies suggested that this asymmetry might arise from a more general bias toward the left primary and non-primary auditory cortices for the monaural perception of tones (Devlin et al., 2003) and CV syllables (Stefanatos et al., 2008). The observation of leftward superiority in primary cortices led these authors to suggest the existence of a more general lateralization for auditory processing than can in turn create a bias and contribute to lateralized speech-specific

processing (Devlin et al., 2003). In our EEG study, we could not disentangle the contribution of primary (auditory domain general) and non-primary (language-specific) cortices to our relatively lateralized responses because of the poor spatial resolution of surface recordings. And since we did not compare responses for CV syllables and other stimuli, we cannot conclude on the lateralization specificity in infants.

In the monaural paradigm, we did not find any left-right differences for P2 amplitude, perhaps because this was alleviated by the strong contra-laterality effect that we observed whatever the ear of stimulation. We also suspect that P2 responses and their lateralization might have been modulated by attention orientation to the sides of the auditory space. Indeed, the side of syllable presentation remained constant within each block of trials, which might have oriented the infants' attention to one side. In dichotic listening tasks where subjects are asked to report the perceived syllable, a forced attention condition can modulate the degree of perceptual lateralization: reports from the right ear are more frequent when this ear is attended, and less frequent when the left ear is attended (Bryden, Munhall, & Allard, 1983; Hugdahl & Westerhausen, 2016). On the contrary, responses to the binaural paradigm might better represent the intrinsic lateralization, not affected by attention modulations.

Regarding P2 latency, we observed differences between the left and right hemispheres only when syllables were presented monaurally. Ipsilateral responses were delayed in the left compared to the right hemisphere, which is consistent with our previous study showing a similar asymmetric pattern in another group of typical infants but not in infants with corpus callosum agenesis (see chapter 4; (Adibpour et al., submitted)). These observations suggested that this delay might result from an inter-hemispheric transfer of information, mediated by callosal connections. This transfer further seems to be asymmetric, being predominant in the right-to-left direction. A recent study in adults has described similar asymmetry in the auditory inter-hemispheric connectivity, demonstrating that TMS applied over the right, but not the left auditory regions, changes the inter-hemispheric functional connectivity between these regions during resting-state in proportion to the volume of auditory callosal fibers (Andoh et al., 2015). Similarly, some studies have reported a more broad and inter-hemispheric pattern of functional connectivity for the regions of right hemisphere, but stronger intra-hemispheric connectivity for the left hemisphere, especially for regions located within the language network (Gotts et al., 2013). Our studies suggest that such an asymmetric pattern of inter-hemispheric connectivity might be already present in early development.

Besides, we observed a delay in ipsilateral compared to contralateral responses whatever the ear of stimulation, which might be an additional sign of attention modulation by the paradigm based on blocks of CV syllables in one ear side. On the contrary, in our previous study (see chapter 4), we observed

simultaneous contra- and ipsilateral responses following random presentation of “babble noise” (i.e. overlaid segments of speech) to each ear, in infants with corpus callosum agenesis, and in typical infants when stimuli were presented in the right ear. These differing results might result from differences in the experimental paradigms between the two studies, leading to different attention orientation of infants.

From a structural point of view, we also observed some asymmetries of acoustic radiations (lower diffusivities in the left than right tracts), suggesting different microstructure of auditory pathways. Asymmetry of acoustic radiations was not previously studied in infants, but leftward asymmetries of microstructure have been reported in a few other white matter tracts in the language network (e.g. arcuate, superior and middle longitudinal fascicles) during the first postnatal semester (Dubois et al., 2016). In adults, previous post-mortem findings have reported more myelinated axons in the left than the right posterior superior temporal lobe, an area posterior to acoustic radiations (Anderson et al., 1999). Future work is needed to confirm the presence of this asymmetry and investigate whether it relates to other regional asymmetries. Nevertheless, we should interpret our results with caution due to two main reasons. First, the acoustic radiations are quite short in length and they partially cross optic radiations at the level of thalamus to the auditory cortex. Although their reconstruction with probabilistic tractography (Behrens et al., 2007) was feasible in infants despite the immaturity of fibers, it was still challenging in the small brain of infants, and our DTI indices might be prone to partial volume effects with other tracts. Second, we could not confirm that such asymmetry is related to a functional asymmetry in terms of contralateral P2 latencies. Yet, it remains to be investigated whether this asymmetry would be reflected in earlier cortical responses (P1).

3.5.2. Functional and structural markers of maturation in the auditory system

At the functional level, we observed a decrease in P2 latency with increasing age of the infants whatever the experimental paradigm, which has also been found for different auditory stimuli in several studies (Barnet et al., 1975; Novak et al., 1989; Kushnerenko et al., 2002; for a review see Wunderlich & Cone-Wesson., 2006) but not all in awake babies (Little, Thomas, & Letterman, 1999; Rotteveel et al., 1987), maybe because environmental factors modulate the babies’ responses. As for the consistent decrease in P1 visual latency (McCulloch, Orbach, and Skarf 1999; Lippé et al. 2007; Dubois et al. 2008), it is also possible that age effects would have greater impact on earlier responses than P2, which we could not reliably identify so far in each infant.

This decrease in the latency of responses suggests a progressive functional efficiency over the course of development. Several candidate maturational processes might contribute for auditory responses, e.g. maturation of cochlea, brainstem nuclei, auditory cortices and other cortical sources, as well as myelination of auditory white matter pathways. Here we expected the myelination of acoustic radiations to affect the speed of P2 latencies, since it starts after birth and progresses slowly until about 3-4 years of age, as demonstrated in post-mortem studies (Yakovlev & Lecours, 1974). Additionally, with the insights from chapters 3 and 4 we now suspect that maturation of auditory callosal fibers might also contribute to the speed of P2 responses. In our infant cohort, DTI indices showed maturational patterns (increase in FA and decreases in transverse and parallel diffusivities) as expected from previous developmental studies (Dubois et al., 2008; Dubois et al., 2014; Geng et al., 2012; Partridge et al., 2004). Among these indices, transverse diffusivity demonstrated the highest correlation with the infants' age, which is consistent with previous studies in animal models of demyelination (Song et al., 2003; Song et al., 2005) and in infants (Dubois et al., 2008; Dubois et al., 2016).

3.5.3. Linking the functional and structural markers of maturation

Although both the speed of P2 responses and transverse diffusivity in auditory pathways showed maturational patterns, we did not observe direct relationships between the two, contrarily to our previous observations of the visual system for P1 response and optic radiations (Dubois et al., 2008), and for P1 interhemispheric transfer and visual callosal fibers (Adibpour, Dubois & Dehaene-Lambertz., under review). It is possible that other maturational mechanisms than myelination contribute to the decrease in P2 auditory latency throughout development. P2 is not an early cortical response, and it probably arises from computations engaging multiple generators. In support of this view, source-localization of P2 in response to syllables in 6-month-olds have proposed sources in the anterior cingulate cortex in addition to the temporal areas (Ortiz-Mantilla, Hämäläinen, & Benasich, 2012). And P2 latencies might be also impacted by attention orientation as we previously discussed.

In addition to acoustic radiations, we investigated whether the myelination of auditory callosal fibers was related to the speed of P2 responses, as we previously suspected these responses to rely on an inter-hemispheric transfer of information (see chapter 4; Adibpour et al., submitted). Although it should be confirmed in a larger cohort of infants, the possible relationship that we observed for the left ipsilateral response and auditory callosal fibers, is consistent with our previous finding of asymmetric transfer. Previous studies in adults further suggested that while the right-ear stimuli can access the left hemisphere processing resources through the strong contralateral pathways, left-ear stimuli might access these

resources through callosal connections. Westerhausen et al. (2008) demonstrated that the accuracy of reports from the left, but not the right ear, is related to the strength of inter-hemispheric connections between superior temporal regions (Westerhausen et al., 2008). Left-ear reports in dichotic paradigm are also disrupted in commissurotomy patients (Milner, Taylor, & Sperry, 1968; Sparks & Geschwind, 1968) and in patients with lesions to posterior part of corpus callosum (Pollmann et al., 2002). Although these studies support that responses to left-ear stimuli in the left hemisphere might be mediated by callosal transfer of right responses, other developmental mechanisms might be considered to explain the maturational patterns of P2 responses observed during infancy, such as cortical maturation. For example, in aging population, changes cortical gray matter is suggested to relate to the slow-down of auditory responses (Price et al., 2017).

3.6.Conclusion

This study highlighted lateralization and maturational processes in the auditory system both at the functional and structural levels, with congruent and different patterns compared to the visual system during the first semester of infancy. Several perspectives might be considered to further explore this issue in more sensitive ways. Using magnetoencephalography (MEG) may enable us to identify early responses (P1) and localize cortical sources more reliably than with EEG. Besides, complementary MRI approaches would provide us with a quantitative evaluation of cortical maturation in auditory regions (Lebenberg et al, submitted). Finally, characterizing the brain structural networks in infants with corpus callosum agenesis would give us a rare benchmark to model the role of callosal connections in the development of auditory system.

Chapter 4

Early asymmetric inter-hemispheric transfer in the auditory network: insights from infants with corpus callosum agenesis

Preface:

In this chapter, we studied the role of corpus callosum in the auditory network during infancy following the questions raised in the study in chapter 3. Similar lateralized presentation of stimuli (in one ear) were used, to study hemispheric ERP responses and to compare them between typical infant and infant with callosal agenesis. Through this comparison, we assessed the contribution of callosal connectivity to auditory responses recorded over each hemisphere.

4. Role of callosal pathways in infant auditory network

4.1. Abstract

The left hemisphere specialization for language is a well-established asymmetry in the human brain. Structural and functional asymmetries are observed as early as the prenatal period suggesting genetically determined differences between both hemispheres. The corpus callosum is a large tract connecting mostly homologous areas; some have proposed that it might participate in an enhancement of the left-hemispheric advantage to process speech. To investigate its role in early development, we compared 13 3-4-month-old infants with an agenesis of the corpus callosum (“AgCC”) with 18 typical infants using high-density electroencephalography (EEG) in an auditory task. We recorded event-related potentials (ERP) for speech stimuli (syllables and babbling), presented binaurally (same syllable in both ears), monaurally (babbling in one ear) and dichotically (syllable in one ear and babbling in the other ear). In response to these stimuli, both groups developed an anterior positivity synchronous with a posterior negativity, yet the topography significantly differed between groups likely due to the atypical gyration of the medial surface in AgCC. In particular, the anterior positivity was lateral in AgCC infants and covered the midline in typical infants. We then measured the latencies of the main auditory response (P2 at this age) for the different conditions on the symmetrical left and right clusters. The main difference between groups was a ~60 ms delay for the ipsilateral response to babbling presented in the left ear in typical infants relative to AgCC, whereas no difference was observed in the case of a monaural right stimulation. We suggest that our results highlight an asymmetrical callosal connectivity favoring the right-to-left hemisphere direction in typical infants. This asymmetry, similar to recent descriptions in adults, might contribute to an enhancement of left lateralization for language processing beyond the initial cortical left-hemisphere advantage.

Keyword: Corpus callosum, Corpus callosum agenesis, Brain development, EEG, Auditory network, Asymmetric interhemispheric transfer

4.2.Introduction:

The left hemisphere specialization for language processing is a well-established example of hemispheric lateralization in the human brain consistently demonstrated in adult studies over the years both at the structural and functional level (Toga & Thompson, 2003; Van Essen, 2005; Devlin et al., 2003; Giraud et al., 2007; Mazoyer et al., 1993; Pallier et al., 2003). In fetuses and preterm neonates, hemispheric asymmetries are already clearly visible, especially in perisylvian areas. At the macro-structural level, the yakovlean torque that raises and pushes the right hemisphere forward relative to the left is observed before term age featuring the common characteristic of the human brain: right frontal and left occipital petalia, a more ventral and horizontal left than right Sylvian fissure, a larger left than right *planum temporale*, and a deeper right than left superior temporal sulcus (Dubois et al., 2010; Dubois et al., 2015; Glasel et al., 2011; Habas et al., 2012; Leroy et al., 2011). Inter-hemispheric differences are also observed at the microstructural level and in the maturational calendar of the superior temporal and inferior frontal region and of the arcuate fasciculus (Leroy et al., 2011). Finally, several functional MRI and NIRS studies have reported larger activations to speech in the left than the right *planum temporale* and more generally in the left than right hemisphere during the first months of life (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Mahmoudzadeh et al., 2013; Pena et al., 2003; Shultz et al., 2014).

Thus, the left-hemispheric functional advantage for speech processing described in adults appears to be rooted in the first stages of development, suggesting a strong genetic component. The strength of this left-lateralization for speech is difficult to compare between infants and adults. Nevertheless, the functional reorganization after a lesion suggests a better plasticity at an early age: linguistic functions may move to the contra-lateral hemisphere with less subsequent deficits in infants than later on suggesting a strengthening of the left hemispheric specialization for speech with age (Bates, Vicari, & Trauner, 1999; Dehaene-Lambertz, Pena, Christophe, & Landrieu, 2004). Thus, other factors beyond the initial left-hemispheric bias might contribute to speech lateralization. The corpus callosum, which gathers most of the white matter fibers connecting both hemispheres (Aboitiz et al., 1992), has been suggested as a candidate factor (Jeeves & Temple, 1987; Karbe, Herholz, Halber & Heiss, 1998; Selnes, 1974). Caminiti et al. (2009) reported a relative stability of the corpus callosum's structure over the course of evolution between chimps and humans despite the increase in the brain size and thus distances between brain areas. They hypothesized that the "relative" slowdown of the inter-hemispheric transfer between humans and chimps incites each hemisphere to specialize. Other authors have postulated a more active role of the corpus

callosum either through inhibition from one hemisphere to the other (Cook, 1984; Dennis, 1981; Karbe et al., 1998), or excitation (Yazgan et al., 1995).

Studies in adults with corpus callosum agenesis (AgCC) favor a weak modulation of the linguistic left hemispheric advantage by the corpus callosum. Using functional magnetic resonance imaging (fMRI), Pelletier et al. (2011) found similar lateralization indices in six AgCC adults relative to controls in expressive and receptive tasks once controlled for IQ. On the other hand, using Magnetoencephalography (MEG), Hinkley et al. (2016) observed a reduced language lateralization in AgCC compared to controls during expressive linguistic tasks as Komaba et al. (1998) reported in one patient studied with PET and a Wada test as well as Rieker et al. (2007) in another case studied with fMRI. Here we explored the role of this tract during the first stages of language acquisition using high-density electro-encephalography (EEG, 128 channels) in 3-4 month-old infants with a corpus callosum a/dysgenesis and typical infants.

The growth of fibers constituting the corpus callosum starts during the second trimester of pregnancy and all callosal connections are in place toward the end of gestation. This tract is heterogeneous, constituted of different types of fibers connecting mostly, but not always, homologous areas (Innocenti, 1986). During infancy, pruning of useless fibers occurs (Kostović & Jovanov-Milošević, 2006), and myelination progresses until the end of adolescence, accelerating the inter-hemispheric transfer time (IHTT) (Brody et al., 1987; Yakovlev & Lecours., 1967). This IHTT is variable along the tract, depending on the diameter of the fibers, on their state of maturation, and on the distance the signal travels between two connected areas (Ringo et al., 1994). In adults, the visual IHTT is the slowest (Caminiti et al., 2009), but given the fast maturation of visual areas during the first trimester of life, myelination might compensate for the longer distance between visual areas at this age relative to the closer but less mature auditory areas. The question of when these fibers are sufficiently mature to be functionally efficient is still unknown. Neonates are able to transfer tactile and haptic information from one hand to the other (Sann & Streri, 2007), suggesting that somato-sensory inter-hemispheric connections are rapidly efficient. By contrast, in the visual domain, de Schonen and Mathivet (1990) did not find any signature of visual interhemispheric transfer at 10 months due to infants' difficulties in generalizing learning from one visual hemifield to the other (de Schonen & Mathivet, 1990). They further postulated that visual integration between both hemifields does not emerge before 24 months (Liégeois et al., 2000). However, in a recent study using event-related potentials (ERPs) during the first semester of life, we were able to measure the inter-hemispheric transfer time (IHTT) for faces presented in the left and right hemifield (Adibpour et al., under review). The IHTT of the visual P1 decreased during the first semester of life from 315 ms to ~80 ms, and

this acceleration correlated with the maturation of the splenial fibers. We also showed that a face frequently presented in one hemifield did not elicit a novelty response when presented in the other hemifield, revealing that fibers connecting the fusiform gyrus were sufficiently mature to convey information on face identity between hemispheres. However, we did not record any evidence for such a transfer when the face was rarely presented confirming de Schonen et al's observations that maturation is far from being complete in the first semester of life (de Schonen & Mathivet, 1990). Whether inter-hemispheric auditory connectivity is efficient enough or not to convey speech information during the first months of life remains an open question.

The early development of callosal fibers can be disrupted due to a genetic disease (Bedeschi et al., 2006; Bonneau et al., 2002), environmental factors (Evrard et al., 2003), or no identified causes (Paul et al., 2007), and a partial or complete absence of the corpus callosum might occur with no other brain malformations (isolated agenesis: AgCC). With a prevalence of at least 1/4000 births (Guillem et al., 2003), this pathology often has little impact on general cognitive abilities (Chiarello, 1980) but may sometimes coincide with a range of specific cognitive impairments. Particularly in the language domain, AgCC subjects may have difficulties in phonological and rhyming processing, syntax and linguistic pragmatics (Sanders, 1989; Temple & Ilseleya, 1993; Temple et al., 1989).

In the present study, we explored the callosal auditory transfer in 3-4-month-old infants. We studied auditory-evoked potentials (ERPs) for speech stimuli presented binaurally (in both ears), monaurally (in one ear) or dichotically (different stimuli in both ears) in a group of 13 AgCC and 18 typical infants. We compared the ERP topography but mainly the ERP latencies in both groups. Due to the crossing of the projection pathways, the hemisphere contra-lateral to stimulation is reached first; information is then transferred to the ipsi-lateral hemisphere, and the efficiency of the corpus callosum can be estimated by the delay between contra and ipsi-lateral responses. This strategy is efficient in the visual domain in which the neural pathways clearly direct each visual hemifield to the contralateral hemisphere; however, in the auditory domain, numerous crossings occur at the subcortical level, and the ipsilateral pathway has a strong cortical projection, which makes it difficult to separate the direct ipsilateral response from the response transferred from the contra-lateral hemisphere through the corpus callosum. We thus reasoned that electrical components depending on the direct ipsilateral and contralateral connectivity would have a similar latency in both groups but that any response depending on a corpus callosum transfer would be significantly different. Two results were possible: 1) the most obvious is that in normal infants, ipsilateral responses are slower than contralateral responses because of the transfer delay, with a slower response in

normal infants than in AgCC. 2) the second possibility is that ipsilateral latencies are similar in both groups, in which case, we may conclude that there is no inter-hemispheric transfer in typical infants at the processing stage we analyzed (P2 component of infant's auditory evoked potential) due to the immaturity of the corpus callosum. We also studied whether left-to-right and right-to-left transfer were equivalent (i.e. whether the size of the effect for each stimulation side was the same) since in adults, an asymmetric inter-hemispheric transfer of neural information is described between auditory cortices at rest (Andoh et al., 2015) and during auditory motion processing (Krumbholz, Hewson-Stoate, & Schönwiesner, 2007) .

4.3. Materials and Methods:

4.3.1. Subjects:

We studied 13 infants with an agenesis of corpus callosum (AgCC) between 10.9 and 18.4 weeks (mean age: 16.3 ± 2.2 , 4 girls and 9 boys). Agenesis was detected during gestation by ultrasonography monitoring followed by an anatomical MRI to detect other brain anomalies. Three out of the 13 infants had a partial agenesis with at least no splenium, where auditory callosal fibers cross, and the remaining 10 infants had a complete agenesis of the tract. At 2 years of age, developmental quotient was in the normal range (87 to 112), except for one girl who was also dysmorphic and had a dysplasia of the aortic valve. At 8-10 years of age, 9 out of 13 children followed a normal academic curriculum with special help for three of them due to reading difficulties. Therefore, 6/13 had some cognitive difficulties in following a normal school curriculum. By contrast, one of them was particularly gifted at school, being one year ahead in his curriculum. We also studied 18 typical infants (healthy and born full-term) aged between 9.6 and 17 weeks (mean age: 13.9 ± 2 , 8 girls and 10 boys). We have no follow-up for these infants but should represent the normal population as no difficulties were noted during pregnancy, birth, or the first months of life. The study was approved by the regional ethical committee for biomedical research. All parents were informed about its content and goals and gave written, informed consent.

4.3.2. EEG data acquisition:

EEG was recorded by a 64-electrode-net (EGI, Eugene, USA) referenced to the vertex. The net was placed on the infants' heads relative to anatomical markers, and earphones were placed over the ears to present the auditory stimuli. The infants sat on their parents' laps. To keep them calm, distracting visual stimuli unsynchronized with the auditory stimuli were presented on a screen in front of them. EEG was continuously digitized at a sampling rate of 250 Hz during the whole experiment (net amp 200 system EGI, Eugene, USA). The experiment was stopped as soon as infants became restless.

4.3.3. Stimuli:

Two consonant-vowel syllables (/ba/ and /ga/) were produced by a female speaker with the same flat intonation and matched for intensity, total duration (285 ms), pre-voicing, and voiced formant transition duration (40 and 45 ms respectively). We further created a ‘babble’-like sound (duration 3s) covering the same range of frequencies, dynamics, and timbre as the syllables by superposing several sentences produced by the same speaker, asynchronously in order to avoid any word recognition.

4.3.4. Experimental paradigm:

As in our usual design (Dehaene-Lambertz & Dehaene, 1994), each trial comprised 4 syllables, spaced by an interval of 600 ms. The last syllable was either similar or different from the first three syllables in order to constitute a standard or a deviant condition, and the repeated syllable (/ba/ or /ga/) was randomly chosen for each trial. Syllables were presented either bilaterally or monaurally in the left or right ear. Following a monaural stimulation, both contralateral and ipsilateral pathways contribute to the measured responses, so we aimed to saturate the ipsilateral pathway by simultaneously presenting a complex and continuous stimulation in the opposite ear (Kouider & Dupoux, 2005). We thus played the babbling noise starting at 600 ms before the first monaural syllable, which lasted for 3s, thus during the presentation of the syllable train.

The experiment consisted of 360 trials separated by 2 s of silence, corresponding to 30 repetitions X 2 conditions (4th syllable to be standard or deviant) X 2 syllables (/ba/ /ga/) X 3 sides of presentation (both ears, left ear, right ear). The trial order was randomized. Stimulus presentation and synchronization with the recording system were carried out using the EXPE software (Pallier, Dupoux, & Jeannin, 1997) on a PC compatible with a Pro-audio Spectrum 16 D/A Board. Syllables were played through earphones at a comfortable hearing level.

4.3.5. EEG pre-processing:

EEG recordings were band-pass filtered between 0.5 and 20 Hz using zero-phase lag filter from EEGLAB (Delorme & Makeig, 2004), and further processed using MATLAB toolboxes: EEGLAB and Brainstorm (Tadel et al., 2011). Two of our initial goals were to compare the ERPs when the syllables were presented bilaterally and monaurally as well as to study discrimination responses depending on the presented side. However, the response to the last syllable was weak, likely attenuated by the superimposed babbling. The insufficient signal to noise ratio associated with the relatively small number of ACC infants

prevented robust analyses of the change of syllable. Thus, we focused our comparisons between groups on the first syllable of the bilateral and monaural trials since the amplitude of the response is large for the first syllable in this paradigm and decreases with repetition (Dehaene-Lambertz & Dehaene, 1994) and also on the response to the babbling. Therefore, the signal was segmented into epochs of 1400 ms: [-200, +1200] ms relative to the onset of the first stimulus in the trial (i.e. the first binaural syllable or the babbling). Channels contaminated by movement or eye artifacts were automatically rejected on a trial-by-trial basis based on amplitude variations inside an epoch: each channel epoch was rejected when the fast average amplitude exceeded 250 μ V, or when deviation between fast and slow running averages exceeded 150 μ V. Electrodes were rejected for the entire recording if they were marked as bad in more than 70% of the epochs, and trials were rejected if more than 50% of electrodes were marked bad. Recordings were then re-referenced by subtracting the average activity of all channels over the brain to obtain average-reference recordings then baseline-corrected over the first 200 ms of the segment (i.e. before the onset of noise presentation).

Signals for comparable trials were then averaged together to measure auditory-evoked potentials. In order to increase the signal to noise ratio and because we focused on the first syllable, we merged standard and deviant trials and trials with /ba/ or /ga/ as repeated syllable. It led to 120 trials per side of syllable presentation (left/right/both ear(s)), and after the pre-processing stage, we kept on average 60/60/60 correct trials in the healthy group, and 74/74/75 trials in the AgCC group for the left/right/binaural trials.

4.3.6. Analyses of auditory-evoked responses in typical and AgCC infants:

We analyzed the ERPs to three types of sound presentation: 1. binaural stimulation (bilateral presentation of a syllable), 2. monaural noise (focusing on the time period between the noise onset and the presentation of a monaural syllable at 600 ms), 3. dichotic stimulation (babbling in one ear, a syllable in the other ear, for a time period of 600 ms after the trial onset).

Comparison of ERPs topographies in typical and AgCC infants: We first aimed to compare the voltage topographies between the two groups. To avoid topography differences being explained by a difference in voltage amplitude rather than a genuine difference over the scalp, we “scaled” the EEG signal in each infant: the signal recorded at each electrode and at each time point was converted to a z-score based on the mean and standard deviation of the time series for all electrodes obtained after averaging all trials over the time-window [-200 1200] ms. For each type of sound presentation (binaural syllables,

monaural noise, dichotic stimulation), we performed unpaired t-tests between the two groups on rescaled amplitudes, for each channel, and each time sample during a time-window of 600ms from the stimulus onset (either syllables or noise). We first identified clusters showing group differences by clustering neighboring channels and time-samples with a probability below 0.1 and computed their significance probability (noted p_{cor}) using nonparametric statistics (Maris & Oostenveld, 2007). This was done by performing similar t-test comparisons and cluster extractions for 5000 random permutations of the group labels on the original data and computing p_{cor} based on the number of times the real data produced clusters with higher t-values than the shuffled data.

Comparison of P2 characteristics in typical and AgCC infants: We secondly compared the two groups based on the P2 component, since it is the most robust auditory response at this age and can be identified in each infant contrarily to earlier weaker responses (Wunderlich & Cone-Wesson, 2006). This component peaks around 150-350 ms and corresponds to a bilateral positive response over the anterior electrodes synchronous with a bilateral negativity over the posterior electrodes (Dehaene-Lambertz & Dehaene, 1994). To reliably identify the component in both hemispheres, we considered the best set of electrodes for each group, which differed across groups given the topography differences highlighted by the previous analysis. Based on the topography of the grand average computed over all trials and all infants in each group, these sets were determined to cover the positive pole of the P2 component and consisted of 9 left and right symmetrical electrodes. In typical infants, the two sets comprised 9 electrodes around F3-F7 and F4-F8 in the left and right hemispheres respectively. In AgCC infants, the sets were more lateral, around T7 and T8 extending up to F3 and F4 anteriorly and to P7 and P8 posteriorly (Figure 4.2.a).

In each infant and for each type of sound presentation (binaural syllables, monaural noise, dichotic stimulation), P2 was identified as the first distinguishable positive peak on ERPs averaged over the left and right sets independently. We then measured individual P2 latency as well as P2 amplitude from the average amplitude over a 50-ms time window centered on the peak latency of the original, unscaled data.

To compare the typical and AgCC infants, we performed the following analyses of variance (ANOVAs) for each characteristic latency/amplitude as the dependent variable. In the ANOVA for the binaural condition, we considered the group (typical / AgCC) as a between-subject factor, the cerebral hemisphere (left / right) as a within-subject factor, and the interaction between factors. In the ANOVAs for the monaural and dichotic conditions, we considered the brain response side (contralateral/ipsilateral relative to the stimulated ear) as an additional within-subject factor as well as interactions between the different factors. For significant effects or interactions, we further performed post-hoc analyses using t-

tests to detect the significant differences between conditions (p-values were corrected for multiple comparisons using the False Discovery Rate (FDR) approach).

Comparison of P2 responses to different stimulations: We finally investigated whether P2 characteristics were modulated by the type of sound presentation in our paradigm. We thus performed a ANOVA on each characteristic latency/amplitude as the dependent variable with the stimulation type (binaural syllables / monaural noise / dichotic stimulation) as a within-subject factor and group as a between-subject factor (typical / AgCC). For the response to monaural and dichotic stimulations, we averaged the characteristics across the two response sides (contralateral and ipsilateral) in order to keep the same sample size as for the response to binaural stimulation.

4.4.Results:

4.4.1. Different ERPs topographies in typical and AgCC infants

We first compared the topography of auditory ERPs between typical and AgCC infants using cluster-based analyses for the three types of auditory stimulation (binaural presentation of syllables, monaural presentation of babbling, dichotic presentation of opposite-side babbling, and syllables).

As can be seen in figure 4.2.a, the anterior positivity synchronous with a posterior negativity typical of an auditory response at this age was observed in both groups, but the anterior positivity fused at the midline in healthy controls. This was not the case in AgCC infants in whom the positivity appeared much more lateral than in controls. These topographical differences were objectivized by the statistical analyses for each type of stimulation.

Binaural stimulation (response to syllables): The difference in topography between both groups was statistically significant over a fronto-medial cluster of 12 electrodes during the time window [396-556] ms post syllable onset ($p_{\text{cor}} = 0.031$, Figure 4.1.a) in which a weaker activity was recorded in AgCC relative to typical infants.

Monaural stimulation (response to babbling): As can be seen in figure 4.1.b and 4.1.c, the response was more lateral in AgCC than in normal infants, yielding a significant difference between groups on a contralateral left temporal cluster when babbling was presented in the right ear (7 electrodes in the time window [76-568] ms post noise onset, $p_{\text{cor}} = 0.034$, Figure 4.1.b). By contrast, no significant difference was observed for babbling presented in the left ear, although visual inspection of the ERP shows a similar pattern (Figure 4.1.c).

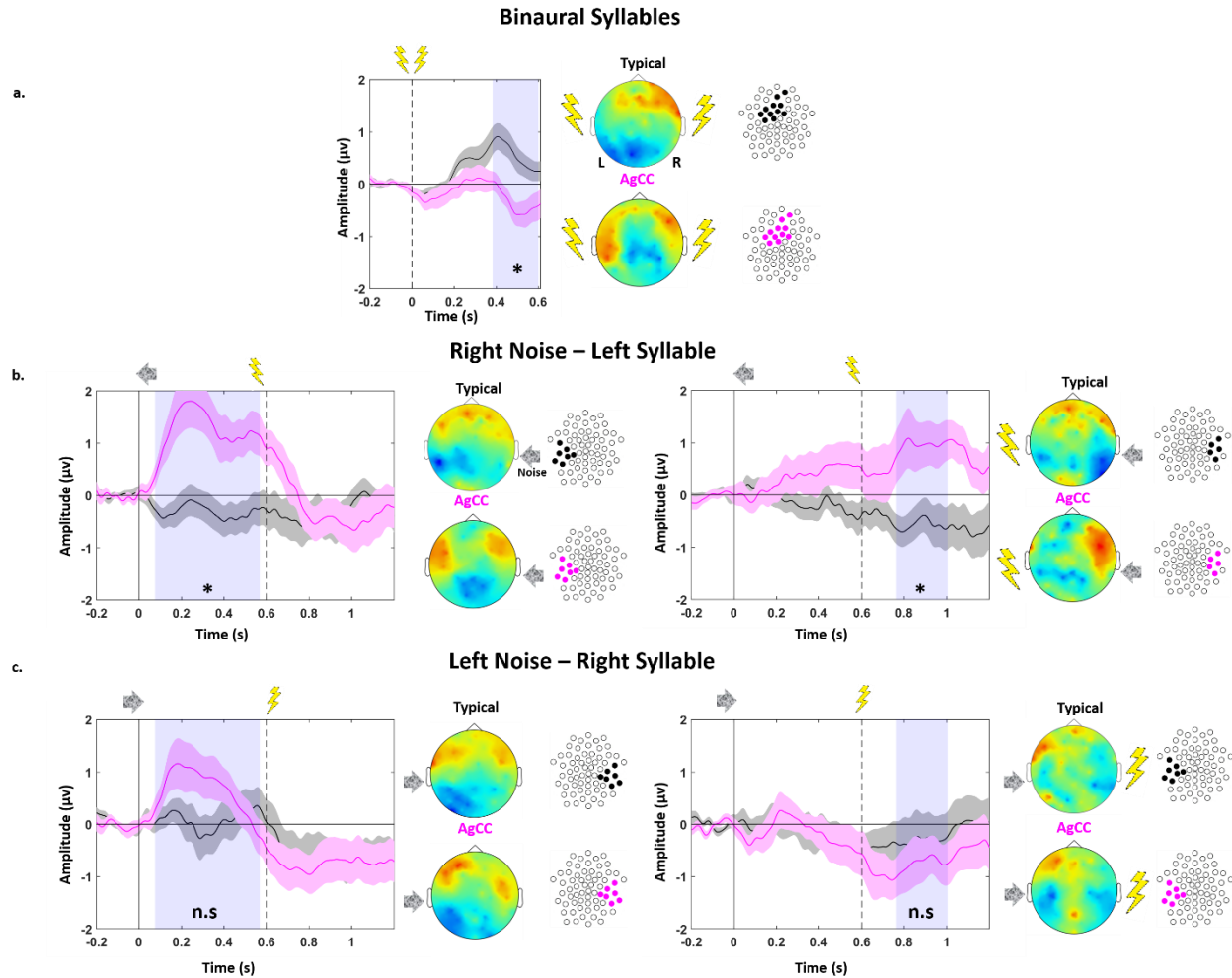


Figure 4.1: Topographical differences between typical and AgCC infants: ERP time courses of the grand average responses in typical (black) and AgCC (magenta) infants for a) binaural trials; b) dichotic trials: right-ear babbling/ left-ear syllable trials; c) dichotic trials: left-ear babbling / right-ear syllable. In a) and b), significant differences between both groups are observed for the highlighted clusters and over the time-windows shaded in light blue (asterisk correspond to $p < 0.05$ and also to marginally significant trends). In c), no group difference was observed, thus we highlighted symmetrical clusters compared to b) (n.s.: non-significant). 2D voltage topographies correspond to these time-windows.

Dichotic stimulation (response to the syllable in the presence of contra-lateral babbling): As for the previous analysis, a difference between groups was only observed for one side of presentation, i.e. a marginally significant trend when the syllable was presented in the left ear (babbling in the right ear) over a contralateral right temporal cluster (5 electrodes during the time window [164-404] ms post-dichotic onset, $p_{\text{cor}} = 0.093$, Figure 4.1.b.), whereas no significant cluster was identified for syllables in the right ear (babbling in the left ear) (Figure 4.1.c). Thus, the difference between the two groups was more visible for the trials in which babbling was presented in the right ear and syllables in the left ear. Moreover, the difference with respect to noise was higher than for syllables.

4.4.2. Different P2 latencies in typical and AgCC infants and across brain hemispheres

The P2 characteristics were reliably measured in each infant over the left and right sets of electrodes, covering the positive peaks in each group (see Figure 4.2 for an example of P2 topography, and Sup. Figure 1 for the identification of P2 peaks based on ERP time courses for each type of auditory stimulation). ANOVA results for the P2 latency are summarized below and detailed in Table 4.1, Figure 4.2. The complete ANOVA results for the P2 amplitude are presented in Supplementary Information.

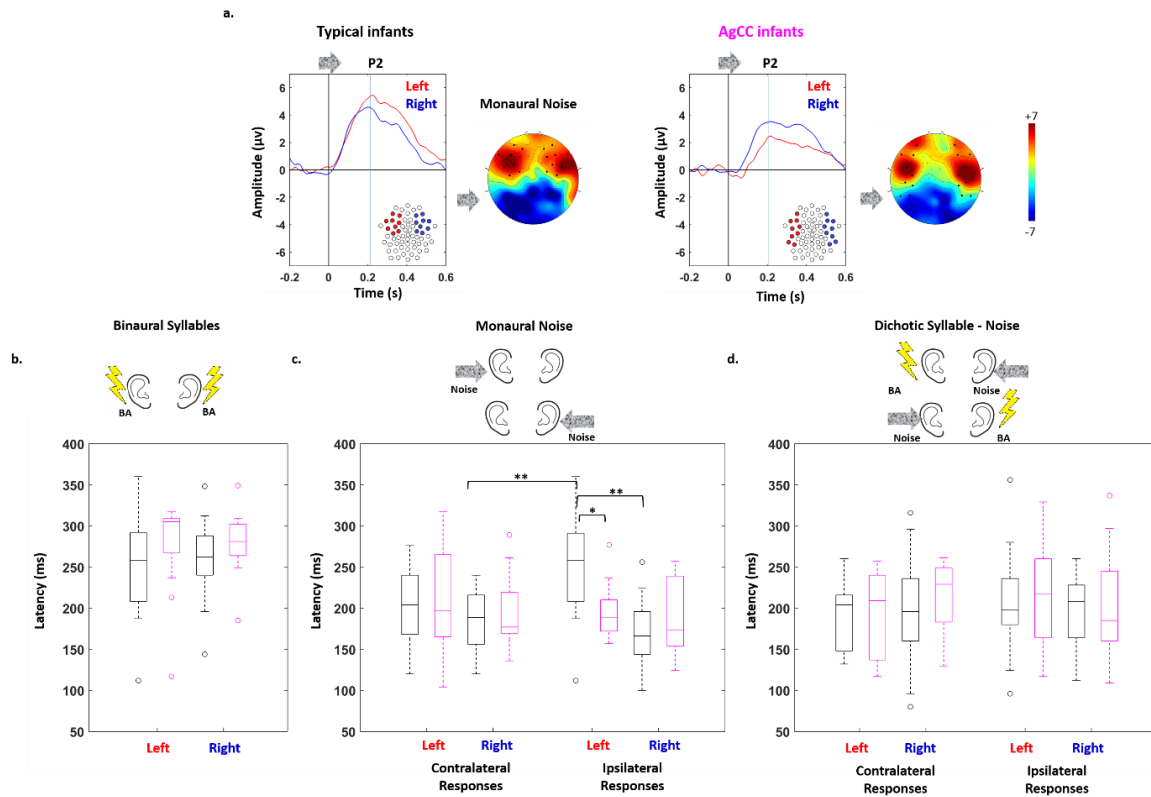


Figure 4.2: Comparison of P2 response latency between typical and AgCC infants: a) Grand average ERP time courses in response to monaural noise presented to the left ear, averaged over left (red) and right (blue) sets of electrodes optimized for typical (left panel) and AgCC (right panel) infants (averaged ERP time courses for other stimuli are shown in Sup Fig 1). P2 latency was measured as the delay between the stimulus onset and the first positive peak. Box plots represent the latency of P2 responses measured in typical (black) and AgCC (magenta) infants, in each hemisphere, following stimulation by b) binaural syllables, c) monaural babbling and d) dichotic noise-syllable. Bilateral responses are considered in b), while both contralateral and ipsilateral responses are shown in c) and d). Differences between response latencies are highlighted with asterisks (* $p < 0.05$; ** $p < 0.005$).

Binaural stimulation: We detected no main effect of group (AgCC: 278 ms vs typical: 256 ms), nor hemisphere (Left: 264 ms vs Right: 267 ms), nor any interaction between group and hemisphere (Figure 4.2.a; Table 4.1).

Monaural stimulation (response to babbling): We observed a main effect of hemisphere but no main effect of group or response side (see table 4.1 for complete results). In typical infants, the contra-lateral

response was faster than the ipsilateral response for left ear noise: 186 vs. 254 ms ($p=.003$), whereas for right ear noise, a weak trend suggested faster ipsi-lateral than the contralateral response 169 vs. 202 ms ($p=.097$). The within-hemisphere latency difference for the ipsi- and contra-lateral noise was significantly larger in the left hemisphere (85 ms vs 16 ms, $p=0.045$ interaction hemisphere X response side) due to the significantly slower ipsi-lateral response in the left than the right hemisphere (254 vs 202 ms, $p=.002$). This slow left ipsi-lateral response in normal infants was also significantly different from the latency in the same condition in AgCC infants (254 vs 197 ms, $p=.01$) suggesting that in typical infants, the left ipsilateral response comprised a transferred component through the corpus callosum but not the right ipsilateral response (Figure 4.2.b). For the AgCC infants, there was no significant difference between the latencies of the ipsi- and contralateral responses.

Table 4.1: ANOVAs of P2 response latency in the binaural, monaural and dichotic trials: Each row corresponds to the results of the ANOVAs on P2 latencies considering the group (typical / AgCC infants) as a between-subject factor, the cerebral hemisphere (left / right) and the brain response side (contralateral/ipsilateral relative to the stimulus) as within-subject factors, as well as interactions between them. The main effects and their interactions are first reported, followed by post-hoc analyses using t-tests (significant p-values, corrected for multiple comparisons are highlighted by asterisks: ** $p<0.005$; * $p<0.05$).

Binaural	Monaural	Dichotic
group : $F(1,29) = 1.8, p > 0.1$	group : $F(1,29) < 1$	group : $F(1,29) < 1$
hemisphere : $F(1,29) < 1$	hemisphere : $F(1,29) = 21.9, p < 0.005$ **	hemisphere : $F(1,29) < 1$
	response side : $F(1,29) < 1$	response side : $F(1,29) < 1$
group x hemisphere : $F(1,29) < 1$	group x hemisphere : $F(1,29) = 5.7, p = 0.023$ *	group x hemisphere : $F(1,29) < 1$
	group x response side $F(1,29) = 3.7, p = 0.065$	group x response side : $F(1,29) < 1$
	hemisphere x response side $F(1,29) = 4.4, p = 0.045$ *	hemisphere x response side $F(1,29) = 1.7, p > 0.1$
	group x hemisphere x response side $F(1,29) = 5.3, p = 0.029$ *	group x hemisphere x response side $F(1,29) < 1$
	ipsi L > ipsi R Healthy, $t = 5, p < 0.005$ ** ipsi L > contra R Healthy, $t = 4.5, p < 0.005$ ** ipsi L > contra L Healthy, $t = 2.4, p = 0.097$ ipsi R < contra L Healthy, $t = -2.4, p = 0.097$ ipsi L vs. ipsi R AgCC, $t < 1$ ipsi L vs. contra R AgCC, $t < 1$ ipsi R vs. contra L AgCC, $t = -1.4, p > 0.1$ ipsi L vs. contra L AgCC, $t = -1.1, p > 0.1$ ipsi L Healthy > AgCC, $t = 3.3, p = 0.01$ *	

Dichotic stimulation (response to syllables in the presence of contra-lateral babbling): None of the main effects of group, hemisphere, response side, or interactions was significant (all F values < 1 , Figure 4.2.c; Table 4.1).

To summarize, differences between groups were observed only for a monaural stimulation, thus in response to babbling, characterized by a slower left ipsi-lateral response in typical infants relative to AgCC.

4.4.3. Different P2 latencies depending on the paradigm of auditory stimulation

When comparing P2 latencies for the three types of auditory stimulation, we observed a main effect of the stimuli type (respectively 266/200/201 ms for binaural syllables/monaural noise/dichotic syllables: $F(1,58) = 50.1, p < 0.001$, Figure 4.3) but no effect of group ($F < 1$). Post-hoc analyses revealed a longer

latency for binaural syllables than for both monaural babbling ($t(1,61) = 9.1, p < 0.001$) and dichotic noise-syllable stimulation ($t(1,61) = 9.1, p < 0.001$), and there was no difference in P2 latency between monaural babbling and dichotic noise-syllable stimulation ($t(1,61) < 1$).

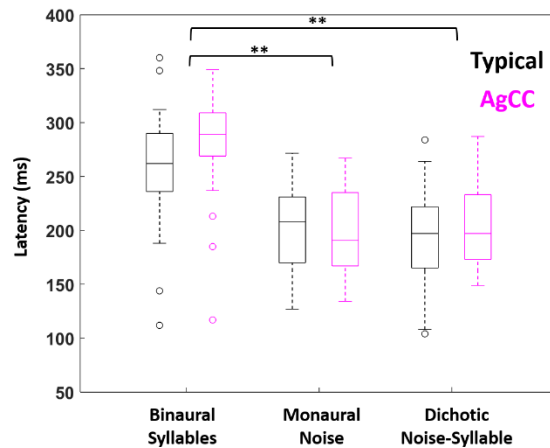


Figure 4.3: Influence of the paradigm on P2 response latency: Box plots represent the P2 latencies averaged over both hemispheres (left and right sets of electrodes, corresponding to both contralateral and ipsilateral responses) in response to binaural syllables, monaural babbling, and dichotic noise-syllables in typical (black) and AgCC (magenta) infants. Differences between response latencies are highlighted with asterisks (** $p < 0.005$; * $p < 0.5$), showing that responses for binaural syllables are slower than for other stimuli.

4.5. Discussion:

In this study, we compared infants with corpus callosum agenesis to typical infants in order to understand the role of the callosal fibers in auditory responses during early development, in terms of topography, latency, amplitude, and lateralization. Note that we are studying a late response, the auditory P2, which is a high-level component originating from associative cortices. First, we observed a different P2 topography between groups. The anterior positivity extended more toward the lateral temporal regions in AgCC and over the midline in typical infants. Second, we found no difference in amplitudes between ipsi- and contralateral responses nor between typical and AgCC infants, suggesting an efficient and robust ipsilateral auditory pathway at this age. Third, the ipsilateral P2 was slower in typical infants compared to AgCC infants for left-ear but not for right-ear babbling. As the ipsi-lateral response corresponds to both the direct pathway and to the trans-hemispheric transfer, this difference in responses to a lateralized sound indicates an asymmetric transfer of the auditory responses between hemispheres.

4.5.1. Altered topography of auditory responses in AgCC infants

The corpus callosum is a large tract connecting both hemispheres. In the case of agenesis, the would-be callosal fibers, which no longer cross the midline, become oriented along the anterior-posterior direction, constituting an aberrant tract, the Probst fibers. A recent tractography study in 12 children with corpus callosum dysgenesis revealed the complex connectivity of these fibers, which is not limited to frontal-occipital regions (Bénézit et al., 2015). Numerous fibers along the Probst main tract connect temporal and parietal areas. The fact that the Probst fibers do not degenerate and furthermore have similar DTI characteristics as remnants of the corpus callosum in the case of partial callosal agenesis (Bénézit et al., 2015) prove that they are functional and may propagate activity within the hemisphere to unexpected areas altering the voltage topography on the scalp.

Additionally, the absence of crossing callosal fibers affects the gyration of the cortex, the most obvious difference from a typical brain gyration being the orientation of the sulci on the medial surface of the brain which is vertical instead of wrapped around the corpus callosum. At a micro-structural level, the lack of callosal fibers might also change the vector orientation of the electric field within the cortical columns. All these factors might affect the surface topography in AgCC. Unfortunately, without an MRI in each infant, a correct reconstruction of the active sources of the auditory P2 was not possible. However, the group difference for the frontal positivity is congruent with the proposal of a source in the anterior cingulate cortex in complement of those in the superior temporal cortices at the origin of the P2 (Ortiz-Mantilla et al., 2012). Indeed, it is at this level that the difference of gyration is maximal between groups and thus might affect the surface topography most strongly.

4.5.2. A strong contribution of the ipsi-lateral pathway to auditory processing in the developing brain

The input to each ear travels to both hemispheres through an ipsi- and contralateral pathway. The responses are subsequently transferred from one hemisphere to the other through the callosal fibers. Subjects lacking callosal splenial fibers are thus the only adequate model to evaluate the respective contribution of contra- and ipsilateral pathways on auditory ERPs. In human adults and animals, contralateral pathways are generally predominant relative to ipsilateral pathways (Majkowski et al., 1971; Rosenzweig, 1951) until the auditory cortices; however, depending on the task (e.g. attention oriented toward on ear) and on the stimulus (e.g. speech vs music), the predominance of one hemisphere over the other might vary at the cortical level. Here, in AgCC infants, the P2 following monaural babbling was simultaneously recorded over both hemispheres, revealing that both pathways were equally efficient at

three months of age. The lack of differences in amplitude on the clusters ipsi- and contralateral to the stimulated ears further emphasizes the strength of the ipsilateral response at this age. As there was also no difference in ERP amplitude between AgCC and control infants (see Supplementary Information), we may hypothesize that it is the common rule at this age. Our stimulus presentation was passive, and all stimuli were speech, limiting the generalization of our results, yet we show here that a robust ipsilateral pathway ensures that both hemispheres are *a-priori* similarly reachable by the auditory stimulation without trans-hemispheric connectivity. It may explain why linguistic left-lateralization, especially in receptive tasks, is similar in AgCC adults and in controls (Pelletier et al, 2011).

4.5.3. Asymmetry of inter-hemispheric connections

To grasp the role of the corpus callosum, we compared AgCC and control infants listening to monaural babbling. The two groups notably differed in the latency of the ipsi-lateral left response when babbling was presented in the left ear. We interpreted the delay in the peak of the ipsi-lateral left P2 as resulting from a superposition of the ipsilateral-direct response and the inter-hemispheric transfer of the contralateral response. Taking either the lag between the contra and ipsi-lateral response in the typical infants (69 ms) or the difference between AgCC and typical infants (57 ms) for the ipsi-lateral left response provides a similar estimation of the inter-hemispheric transfer time of auditory information at this age. Although slow relative to adult IHTT values, which are estimated to be a few ms (from 3 ms for tactile stimuli to 10-30 ms for visual stimuli depending on their complexity), a value of ~60 ms is in agreement with the values we obtained for the visual P1 transfer around the same age, the distance being longer for a visual transfer than for an auditory transfer. Using visual hemifield presentation of faces, we measured an acceleration of the IHTT during the first semester of life from around 315 ms at six weeks of life to 84 ms four months later (Adibpour, Dubois and Dehaene-Lambertz. submitted). By contrast, it was surprising to record no difference between groups for right-side babbling, suggesting that there was no or little left-to-right inter-hemispheric transfer at this age for this type of auditory information. In the experiment cited above (Adibpour, Dubois and Dehaene-Lambertz. submitted), there was no asymmetry in the transfer delay for the visual P1. However in adults, a similar asymmetry in the auditory inter-hemispheric connectivity was described: TMS applied over the right but not the left auditory cortex changed the functional connectivity between auditory cortices during resting-state in proportion to the volume of auditory callosal fibers (Andoh et al., 2015). Similarly, Gotts et al (2013) reported stronger functional connectivity within the left hemisphere, especially for regions located within the language network, whereas the right hemisphere

interacts more widely with both hemispheres (Gotts et al., 2013). This asymmetrical pattern may therefore find its roots during early development.

How this asymmetry in inter-hemispheric communications affects language lateralization is not yet clear. It might facilitate language learning by integrating all information in the same areas instead of distributing resources in both hemispheres. Although brain plasticity is sufficient to allow linguistic reorganization in the right hemisphere in the case of an early left-sided lesion (Bates et al, 1999), competing hemispheres might be deleterious when attentional resources are limited as is the case in young children. It may explain why AgCC children may have learning difficulties as pointed out by Sander (1989) and Temple et al (1989, 1993) and as seen in our cohort in which 6 out of 13 required extra help to follow their primary school cursus. However, corpus callosum agenesis might also be the visible symptom of more diffuse neural anomalies not seen with currently available MRI, which alleviates the hypothesis of a unique role of corpus callosum transfer in these difficulties.

We might have expected a similar effect for the subsequent syllable presented in the other ear than the babbling, but there was no difference between groups nor delays of the ipsilateral left response for a left-ear syllable. However, in this case, the left hemisphere was saturated by the continuous babbling in the right ear projecting to the left hemisphere and blocking the right-to-left transfer. Still, no evidence of a left-to-right transfer was observed. Although the amplitude was much weaker for the dichotic syllables relative to the same syllables presented binaurally likely due to the masking noise, the P2 latency was shorter (~66 ms). We interpret this acceleration of the P2 peak as the attention trigger that preceded the babbling in 2/3 of the trials.

4.6.Conclusions:

Our study on the developing auditory network reveals an asymmetry between left-to-right and right-to-left effective connections, whereas the current structural approaches (e.g. diffusion imaging combined with tractography) cannot dissociate them. Our conclusions rely on the simple hypothesis that infants with corpus callosum agenesis have a similar auditory network except the missing corpus callosum. While our conclusions may be oversimplified, our interpretation is sensible, given the relative similarity in latencies and amplitudes of the auditory responses between both groups aside the notable exception of the left ipsilateral response for monaural stimulation we have discussed above. This result enters in the now large amount of evidence showing that the human brain architecture is lateralized very early on and differently depending on the cognitive domain and brain areas. Why evolution has selected this asymmetric

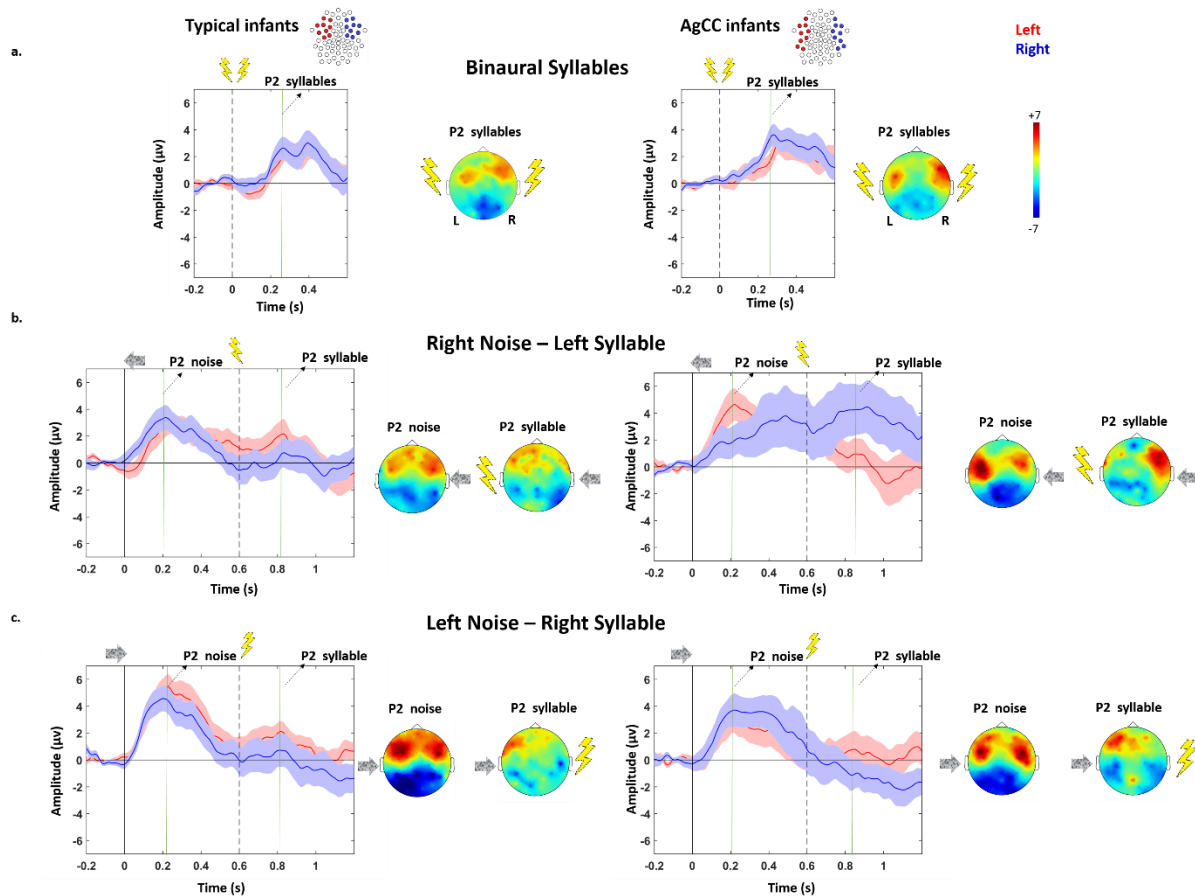
architecture and how it contributes to the development of complex cognitive functions remains to be understood.

4.7. Supplementary information:

ANOVAs with the same factors as the ANOVAs performed on the P2 latencies were performed on the P2 amplitudes.

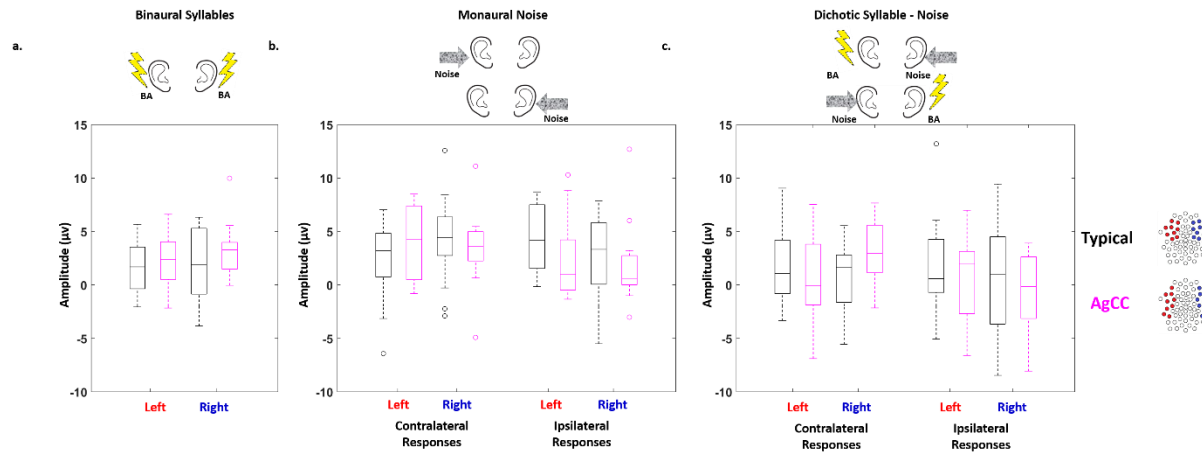
4.7.1. Do P2 amplitudes differ in typical and AgCC infants apart from differences in ERPs topographies?

We compared both groups for potential differences in their P2 response amplitude in response to the different stimuli (binaural, monaural and dichotic stimuli). Sup. Figure 4.1 illustrates the time course of the grand average ERPs for both groups of infants, providing a schematic view of the P2 time-course.



Sup. Figure 4.1: Auditory-evoked responses to different stimuli in typical and AgCC infants: ERP time course of the grand averages recorded in typical (left panel) and AgCC infants (right panel), corresponding to: a) binaural trials; b) trials with syllables in the left ear and babbling in the right ear; c) trials with syllables in the right ear and babbling in the left ear. The voltage was averaged across the channels highlighted in red (left cluster) and blue (right cluster) on the channel maps presented on the top row. These clusters were located on the P2 maxima in each group. Time zero marks the onset of the presentation of noise, and the dashed line marks the onset of the syllable 600 ms after the onset of the noise in (b) and (c) trials.

No significant difference between the two groups was revealed by the ANOVAs. Sup. Figure 4.2. and Sup. Table 4.1. summarize the statistical analyses.



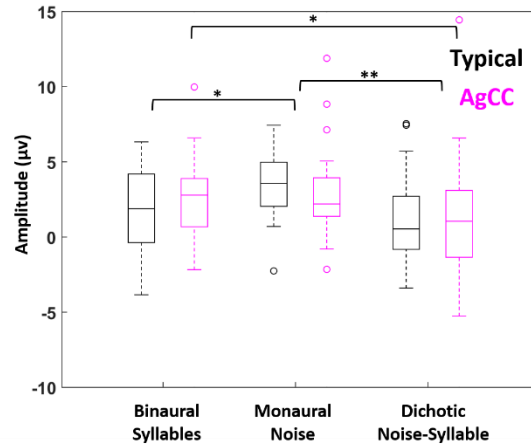
Sup. Figure 4.2. P2 response amplitude comparison between typical and AgCC infants: Box plots represent the amplitude of the P2 response measured in typical (black) and AgCC (magenta) infants following stimulation by a) binaural syllables, b) monaural babbling (contralateral and ipsilateral responses are shown), and c) dichotic noise-syllable (contralateral and ipsilateral responses are shown in reference to monaural syllable).

Sup. Table 4.1: Comparison of the P2 response amplitude between typical and AgCC infants: The P2 response amplitude was compared between the two groups for different auditory stimuli. The main effects and their interactions are reported.

Binaural	Monaural	Dichotic
group : $F(1,29) = 1.8, p > 0.1$	group : $F(1,29) < 1$	group : $F(1,29) < 1$
hemisphere : $F(1,29) = 1.1, p > 0.1$	hemisphere : $F(1,29) < 1$	hemisphere : $F(1,29) < 1$
	response side : $F(1,29) < 1$	response side : $F(1,29) = 1.2, p > 0.1$
group x hemisphere : $F(1,29) < 1$	group x hemisphere : $F(1,29) < 1$	group x hemisphere : $F(1,29) = 2.0, p > 0.1$
	group x response side $F(1,29) = 2.5, p > 0.1$	group x response side : $F(1,29) = 1.8, p > 0.1$
	hemisphere x response side $F(1,29) = 2.2, p > 0.1$	hemisphere x response side $F(1,29) = 1.7, p > 0.1$
	group x hemisphere x response side $F(1,29) = 1.4, p > 0.1$	group x hemisphere x response side $F(1,29) = 3.7, p = 0.062$

4.7.2. Do P2 amplitudes depend on auditory stimulation?

ANOVAs on the P2 amplitude with the type of auditory stimulation revealed a main effect of stimuli type ($F(1,29) = 12.5, p < 0.001$) but no effect of group ($F < 1$). The interaction group x stimuli type ($F(1,29) = 1.7, p = 0.188$) was non-significant. Post-hoc analyses demonstrated that the P2 amplitude was significantly weaker in response to dichotic stimulation compared to binaural stimulation ($t(1,61) = -2.2, p = 0.032$) and monaural stimulation ($t(1,61) = -5, p < 0.001$), likely due to the masking effect of the babbling in the other ear. The P2 amplitude was also weaker in response to binaural syllables relative to monaural noise stimuli ($t(1,61) = -2.6, p = 0.02$), but both stimuli were highly different in complexity, length, and intensity envelope. These findings are illustrated in Sup. Figure 4.3.



Sup. Figure 4.3: Influence of the paradigm on the P2 response amplitude: Box plots represent P2 amplitudes averaged over both hemispheres (left and right sets of electrodes, corresponding to both contralateral and ipsilateral responses) in response to binaural syllables, monaural babbling, and dichotic noise-syllables in typical (black) and AgCC (magenta) infants. Differences between response amplitudes are highlighted with asterisks (** $p < 0.005$; * $p < 0.5$), showing that responses for binaural syllables are slower than for other stimuli.

4.7.3. Are P2 amplitudes in response to monaural stimuli stronger over the contralateral compared to the ipsilateral hemisphere?

Finally, because the ANOVA revealed a significant difference in voltage topography between groups only for right-ear babbling, we investigated the amplitude of the ipsi- and contralateral responses to left and right babbling in both groups with paired t-tests. In typical infants, the P2 amplitude was similar over the left and right hemispheres for the contralateral ($t(1,18) = -1.3$, $p = 0.194$) and ipsilateral response ($t(1,18) = 1.3$, $p = 0.192$). In AgCC infants, the P2 amplitude was also similar over the left and right hemispheres for both the contralateral and ipsilateral responses ($t < 1$).

Chapter 5

General discussion

5. General discussion

In an attempt to investigate the ontogeny of lateralized functions in the human brain, we employed non-invasive neuroimaging techniques to study the neural correlates of face and speech processing in early infancy. We started by establishing some of the basic developmental properties of visual and auditory networks, studying how the neural substrates of early visual and auditory perceptions change over the first semester of infancy. We assessed this first aspect from both a functional and an anatomical point of view, through measures that have developmental relevance: latency of the brain responses recorded with EEG and DTI measures sensitive to the myelination of the white matter pathways. Next, using paradigms with lateralized presentation of stimuli (faces in one visual hemifield, and syllables in one ear), we asked whether hemispheric differences existed in the neural correlates of face and speech processing. We further studied how efficiently the face and speech processing networks exchange information across the two hemispheres and whether this inter-hemispheric communication impacts hemispheric functional differences.

In this final chapter, I briefly summarize the findings of the studies presented in Chapters 2 to 4 and try to discuss them in light of the existing literature. I will then attempt to illustrate how they fit into and complement the bigger picture of the developmental trajectories of face and speech processing abilities, in terms of their neural implementations. Throughout the discussion, I highlight the limitations of our studies and refer to the methodological limitations which are further detailed in the appendix on methodology. Finally, I describe some perspectives for the questions on early brain lateralization, with respect to their implications on the studies of neurodevelopmental outcomes.

In Chapter 2, we focused on the development of visual network and lateralization of face processing between 1 and 6 months of infancy. By presenting a face in a single visual hemifield, we recorded the first response appearing over the hemisphere contralateral to the side of the presentation of faces. Tracking the gradual propagation of this first response to the ipsilateral hemisphere provided us an estimation of delay for the interhemispheric transfer of the visual response. Both the latency of early contralateral responses and interhemispheric transfer time decreased with increasing age of the infants, revealing an increasing functional efficiency over the course of development. We further quantified the structural maturation of early visual pathways and interhemispheric callosal pathways, and found that they relate to the functional efficiency of the corresponding responses beyond the infants' age. Furthermore, we observed that only the right hemisphere demonstrated evidence for face discrimination when presented in the left visual hemifield. The discrimination responses enlarged with infants' increasing age, while there

was no evidence of face discrimination in the left hemisphere. To evaluate if the right hemisphere advantage holds for stimuli other than faces, we used car images in a follow-up experiment with the same design. This work is still in progress and remains to be fully investigated, but preliminary results do not suggest such a right-hemisphere advantage for discriminating car images.

In Chapters 3 and 4, we focused on the development of auditory network and lateralization of speech processing between 1 and 6 months of infancy. In a paradigm with binaural presentation of syllables, we found a weak trend for stronger responses over the left than the right hemisphere, suggesting a left-hemisphere lateralization for syllabic perception. When syllables were presented monaurally, responses appeared bilaterally over the hemispheres contralateral and ipsilateral to the presentation ear, the former being stronger and faster than the latter. Ipsilateral responses were delayed in the left relative to the right hemisphere, raising questions about the underlying mechanism. This result was clarified thanks to infants with corpus callosum agenesis: Utilizing a slightly different paradigm to compare infants with corpus callosum agenesis to typical infants, we found no latency difference between the left and right responses in the absence of callosal fibers, whereas we found similarly delayed ipsilateral responses in the left compared to the right hemisphere in typical infants. This observation suggested that the callosal fibers are differently mediating the left and right responses.

The latencies of the auditory responses decreased with age, as expected from their functional maturation. We further quantified the structural maturation of early auditory pathways and interhemispheric auditory callosal fibers. Contrary to the visual network, we observed no relationship between the structural maturation of early auditory pathways and the conduction speed of auditory responses beyond age. This finding motivated a number of questions about the contribution of different sources and pathways to the recorded auditory responses. Taking into account the insights on the role of callosal fibers in the left-right differences of ipsilateral response latencies, we further tested the relationship between the microstructural properties of interhemispheric callosal connections in the auditory network and the speed of the left and right hemisphere responses. These analyses suggested a weak inter-dependency between the two parameters, only for ipsilateral responses over the left hemisphere, which might be related an asymmetrical role of callosal fibers.

5.1. Functional relevance of structural maturation

We intended to relate the structural and functional measures of development in two systems that have a different exposure to environmental inputs from the gestation on and differ in developmental

trajectories. Input to the visual system is limited during gestation to a pink light with a sensitivity to light movement (Reid et al., 2017), but the auditory system already receives a rich amount of inputs *in utero*, such as mother's arterial blood flow, heartbeat, maternal speech but also external noise and voices. The two systems also differ with respect to maturational timelines. In the visual system, myelination of projection pathways progresses very intensely up to about six months of age, while in the auditory system this process occurs at a slower speed until 3-4 years of age (Yakovlev & Lecours., 1967; Brody et al., 1987).

We focused on white matter maturation and correlated structural and functional parameters that have developmental relevance based on common underlying biological phenomenon of myelination. The type of structure-function relationship that we assessed, is restricted in the sense that white matter myelination is only one among the several aspects of brain development. Nevertheless, it plays a key role in learning and cognitive development, increasing the speed of neural information transmission and thus the synchrony of impulse conduction between distant cortical regions (Fields, 2008). Thus, studying the structural maturation of white matter and its functional counterpart, may clarify some aspect of cognitive development.

Visual system: We followed the approach of Dubois et al. (2008), relating the speed of brain responses to the maturation of white matter pathways. We demonstrated that in the visual system, the maturation of projection and interhemispheric cortico-cortical pathways is related to the speed of early visual responses and their interhemispheric transfer. The directionality of this relationship cannot be assessed with our approach, but the interdependency might be in both directions: while the myelination increases the speed of activity, myelin induction itself might depend on neural activity (Barres & Raff, 1993; Demerens et al., 1996). Considering more white matter pathways for evaluating similar structure-function relationships could be an informative approach for determining the specificity of the correlations we tested.

Auditory system: We did not find similar structure-function relationships between the maturation of auditory responses and auditory pathways. A few explanations are possible. First, contrary to optic radiations, myelination of acoustic radiations is much slower in the early months of infancy (Yakovlev & Lecours., 1967). Therefore, it is possible that our methods were not sensitive to these slow changes of myelination. It could be informative to study a broader age-range (through childhood) to capture these slow modifications. Second, we focused on the P2, which appears between [150 350] ms in the first semester and is the most robust and identifiable component of auditory ERP at this age. However, it is not the earliest response that reaches the cortex and might encompass the activity from several regions. It was

proposed that some of the sources of P2 are distributed over temporal and even cingulate cortices (Ortiz-Mantilla et al., 2012). Thus, the maturation of these regions and of their white matter connectivity might be important parameters to consider in further models. A future direction that might help in this case would be the reconstruction of EEG sources using adapted head models for infants. This is discussed in the methodological appendix. Third, we simplified our model by using the average maturation of the acoustic radiations in both hemispheres, while the contribution of the contralateral and ipsilateral pathways to the ERPs in each hemisphere should be disentangled. Finally, the comparison between the left and right hemisphere responses suggested that P2 might, at least partially, include responses that are transferred from the opposite-side hemisphere. This might need to be further taken into account. In a first attempt to consider the contribution of interhemispheric transfer callosal pathways, we tested the correlations between the microstructural properties of auditory callosal fibers and the speed of auditory responses beyond age. The first evaluation of such correlations suggested that callosal fibers might play a role only for the speed of ipsilateral responses in the left hemisphere, i.e. responses that were shown to be delayed relative to their right hemisphere counterparts. However, this correlation relied only on a few sample points, that need further confirmation.

Before going further in the discussion, it is also noteworthy to mention that our measures of myelination are approximate and constrained by the limited sensitivity of DTI measures to different developmental processes, and so are our structure-function relationship assessments. While transverse diffusivity is suggested as the most sensitive DTI measure for the myelin contents of neuronal fibers (Song et al., 2003; 2005; Dubois et al., 2008), it still captures other developmental processes (Dubois et al., 2016). We discuss these technical considerations and other potential interesting measures in more detail in the appendix on methodology.

Integrating cortical measures: The models we have tested so far may be oversimplified, since the delay in the responses might not solely relate to delays of white matter conduction but also to delays in neural computations at the sensory, sub-cortical and cortical levels. Even in the visual system where the correlations between functional and structural measures were significant, still some variability in the speed of responses remained unexplained by the microstructural properties of pathways. This might be due to other parallel maturational processes: at the same time that myelination is progressing, the synaptogenesis and growths of the dendritic tree is intense (Huttenlocher & Dabholkar, 1997; Kostović & Judaš, 2015; Travis, Ford, & Jacobs, 2005). Thus, in a more elaborated and realistic model, the respective weight for both white matter and cortical maturation and even subcortical nuclei and pathways might be considered.

In perspective of this work, we would like to integrate measures of cortical maturation in our model, in particular for the study of the auditory network. The cellular events participating in cortical maturation (e.g. growth of dendritic trees, synaptogenesis and intra-cortical axons myelination, etc.) change not only the water content in each voxel but also the tissue composition, i.e. increasing iron and myelin content. These changes affect the MRI signal. Thus, cortical maturation can be indirectly measured based on normalized relaxometry parameters (Leroy et al., 2011) or by combining quantitative relaxometry parameters with diffusion parameters (Lebenberg et al., in preparation). We would like to implement this latter multi-parametric approach in order to benefit from the complementary information that different parameters provide on cortical maturation.

Structure-function relationships in adults: Our results are in relative agreement with a few similar adult studies, with the general aim of relating the inter-individual differences in tissue microstructure to the differences in functional responsiveness measures. Horowitz et al. (2015) recently demonstrated that inter-individual variability in the conduction speed of interhemispheric transfer of visual and tactile information (assessed by EEG) were related to the inter-individual differences in axonal diameter (quantified through diffusion MRI) in the callosal fibers connecting primary visual and somatosensory cortices (Horowitz et al., 2015). Although this study is similar to our infant study for interhemispheric transfer of visual information, the structure-function relationships may rely on different microstructural parameters. In infants, our DTI parameters mostly reflect developmental mechanisms such as myelin propagation and increasing coherency of fibers following the pruning of axons. In adults, measure of axonal diameter might also be sensitive to variability in the intra-axonal diameter as well variability in the myelin contents in inter-axonal spaces.

Similar questions have been pursued in the aging population, searching for neuroanatomical bases of age-related slowing of neural responses. Price et al. (2017) employed a whole-brain voxel-wise approach to relate the latency of magnetic visual and auditory evoked fields (MEG) to age-related changes in the gray matter volume and white matter microstructure (estimated by diffusion MRI) across the whole brain. They computed two types of age-related delays for the cortical responses: a constant and a cumulative delay, with the constant delay equally affecting the whole ERP and the cumulative delay increasing over the time-course of the response, potentially summing the delays from different processing stages. The constant delay of visual responses correlated with the microstructural changes in the optic radiations and splenium of the corpus callosum, whereas the cumulative delay of auditory responses correlated best with the gray matter thinning in the left posterior part of the superior temporal gyrus, beyond age effects (Price et al.,

2017). In addition to these regions that are part of the visual and auditory networks, the authors also reported correlations between the cumulative delay of auditory responses and regions of left superior lateral occipital cortices, which are not involved in auditory processing, but might share similar structural properties as the posterior part of the superior temporal gyrus throughout aging. A point requiring emphasis here is the different mechanism underlying the structure-function interdependencies in the visual and auditory networks in the aging population. While the functional properties of the visual responses were related to the microstructural properties of the white matter, i.e. efficiency of signal transmission across distant brain regions, properties of auditory responses were related to the cortical gray matter and thus efficiency of local cortical processing. Studies of aging and development period have suggested that for some of the regions in the white matter (Yeatman, Wandell, & Mezer, 2014), and gray matter (Douaud et al., 2014), changes in the aging period mirror the earlier developmental ones. This analogy should be taken with caution. Nevertheless, the Price et al.' findings (2017) suggest that considering measures of cortical maturation in addition to white matter maturation might provide us with a more realistic model for explaining the functional properties of the auditory responses during development as well.

To summarize, our study is a first step in relating functional and structural measures of development and that of lateralized functions. It attests that diffusion MRI is able to capture fine microstructural properties of the brain wiring across regions, that can explain, not necessarily in a predictive sense, the variability in neural responses raised from these circuitries. It falls within the early evidence that prove the feasibility of performing such studies *in vivo* during the early developmental period and encourages extensions of such studies to other brain networks such as somatosensory and motor networks.

5.2. Neural correlates of early lateralization

Our second goal was to study the neural correlates of lateralized functions in the infant brain. As we described in the first chapter, infants' behavioral studies already suggested the presence of these functions early on but these studies were indirect. One insight that EEG offered in addressing the question of lateralization, was the timing of neural computations required for face and speech processing. As addressed in the appendix on methodology, the temporal precision of EEG responses is indeed accompanied by its limited spatial resolution, making it difficult to infer information on the sources of responses. We used lateralized presentation of stimuli in our EEG experiments to recover responses over the left and right hemispheres and gain better separation of responses over the two hemispheres despite the low spatial

resolution of EEG. This strategy was helpful for the study of face processing lateralization but it remained more limited for evaluating speech processing lateralization. We also highlighted a number of structural asymmetries in the regions of visual and auditory networks, which do not necessarily relate to these functional lateralizations, but may offer better characterization of infant brain architecture.

5.2.1. Early lateralization of face processing

In our study of lateralization for face processing, we used a divided visual field and rapid presentation of faces to evaluate each hemisphere's capability to discriminate between frequently presented and novel face images. The discrimination responses appeared over right occipito-temporal cluster of electrodes for left hemifield faces. They appeared already from ~ 300 onwards, on ERP components (N290 and P400) that are face-sensitive in infants (de Haan et al, 2002; Halit et al., 2003), and indicative of slower computations compared to adult's counterparts, i.e. the N170 component of visual ERP. From the de Heering and Rossion's study (2015), that used a frequency-tagging approach, it can also be inferred that face-categorization occurs at least as fast as the frequency of presentation of faces (1.2 Hz, i.e. ~ 830 ms).

The right hemisphere advantage that we reported might not be specific to faces. Without a control stimulus, it is difficult to address this issue. In a follow-up study, we used the same paradigm with car images in addition to faces. If the right hemisphere advantage holds for a car discrimination, then it could be inferred that the right hemisphere is better at extracting information and performing computations for within-category discrimination of stimuli beyond faces at least when a fast presentation is used. Some of the previous infant studies have addressed the question on specificity of a right hemisphere advantage to a limited extent, mostly for between-category discrimination. Using NIRS, Otsuka et al. (2007) and Nakato et al. (2009) demonstrated a right hemisphere superiority, when comparing responses to images of faces and of simple vegetables. However, vegetables might not be perceived as another category of objects in early infancy, and in that case the right-lateralized responses might relate to the ability of infants to recognize a category. Emberson et al. (2017), again using NIRS, reported a weak right-hemisphere lateralization for shape processing, comparing variable to repeated geometrical shapes that contoured schematic inner facial features (eyes and mouth). However, due to the presence of inner schematic facial features within the shape contours, it is difficult to associate the right-lateralized responses to pure shape processing abilities. De Heering and Rossion's EEG study (2015) controlled for lower-level visual properties of face images and asked whether the right hemisphere advantage found for face-category perception, still

holds if the face images were phase-scrambled, making the face-structure unrecognizable while maintaining their lower-level visual properties (e.g. luminance). The answer was no, indicating some specificity of their right hemisphere responses. Although this is a nice control for low-level features of images, it still remains unclear whether or not their right lateralized frequency-tagged response would be observed if another category of objects (other than faces), was presented with a specific frequency among the pool of other type of images. The control car stimuli that we used would add another category of control stimuli to the existing ones.

A direction to be investigated in the future is the structural relevance for this functional right-lateralization of early face processing abilities. As mentioned previously, with the small size of the fusiform face area ($\sim 250 \text{ mm}^2$), this task is more challenging than for studies of larger size language areas. Nevertheless, postmortem studies are starting to identify regions within the fusiform gyrus that have different cytoarchitectonic properties, which are associated to different functional domains: i.e. FG2, FG3 and FG4 comprising face-, place- and word- sensitive processing (Weiner et al., 2016). The microstructural changes in the posterior fusiform gyrus (approximate location of FG2) between children and adults, as it is reflected in T1 MRI *in vivo*, has been recently suggested to relate to the increasing face-selectivity of responses in this region (Gomez et al., 2017). Yet, left-right asymmetries have not been reported so far for these regions and their white matter connectivity, and remain to be investigated in the future both in adults and during child development. In infants, due to the low MRI signal contrast in occipital cortical regions it is challenging to perform gray matter analyses not contaminated by the white matter as the MRI signal difference between both compartments is weak at this age. Our study of white matter maturation, highlighted asymmetries of microstructure at the level of optic radiations, the left being more mature than right that is in agreement with a few reports in children and adult studies (Dayan et al., 2015; Park et al., 2004; Xie et al., 2007). We did not find any functional relevance for this asymmetry, i.e. no latency difference was observed for the early visual responses, suggesting that this asymmetry might be compensated by other potential cortical, subcortical or white matter asymmetries in the opposite direction.

A developmental scenario for the hemispheric lateralization of face processing:

To our knowledge, no study has directly tested the question of lateralization of face processing at birth. However, this question was indirectly addressed in a few studies that focused on face perception in newborns. Simion et al. (1998) tested newborns' face preference while they were wearing patches over one eye, and were presented with a face-like pattern in the temporal or nasal hemifields of the uncovered

eye (Simion, Valenza, Umiltà, & Barba, 1998). The authors did not find any difference related to eyes or interactions between eyes and hemifields for face preference behavior of newborns, suggesting no hemispheric asymmetries. More recently using fNIRS, Farroni et al. (2013) recorded the hemodynamic cortical responses to dynamic face stimuli and reported bilateral posterior activations, with no evidence of right-hemisphere advantage when compared to another moving object (Farroni et al., 2013). Although neither of the two studies support the presence of a right hemispheric advantage for face processing, it is difficult to draw a conclusion based on these scarce evidence, as they might not be completely suited to answer the question on lateralization. For example, in the fNIRS study of newborns, the dynamic stimuli were quite complex and might require several parallel computations beyond the face-related information, that might be more bilaterally distributed at this age. Moreover, the placement of fNIRS sources and detectors in this study cover mostly temporal regions, missing the responses from occipital areas that might be more lateralized. Thus, whether or not face processing abilities are lateralized at birth remains to be addressed in the future.

Studies of older infants however suggest a right hemisphere advantage for processing faces starting from 2 months of age (Tzourio-Mazoyer et al., 2002; de Schonen et al., 1986; de Schonen & Mathivet., 1990; Otsuka et al., 2007; Nakato et al., 2009; de Heering & Rossion., 2015; Adibpour, Dehaene-Lambertz, Dubois., submitted). This early right-lateralization might rely on earlier and faster maturation of the right hemisphere, as proposed by de Schonen and Mathivet (1990), giving advantage to processing of certain facial information (in particular configural information) in this hemisphere (Deruelle & de Schonen., 1998). Yet, this lateralization of configural information might go beyond faces, and account for object shapes as well (Emberson et al., 2017). Thus, early perceptual abilities for faces seem to further channel the facial information to the outperforming right hemisphere for configural processing, following extensive exposure to face stimuli after birth, and therefore generate a bias for face perception abilities in the right hemisphere (Acerra et al., 2002). This bias holds both for processing faces as a category (de Schonen & Mathivet., 1990; Otsuka et al., 2007; de Heering & Rossion., 2015) and also within the face category itself, as suggested by the study in chapter 2.

When putting this early lateralization for face processing in perspective with the later development of face lateralization in children and adults, there seems to be discontinuities of the right hemisphere advantage for face processing during childhood. In children, the face-selective activations are much less clearly observed in fMRI studies compared to object- and place-selective activations (Scherf et al., 2007). Although they tend to enlarge in the fusiform gyrus throughout childhood, their lateralization remains

much weaker than in adults (Gathers et al., 2007; Golarai et al., 2007; Peelen et al., 2009; Golarai et al., 2017). The absence of right-lateralized face responses in children, has pushed forward the idea that face processing lateralization interacts with the emergence of left lateralization for written words during reading acquisition, that would consequently push the face responses to the right hemisphere (Dundas et al., 2012; 2014). This discontinuity of lateralization between infants and children, at first might seem to relate to the differences in the methodologies applied to infants and children. To address this issue, Lochy et al. (2017) employed the same approach, based on entraining the brain's oscillatory activity to the frequency of face presentation, indicating face-sensitive right-lateralized responses in infants and adults (de Heering and Rossion., 2015; Rossion et al., 2015), and reported no lateralization of face responses in 5-year-old preschoolers. They described this sequential presence-absence-presence of face response lateralization throughout infancy to adulthood as a non-linear developmental trajectory of face processing network (Lochy, de Heering, & Rossion, 2017). Yet, this description remains speculative and needs more direct evidence to understand what aspects of face processing are functionally more efficient in different stages of development and what types of facial information are differently processed at each stage. Future work regarding the anatomical maturation of the underlying neural substrates is also required to understand the true developmental trajectory of face processing abilities.

5.2.2. Early lateralization of speech processing

In our study of lateralization for speech processing in chapter 3, we employed paradigms with binaural and monaural presentation of consonant-vowel syllables to evaluate whether hemispheric differences could be found for syllabic perception. In chapter 4, we used different stimuli (including monaural babbling speech) with a similar paradigm. We based our analyses on studying the P2 component of auditory evoked responses, appearing over fronto-temporal regions. This response had a wider spatial distribution compared to the visual responses.

In terms of response amplitude some differences were observed between the studies presented in chapters 3 and 4. While responses to monaural syllables were stronger over the hemisphere contralateral to the stimulated ear (chapter 3), responses to monaural babbling speech were of equal amplitude over the contralateral and ipsilateral hemispheres (chapter 4). This might be related to the paradigms' differences in the organization of trials. With the block design used for monaural syllables, the stimulation was constant for one ear over the trials of a block. Therefore, it is possible that infants' attention was oriented toward the stimulated ear during the presentation of each block. In adults, attention orientation to one side of the auditory space can modulate the degree of perceptual asymmetry, depending on the ear

that is attended (Bryden et al., 1983; Hugdahl & Westerhausen, 2016). Superior contralateral responses to syllables might thus relate not only to the relative strength of these pathways compared to ipsilateral pathways (Majkowski et al., 1971; Rosenzweig, 1951), but be also further amplified by attention orientation. In chapter 4, we did not use the block design to present monaural babbling speech, and did not find stronger contralateral responses in typical infants. It would be thus interesting to study whether or not in a similar paradigm but with random presentation of syllables, to avoid such attentional modulations of perceptual asymmetries, left-right asymmetries are observed for syllabic perception.

It is also possible that with the spatial resolution of EEG, picking up activity from diffused electrical fields from several sources in one single sensor, the question of lateralization cannot be properly addressed. Thus, techniques with finer spatial resolution might be better suited for assessing the functional asymmetry of speech processing. fNIRS and fMRI studies in infants have shown left-lateralized activations in perisylvian regions, when contrasting forward and backward speech, speech and music, mother speech relative to that of a stranger, or speech and biological non-speech stimuli (Pena et al, 2003; Dehaene-Lambertz et al., 2002; Dehaene-Lambertz et al., 2009; Schultz et al., 2014), with the exception of Perani et al., (2011) study. In this study, neonates demonstrated bilateral activations, stronger over the right Heschl's gyrus, when contrasting expressive child-directed speech and silence. Nevertheless, the whole brain analysis demonstrated mainly bilateral activations and even left activations when hummed and flattened speech were compared (supplementary materials, Perani et al., 2011), contradicting the report of a right-lateralized network for speech processing in neonates.

Apart from studying the amplitude of responses, we evaluated their latency. While we observed delayed ipsi- relative to contra-lateral responses to monaural syllables presented in either ear in chapter 3, we found delayed ipsilateral only for left-ear babbling speech stimuli in typical infants in chapter 4. This observation may be related to the role of attention when stimuli are delivered through a block design, orienting attention to one ear, and providing advanced contralateral but delayed ipsilateral responses. However, the two studies merged on the finding that left ipsilateral responses are delayed compared to the right ipsilateral responses. Given that ipsilateral responses could contain information carried through the ipsilateral auditory, as well as information transferred from the opposite-side hemisphere, we proposed two hypotheses. First, the left and right auditory pathways and regions might have different properties, resulting in delayed responses in the left hemisphere. Alternatively, the delay might be related to the interference of interhemispheric connections and asymmetry of interhemispheric callosal transfer of responses. The first view does not seem to be validated by any of our current measures. If the left auditory

pathways and regions have different properties from the right counterpart that promote delayed responses over the left hemisphere, we should have observed similar delays for the contralateral responses, but this was not the case. From our DTI measures, we found an asymmetry of maturation in favor of left acoustic radiations, inciting advanced rather than delayed responses in the left hemisphere. More pathways and cortical regions should be studied to better characterize the microstructural properties of the left and right hemispheres and their potential asymmetries that might contribute to the functional differences. The second view is supported by adult studies suggesting an asymmetric interhemispheric propagation of activity between the left and right temporal areas (Andoh et al., 2015; Gotts et al., 2013). Andoh et al. (2015) reported a change in the interhemispheric functional connectivity only when TMS was applied over the right auditory cortices. Since the magnitude of this change in the functional connectivity correlated with the volume of the auditory callosal fibers, this asymmetric role might be attributed to the corpus callosum rather than to other structures. In infants with corpus callosum agenesis, we found similar response latencies over both hemispheres as well, suggesting that there is no differences in the neural transmission in the left and right pathways in the absence of callosal fibers.

Even in the literature that reported lateralization of speech processing in early developmental period, no link between the functional and structural measures of speech processing asymmetries has been established so far. However, the overlap between the speech-activated regions and the regions of structural asymmetries such as *planum temporale* (Dehaene-Lambertz et al., 2002, Dehaene-Lambertz et al., 2010), might suggest a link between the two. In our study, expect from the weak lateralization for the amplitude of responses to binaural syllables, we did not find a lateralization for monaural syllables as responses were potentially confounded by attentional biases. In the case of monaural syllables, where infants have MRI, data, it would be informative to assess whether the degree of contralateral dominance is related to cortical structural asymmetry measures. For example, we could ask whether infants with stronger contralateral responses to right-ear syllables, have more mature left relative to the right cortical measures. Our study of white matter maturation indicated a microstructural asymmetry in acoustic radiations in favor of the left hemisphere. Yet, as in the visual network, we did not find any functional relevance for this asymmetry, i.e. no latency difference was observed for the contralateral auditory responses. However, since we did not study the earliest cortical responses (P2 is a rather late response), we might have missed this relationship. It is also possible that at the level of P2 response, the asymmetry of other white matter pathways or cortical regions in opposite direction might be compensated. Complementary measures on the cortical microstructural and maturational differences, might indicate such other asymmetries in the same or opposite direction exists at this age.

A developmental scenario for the hemispheric lateralization of speech processing:

Since left-right structural differences appear early on in development, it is likely that they are of genetic origins. Genetic studies have reported numerous genes with asymmetric expression, for example LMO4, which is known to be expressed more in the right hemisphere during the early stage of gestation (Sun et al., 2006). The early asymmetric gene expression pattern, may create an early bias that could be the seed on which auditory input, such as the temporal features of speech signal, might encroach to further accentuate this early hemispheric difference. Following this asymmetry, the left perisylvian regions might get initially tuned for perceiving the speech, through mother's voice as the most prevalent input that infants have (Dehaene-Lambertz., 2010).

Nevertheless, some evidence supports increasing lateralization for many aspects of speech processing, such as vowel, consonant and durational contrasts processing with age (Furuya, Mori, Minagawa, & Hayashi, 2001; Minagawa-Kawai, Mori, & Sato, 2005). At the anatomical level, asymmetrical tempos of maturation is reported in the perisylvian regions, in Broca's area, the posterior superior temporal sulcus and in the parietal segment of the arcuate fasciculus during infancy (Lorey et al., 2011). At the functional level, the left-lateralized responses tend to become more selective to speech, and less responsive to biological non-speech sounds (Shultz et al., 2014). Minagawa-kawai et al. (2011) have proposed a model for development of language lateralization based on an early perceptual asymmetry for the features of the speech input that is further reinforced by the left-lateralized biases of the learning capacities required for language learning (Minagawa-Kawai, Cristià, & Dupoux, 2011)(Figure 5.1).

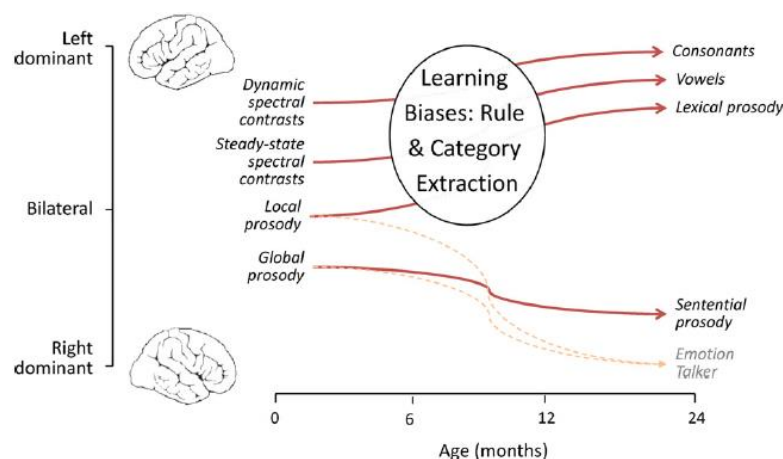


Figure 5. 1: Schematic model of developmental hemispheric lateralization, as proposed by Minagawa-Kawaia et al., 2011. According to this model, early perceptual asymmetry for the features of the auditory input is further reinforced by the left-lateralized biases of the learning capacities required for language learning.

This model departs from an initial lateralization for features of auditory input, and thus can explain speech processing. Yet, it might also account for sign language considering that the left-lateralized biases of learning might still favor the left hemisphere to specialize for language processing. Indeed, studies in congenital deaf people, who *a-priori* do not have early auditory input, have indicated similar leftward structural asymmetries for perisylvian regions: e.g. Heschl's gyrus and *planum temporale* (Emmorey, Allen, Bruss, Schenker, & Damasio, 2003) and functional lateralization for communicative gestures of sign language (Sakai et al 2005).

Another dimension that our studies suggest may contribute to the left-lateralization of speech processing, is the asymmetry of interhemispheric communications in the auditory network. This asymmetry impacted the P2 auditory responses in the left but not the right hemisphere. The comparison between typical infants and infants with callosal agenesis showed that at the level of P2, no transfer might have affected the responses in the right hemisphere (similar response latencies between the two groups). Thus, the observed asymmetry may be related to a facilitation of transfer in the right to left direction. The coincidence of such asymmetric transfer in the auditory network, nesting lateralized linguistic and speech processing abilities, could support an interaction between hemispheric lateralization and interhemispheric communications as proposed by the long-lasting debate (Caminiti et al., 2009; Cook, 1984; Dennis, 1981; Karbe et al., 1998; Ringo et al., 1994; Yazgan et al., 1995). If the asymmetry of transfer induces a true facilitation of interhemispheric communication toward the left perisylvian regions, it might reinforce the left lateralization for speech processing.

5.3. Early efficiency of interhemispheric communications

We studied interhemispheric callosal communications in the visual and auditory networks, first using DTI microstructural measures, indicating structural maturation of the callosal fibers participating in these networks. Next, we investigated functional indices of interhemispheric transfer of information. In the visual network, the interhemispheric propagation of responses was shown to occur in both directions, indicating relative functionality of callosal pathways. Given that callosal fibers are weakly myelinated in early infancy and that myelination of splenial fibers starts at 3 months of age, even such a basic transfer was not guaranteed to exist, although the pathways are in place. The slower transfer times in infants (from 315 to 80 ms between 1-to-6 months of age) compared to adults (between 5 and 30 ms depending on the stimuli) indicated the limitations of this transfer compared to the adult state (Horowitz et al., 2015; Saron & Davidson, 1989; Whitford et al., 2011). The slow transfer of responses from the contralateral to the ipsilateral hemisphere decreased their amplitude, raising questions about the efficiency of these responses.

We further addressed this question using our discrimination paradigm, asking whether face-related information stored in one hemisphere can be recovered on the opposite side. The transfer of visual information appeared to be efficient enough in the left to right direction at least, to allow a face initially presented to the left hemisphere to be recognized as familiar in the right hemisphere. However, we could not assess the efficiency of transfer on the opposite direction, as left hemisphere was not able to discriminate between faces under the conditions of our paradigm.

Identifying the transfer times appeared to be more difficult in the auditory network using the analogue lateralized paradigms that we used in the study of visual network. We could not reliably identify earlier cortical responses and studied responses that included both responses carried through the ipsilateral pathways and the interhemispherically transferred responses. We observed that P2 auditory responses were asymmetrically affected by the interhemispheric communications, i.e. they were impacted in the left but not the right hemisphere. Through this asymmetry, we could estimate the transfer delays at least in the right to left direction. These delays were estimated to vary between 230 and 60 between 1 and 6 months of age in chapter 3 study and approximated to be ~60 ms at 3-4 months of age in chapter 4. The longer delays in chapter 3 study, is probably related to the role of attention that we discussed before. The infants' values were indeed longer than those of adults (~12 ms), shown to be similarly asymmetric (Krumbholz et al., 2007). This asymmetry might suggest a facilitation of transfer in the right to left direction. Nevertheless, suggesting such a facilitation in the right to left direction does not impose an absence of left to right transfer of information as we have limited our analyses to P2 responses. It is possible that a more delayed transfer occurs in the opposite direction and would affect the latency of later responses.

The comparison between visual and auditory networks first highlights longer interhemispheric transfer delays (at least in one direction) in the visual than the auditory network. This is probably due the bigger length of visual relative to auditory callosal fibers, imposing longer delays despite more mature microstructure of visual compared to auditory callosal fibers at this age (Figure 5.2). Moreover, the difference between the two networks also concerned the symmetry of the interhemispheric transfers. This latter difference highlights that callosal fibers may differently interact with lateralized functions within each network in early infancy. While the symmetrical transfer does not favor the transfer of information toward a hemisphere for a specific function, the asymmetric transfer may provide an advantageous route to access the dominant hemisphere and thus reinforce a functional lateralization. With this view, it might be suggested that the early lateralization for face processing abilities does not interact with interhemispheric connectivity. However, speech processing lateralization might do so, consistent with

models of dichotic listening performance describing that callosal pathways serve as a relay for accessing the dominant left hemisphere resources (Kimura., 1961; Hugdahl & Westerhausen., 2016). The interhemispheric transmissions and their interaction with lateralized functions might be mediated by the different roles that callosal fibers play in these networks (Bloom and Hynde., 2005). A transfer of information in both directions may suggest an excitatory, i.e. facilitatory, role of callosal fibers (Galaburda et al., 1990; Yazgan et al., 1995) in the visual network during infancy. In contrast, the asymmetry of transfer might support an excitatory role in one direction and potentially an inhibitory role (Cook, 1984; Dennis, 1981; Karbe et al., 1998) in the opposite direction.

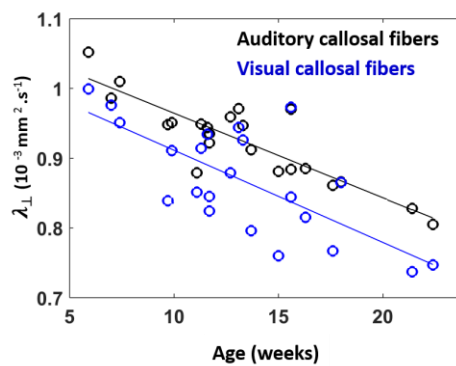


Figure 5. 2. Microstructural maturation of auditory and visual callosal fibers. Lower values of transverse diffusivity (λ_{\perp}) indicate higher maturation. Visual callosal fibers appear to be more mature than the auditory ones.

It should be noted that interhemispheric communications do not only rely on callosal pathway and subcortical, anterior and posterior commissures might be involved in such communications as well. Indeed, it is through these latter pathways that the residual interhemispheric communications in commissurotomy patients are suggested to occur. Thus, one may wonder if these other pathways are contributing to the transfer of responses in infants. We cannot exclude that these pathways might have played an additional role. However, a number of consistent observations across the 3 studies suggest an involvement of callosal pathways. First the correlations between the microstructure of callosal pathways and the speed of interhemispheric transfer (in the visual system), support that the properties of these pathways are related to the variations in the transfer speeds. Second studies of typical infants and infants with corpus callosum agenesis yielded the presence of delay in the ipsilateral responses only when callosal pathways were present. Taken together, these observations suggest that callosal pathways are likely to mediate the transfer of information that we observed in our studies and that these pathways are relatively efficient in early months of infancy.

One interesting question to be addressed in the future is the dependency of the transfer times reported here, on the type of stimuli we used. Indeed, faces and syllables are complex stimuli and eventually may incorporate more cortical delays relative to simpler stimuli as the comparison between adult studies suggest. Thus, it would be interesting to use similar type of paradigms with different stimuli (checkerboards, tones, etc.) and assess the transfer times.

5.4. Perspectives for neurodevelopmental outcomes

A good way to demonstrate that lateralization is an important functional feature of the human brain is to show that its strength is related to functional abilities. With this view, one may ask whether early lateralization could signal better cognitive abilities. We introduce a few examples to highlight that an interaction between the two might exist, and that ontogeny of lateralization might be an important factor to investigate in future studies.

Emerging evidence suggest that early functional and structural asymmetries might be related to linguistic abilities. In normally developing children, the leftward functional lateralization for language production is shown to correlate with better vocabulary scores (Groen, Whitehouse, Badcock, & Bishop, 2012). In the white matter, the leftward lateralization of the arcuate fasciculus has been shown to correlate with better vocabulary and phonological processing of children (Lebel & Beaulieu, 2009). Asymmetry of myelin contents, in favor of the left caudate nucleus and frontal cortex and right extreme capsule, is suggested to relate to the receptive and expressive language abilities in 1 to 6 years old children (O'Muircheartaigh et al., 2013). In preterm infants, microstructural properties of the left superior temporal gyrus at term age has been shown to correlate with language abilities at two years of age (Aeby et al., 2013). Earlier in development, the decreased right-lateralized gyrification in temporal areas in preterm born infants negatively correlates with their reading abilities at 8 years of age (Kesler et al., 2006). Finally, developmental language disorders like dyslexia can coincide with reduced asymmetry of the *planum temporale* (Galaburda et al., 1985; Humphreys et al., 1990). Overall, these reports suggest that early development of lateralization foreshadows the later language development. They may equally signal that the properties of the left hemisphere are commonly best suited to perform linguistic computations and disturbances of these lateralized networks early on has a cost that may not be compensated by the right hemisphere. Reduced lateralization might yield a more general trouble in brain development that expresses both weaker linguistic abilities and weaker lateralization index.

In the case of face processing lateralization some studies have examined its relation to neurodevelopmental outcomes such as in Autism spectrum disorder (ASD). Comparison between at-risk and typical infants at 6-to 11 months of age, has shown that the left visual field superiority for face perception diminishes in at-risk compared to control infants, implying that the right-hemisphere neural bases specialized for faces might be altered between the two groups (Dundas, Gastgeb, & Strauss, 2012). Similar comparative studies have signaled that when looking at faces, a right-lateralized pattern of anterior-posterior gamma-band EEG coherence was observed in typical infants at one year of age that was reversed, i.e. left-lateralized, in at-risk infants who were later diagnosed with ASD (Keehn, Vogel-Farley, Tager-Flusberg, & Nelson, 2015). Although these studies do not show a causal link between early lateralization and development of cognitive abilities, they suggest that assessing the neural bases of lateralization may shed light on our understanding of the neurodevelopmental outcomes.

To conclude, our studies highlighted: 1. A first step toward establishing a link between functional and structural aspects of development *in vivo*, demonstrating the feasibility of performing such studies using non-invasive neuroimaging techniques. 2. A number of functional and structural asymmetries in the visual and auditory network during early infancy, offering better characterization of the ontogeny of lateralization for face and speech processing abilities.

Appendix

EEG and diffusion MRI applied to infants

Appendix: Neuroimaging of the developing infant brain

Behavioral studies of development provide valuable insights on the cognitive abilities of infants but remain indirect and limited to the behavioral output of such a young population. Direct measures of neural substrates from post-mortem assessment also remain limited as no link to functional acquisitions of infants can be made. The studies conducted in this thesis took advantage of the non-invasive neuroimaging techniques to access the functional and structural architecture of the developing infant brain *in vivo*. However, applying these techniques for developmental studies in infant is challenging due to their limited tolerance, cooperativeness, imposing short and adapted experimental procedures. This appendix presents a brief overview on the informativeness of the techniques we used, and illustrates some of the challenges and limitations that one faces when applying these techniques to infant population. Throughout the text, I will also point to the methodological limitations that our studies had.

EEG

Scalp recordings of brain activity have mainly their roots in postsynaptic potentials of pyramidal neurons of cortex. Every time a postsynaptic potential is generated for one single neuron, a small electrical dipole, i.e. oriented flow of electrical current, is created. When several dipoles have similar orientations, an electrical field is generated from their summation that diffuses through the meninges, skull, and scalp and creates a voltage that can be picked up with EEG electrodes. Due to the resistance of different layers, the electrical field is largely attenuated and deformed before reaching the surface of skin and the surface recordings end up having a relatively poor spatial resolution. Yet, the transmission of the electrical field happens very rapidly and allows measuring neural events at a scale of a few milliseconds, providing EEG with a high temporal resolution.

The brain is constantly active (in the presence or absence of external stimuli) and post-synaptic potentials are changing over time. On the top of this background activity, some activity can be raised in response to an external stimulus. In an experimental paradigm, when a stimulus (event) is delivered over several trials, the brain activity elicited in response to that stimulus is time-locked to its onset. This response (Event Related Potentials-ERP) can be recovered through averaging the activity over several trials and be compared between two different experimental conditions. This allows quantification of task-related modulations in the brain activity. ERPs generally represent slow changes of activity, in particular in infants whose responses are slower than adults. When averaging over trials, only the in-phase responses are amplified and the out-of-phase activity weakens to very low amplitudes. Inspection of phase-coherence

across trials, merged to the conclusion that the in-phase responses that represent infant ERPs are mainly below 20 Hz (figure 6.1), validating our choice of filtering ([0.5 20 Hz]) in the infant data.

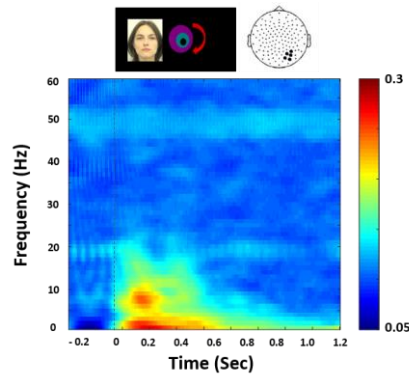


Figure 6.1: Inter-trial phase coherence following a face stimulus. Phase coherence was computed across the trials over different frequencies and time points. Phase-locking values are color-coded. Phase coherence of neural activity is stronger for frequencies below 20 Hz, indicating the frequency range that help in building ERP responses.

Neural correlates of development assessed with event-related potentials

In this thesis, we used ERPs and studied the variations in the time course of the evoked responses, in terms of amplitude and latency, over maturation and across different experimental conditions. We benefited from the time domain information of EEG to study the neural responses that can attest phenomena in a scale that is beyond the power of behavioral methods. For example, the early visual responses (P1) were evaluated at a latency much shorter than what behavioral information (head turn or saccadic eye movements) can be assessed for a response to the perception of a visual stimulus. Being able to record responses appearing faster than the behavioral output of infants, more trials can be achieved in an experimental procedure with EEG compared to a behavioral procedure. In chapters 2 and 3, this temporal resolution allowed us to evaluate the changes in the latency of visual and auditory responses across development between 1 and 6 months of age. By measuring the activity modulations over ERP time course, we could also approximate the timing of neural responses allowing discrimination of two visual stimuli.

Challenges of developmental EEG

Parallel to these advantages, of course EEG has limitations as well. Many of these them are inherent to the EEG technique per se, but more specific problems also emerge when infants are studied. The first limitation is related to the low **spatial resolution** of EEG. Since the electrical field diffuses away from its sources, the response that is picked up at each electrode can contain information from several sources in the brain. All our ERP responses, with the exception of visual P1, were widely distributed over the scalp and

lacked spatial specificity. The P2 auditory evoked responses were distributed over several fronto-temporal electrodes and thus raised questions about the underlying sources that contributed to this response. This was particularly important for our attempt to relate the speed of this response to the structural maturation of the underlying neural substrates. Characterizing the sources of P2 response would inform us about the white matter pathways and cortical regions, whose maturation need to be considered when evaluating the structure-function relationships.

Source reconstruction of surface EEG recordings, could provide a better localization of brain responses. However, the current state-of-art approaches are based on models of adult head and brain that have different properties than that of infants. For example, since the skull is much thinner in infants than adults, the attenuation due to skull resistance should be lower, or the skin or cerebrospinal fluid properties cannot be taken as similar between the two groups. Also, the infant brain tissue does not have the same properties as the adult brain, e.g. myelination and water contents are very different. Therefore, in the early developmental period when the brain and head tissues are changing very rapidly from one month to the next, a realistic source reconstruction would require age-adapted MRI templates, while considering the properties of scalp, skull, fontanelles, cerebrospinal fluid, gray and white matter in infants (Azizollahi et al., 2016). Moreover, studying the source-space activity in pathological situations like corpus callosum agenesis, may need **adapted models** that are currently missing.

Another issue we faced following the low spatial resolution of EEG, was that detection of some of the ERP components were difficult when inspecting the times-series obtained from the average activity over a relatively large cluster of electrodes. For example, for the study of auditory evoked responses we could not reliably measure the earliest cortical response (P1) in each infant. P1 responses might not be well represented in our clusters of analysis where the activity from several sources can superpose and alleviate small-amplitude responses like P1. This problem is intensified when the responses are less developed and are also variable with age. We also attempted to recover more local responses using current source density analyses, to be more sensitive to sources but this approach was not helpful.

EEG provides us with a **high dimensional data**, including several electrodes and timepoints (and possibly frequencies when studying time-frequency measures). The effect of the experimental paradigms thus should be exploited in this rich dataset, basically over all channels and time points, raising a multiple comparison issue as false-positives are likely to be investigated as well. One can correct the problem of multiple comparisons, using approaches such as Bonferroni or False Discovery Rate (FDR). However, these methods can be sometimes conservative to allow some of the true experimental effects survive the

multiple comparison corrections. In infant data, the statistical significance of effects is generally lower and thus effects are less likely to survive this correction. This lower statistical significance might be related to the several sources of variability: The number of trials that can be achieved in infants are generally lower and also variable across subjects and within a subject for different conditions. The responses could be different across infants due to different levels of maturity. Also, some variability can come from the vigilance states of infants that changes along the experiments and between infants as well. Localizations of the responses could also vary across infants due to different head shapes and also changes in placement of EEG net. All these issues can induce some variability in the EEG responses that may reduce the experimental effects and thus their **statistical power**. An alternative less conservative approach, is to use non-parametric statistics (Maris & Oostenveld, 2007) that allow extraction of electrode-timepoint(-frequency) clusters from the data, representative of experimental effects, and use surrogate data with shuffled labels relative to the original data, for baseline comparison. We used this approach in chapter 4, when comparing response topographies between typical infants' and infants with corpus callosum agenesis. Another solution to the multiple comparison issue is to study the effects of interest over predefined clusters of channels and/or over predefined time-windows that were previously investigated in the existing literature. However, this approach is also limited. First, for effects that have not been studied in the literature, sometimes no or very little priors on the choice of electrode/time windows exist. Next, it is possible that certain effects fall outside the predefined clusters/time windows and therefore they are missed. Finally, the common choice of clusters across all infants can attenuate responses that are raised at slightly different locations, either because of actual different localizations across infants or due to the different placement of EEG nets for each infant. Some of the approaches that overcome the issue on the choice of electrodes are using Global Field Power, or Spatial Filters (Schurger et al., 2013) to reduce the data dimensionality by merging the all electrodes data into one single time series, representative of the dynamics of the whole-brain activity with time.

Another limitation we faced in our experimental procedures was lack of quantitative approaches to assess the **looking behavior of infants** when using lateralized paradigms such as that of chapter 2. Since we aimed at focusing infants' attention to the center of screen, we used a number of tricks in the experiment itself and also added a number checks *a posteriori* to make sure that infants gaze was most of the times focused to the center. We recorded videos of infants during the experiment and visually inspected them to keep periods of relative attentiveness in our analyses and reject those infants with several saccadic eye movements to the sides of the screen. However, this approach is not very efficient, as assessment of infants gaze through cameras that are placed relatively far from infants eyes might not

perfectly show the gaze. One approach to try in the future is coupling EEG and eye tracking recordings. This might be more efficient for a precise assessment of looking behavior of the baby, and can further be a step to relate the electrophysiological responses to behavioral responses. However, such methods add some difficulties and limitations to the experimental procedure: eye tracking may need multiple calibrations during the experiments when infants look away and thus can interrupt the experiment several times.

Towards exploring EEG dimensionality

The information buried within the EEG data can be assessed through a wealth of different approaches, each unraveling one dimension of the signal contents. Apart from ERPs, brain activity can be assessed through its frequency contents. Using frequency decomposition methods (e.g. Fourier transform), the raw EEG signal can be considered as a mixture of several overlying signals with different frequencies and it can thus be decomposed into oscillatory patterns of different frequencies. Signal's power can be consequently measured within a frequency band, and its variations can reflect changes in the underlying neural substrates following different cognitive states. The frequency domain information of EEG can allow designing innovative cognitive paradigms that cannot be achieved in behavioral studies. Through entraining brain activity to the frequency of the presentation of a flickering stimulus, one can choose in advance the type of information that is expected to arise, i.e. oscillatory patterns at the frequency of the stimulus. One example of these paradigms was described in this thesis for the study of infant face perception (de Heering & Rossion., 2015). These paradigms can be suited for infant studies, as they are based on fast periodic presentation of images, making the experiment rather short. However, the flickering images might be tiring for infant's eyes and also limitations might exist for the range of frequencies that can be shown to infants. Combining the time- and frequency-domain information, can further allow exploiting the frequency contents of the brain activity over the time and at higher frequencies than ERPs. Besides, connectivity measures can also be used to investigate the coupling between the brain activity recorded over different (distant) areas. Measures of amplitude, phase coupling or amplitude-phase coupling can be used in this regard. The connectivity measures might be particularly interesting for the type of paradigms we used, targeting one brain hemisphere on a specific region and evaluating the propagation of activity to the other hemisphere. They might be informative for the strength and direction of interhemispheric connectivity in the visual and auditory systems and to eventually tackle the question of asymmetric transfer in the auditory system.

Diffusion MRI

The principle of diffusion MRI is to monitor the natural displacement (diffusion) of water molecules inside the brain tissue. By applying the so called “diffusion gradient” over several directions during the MRI acquisition and with a given “b factor”, the diffusion can be measured along different direction, over a finite time interval and within each image voxel. Diffusion is informative on tissue’s microstructure, as its magnitude and direction depend on the obstacles in the environment (e.g. cell membranes) and other properties like the viscosity of the tissue that can restrict or slow down the molecules diffusion (Le Bihan et al., 2001).

Diffusion models

Diffusion Tensor modeling assumes one main direction per voxel for such diffusion, represented by an ellipsoid with measurable eigen vectors and eigen values. Diffusion Tensor Imaging (DTI) provides whole-brain maps of parameters that are representative of tissue microstructure: fractional anisotropy FA, mean diffusivity $\langle D \rangle$ (1/3 of the tensor’s trace) as well as longitudinal $\lambda_{||}$ (parallel to the main axis) and transverse λ_{\perp} (in the perpendicular direction) diffusivities (Beaulieu, 2002). While these parameters can be measured both in the gray and white matter tissue, in this thesis we measured them to study the developing white matter so far.

Considering the size of voxels (a few millimeters) in the current imaging practices, more than one fiber direction probably exists within each voxel, and fibers with different orientations can cross in several areas. Therefore, the tensor model could fail to highlight the crossing fibers. To overcome the issue of crossing fibers, more advanced diffusion models have been proposed that take into account the existence of several crossing fibers within a voxel. Probabilistic diffusion modeling is one among many others attempts to estimate fibers directions inside each voxel more realistically, by considering a distribution of orientations rather than one single orientation within a voxel.

Tractography

In white matter, where axons are organized in bundles of roughly similar orientation, the diffusion becomes more *anisotropic*, channeled along the axons direction (Le Bihan et al., 2001). The 3D trajectory of the different white matter pathways can be reconstructed using tractography techniques. Deterministic tractography reconstructs these trajectories by following the main diffusion direction when moving from one voxel to the next (Le Bihan and Behrens, 2009). Probabilistic tractography is based on estimating the

probability of connections between two regions, given the distributional probabilities across voxels. This allows the reconstruction of pathways outside the main tensor orientation (Behrens et al., 2003). In our studies, we used an adapted probabilistic tractography approach, based on Bayesian estimation of the number of existing fiber directions within a voxel (Behrens et al., 2007). This technique ensures that the number of directions in within a voxel does not exceed one when the data does not support the presence of more than one direction. To do so, a prior distribution, e.g. Gaussian, is considered for each diffusion parameter, with a zero mean but to-be-estimated variance. The variance term is computed from the data, and when too small, it forces the parameter to zero. We applied this method, implemented in FSL software, by considering a maximum of two main directions of crossing fibers within a voxel, and succeeded in reconstructing acoustic radiations that are commonly missed with the deterministic tractography approaches.

White matter maturation

DTI parameters change in the white matter throughout the development as fibers become more compact, coherent and myelinated. While FA increases in most regions, diffusivity parameters decrease with increasing age of infants (Neil et al., 1998; Huppi et al., 1998; for a review see Dubois et al., 2014). Since several processes occur over each developmental stage, it is challenging to study the sensitivity of these DTI parameters to different developmental processes (e.g. growth, pruning, and myelination). Increasing anisotropy is suggested to depict the integrity and coherency of fibers, that does not solely depend on myelination. Decrease in transverse diffusivity is suggested to reflect myelin propagation in the developing infant brain (Dubois et al., 2008; Song et al., 2003; Song et al., 2005), and is shown to change more strongly than the longitudinal diffusivity with the maturation of white matter (Mukherjee et al., 2002). Our observations agreed with these studies, showing the most significant developmental changes in the pathways of the visual and auditory network for transverse diffusivity (Figure 6.2).

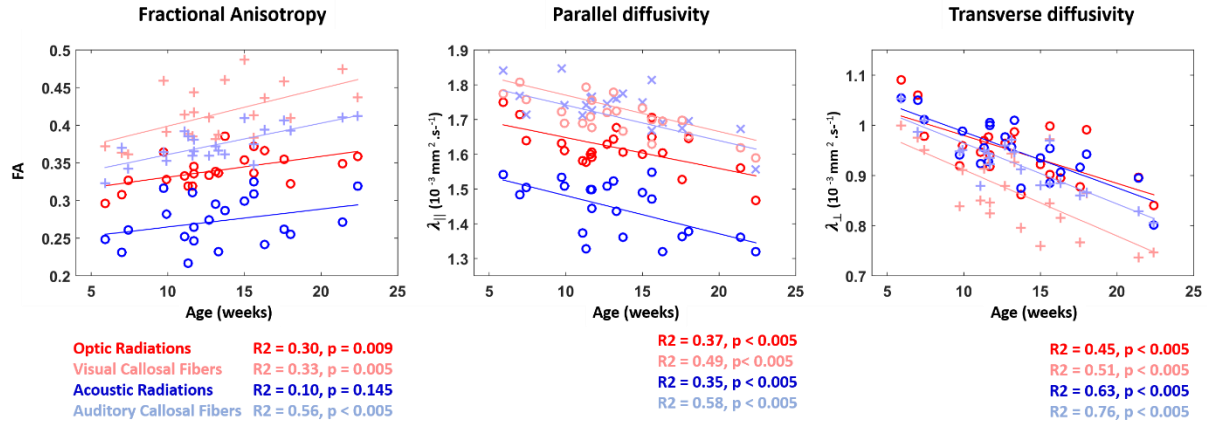


Figure 6.2: Developmental changes in DTI parameters in the reconstructed tracts of the visual and auditory network.

Challenges in diffusion MRI studies of developing brain:

Acquiring good MRI data in babies is a challenging task both at the time of acquisition and in post-processing stages, in order to deal with the problems of lower data quality rooted in shorter acquisitions, motion artifacts and also changes of signal throughout development. The data studied in this thesis were acquired during a short time period (~ 6 mins) when infants were naturally sleeping. The timing constraints allowed acquiring data over relatively low number of diffusion directions (30) and with low b-value (700), limiting the spatial resolution of the acquired data. As a result, some small fiber bundles may not be detectable. The number of diffusion directions and the b-value could both be improved through methods such as High Angular Resolution Diffusion Imaging (HARDI) in order to obtain higher data resolution (Tuch et al., 2002). However, increasing these values comes at the cost of increasing acquisition time. One solution to this issue could be more elaborated acquisition sequences, with multi radiofrequency bands and multi-slice Echo Planar Imaging techniques (Feinberg et al. 2010).

Some other limitations of diffusion MRI in the developmental period are related to the post-processing of the data. Some fibers may not be properly reconstructed due to their **small size** respective to the spatial resolution of images. Moreover, some fibers might not be detected due to their **relative immaturity compared to the adjacent pathways**. This issue is even more intensified when crossing fibers have different maturational stages, thus resulting in improper reconstruction of true trajectories (Dubois et al., 2016). For example, the anterior portion of the arcuate fasciculus was reported to be missing after birth in a number of DTI studies (Perani et al. 2011; Brauer et al. 2013), while its presence is known from histological examinations (Vasung et al., 2010). Abnormal connectivity patterns could also be detected at the locations where fibers of different maturational stages are crossing. For our tractography study, the

short length of the reconstructed acoustic radiations might provide us with less reliable measures compared to longer pathways and thus their maturation assessments should be done with caution. Also, with the current resolution of our data, we might not be able to precisely disentangle the adjacent fibers and some of our measures (eg. Visual and auditory callosal fibers) might be affected by partial volume effects.

Although **DTI parameters** seem to have relative sensitivity to developmental changes (e.g. transverse diffusivity is more sensitive to myelin contents), they are still **approximative** and **capture more than one developmental process**. In addition to diffusion MRI, relaxometry MRI methods could also provide information on tissue microstructure that may aid in better identification of different developmental processes (especially myelination) during white matter development. Some of these methods are based on modeling different pools of water (intra-myelin sheath, intra-axonal, intra- and extra-cellular and free water) in the cerebral tissue that differentially affect the T1 or T2 relaxation parameters. So far, in the interest of developmental studies, these works have shown estimates of fraction of water related to myelin sheath in the developing brain, compatible with the knowledge from postmortem studies (Deoni et al., 2012; Kulikova et al., 2016; Dubois et al., 2016).

Yet, one of the developmental processes that has remained **fairly unstudied** with the current state-of-the-arts MRI measures, is the **pruning of fibers**. This process is especially intense in the first postnatal months of infancy: For interhemispheric callosal fibers a drastic pruning of over 70% of the fibers occurs during the first 4 postnatal months in rhesus monkeys (LaMantia and Rakic, 1990). In human infants, the number of callosal axons is known to be maximal around the term age and their elimination is supposedly extended over the first postnatal year (Kostovic & Jovanov-Milosevic, 2006). Thus, quantifying this process might be especially important for studies of brain development and in particular those of interhemispheric connectivity maturation.

To summarize, EEG and diffusion MRI provide us with a wealth of information about the functional and structural neural correlates of the developing brain. However, adapted experimental paradigms, acquisition and post-processing methods are required for studying infant population.

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