Early Language Development in Preterm Born Infants

VANDORMAEL, Charlotte

Abstract

Background: Preterm birth occurs in up to 12% of births, and therefore affects a large number of newborns worldwide. It has been described in the literature, that early exposure to the extra-uterine environment due to premature birth can have various effects for an infant’s neurodevelopment, and thus can affect aspects of development such as cognition and language. The aim of this Master’s thesis is to assess whether the brain of preterm newborns, who were exposed to language earlier in their extra-uterine environment, show different cortical speech processing. In order to achieve this, we investigated functional brain activation in preterm- and fullterm newborns while listening to forward and backward (in time reversed) speech using fMRI. We hypothesized that early language exposure in the preterm infant would allow for different cortical processing of forward to backward speech in preterm infants compared to fullterm infants...

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Early Language Development in Preterm Born Infants

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Thèse présentée à la faculté de psychologie et des sciences de l’éducation de l’Université de Genève pour obtenir le grade de Master en Neurosciences

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Dr. M. Filippa

Juin 2018
**Early language development in preterm born infants**

**Background:** Preterm birth occurs in up to 12% of births, and therefore affects a large number of newborns worldwide. It has been described in the literature, that early exposure to the extra-uterine environment due to premature birth can have various effects for an infant’s neurodevelopment, and thus can affect aspects of development such as cognition and language. The aim of this Master’s thesis is to assess whether the brain of preterm newborns, who were exposed to language earlier in their extra-uterine environment, show different cortical speech processing. In order to achieve this, we investigated functional brain activation in preterm- and fullterm newborns while listening to forward and backward (in time reversed) speech using fMRI. We hypothesized that early language exposure in the preterm infant would allow for different cortical processing of forward to backward speech in preterm infants compared to fullterm infants.

**Method:** 39 subjects: 19 fullterm infants, tested between their 2nd and 6th day after birth and 20 preterm infants tested at their term equivalent (mean GA of 40.4 ± 0.7 weeks) age using a 3T MRI scanner while listening to forward/backward speech stimuli by their mother and a stranger mother voice. Results of 36 subjects (16 fullterm and 20 preterm) are presented.

**Results:** Our results showed cortical responsiveness to sound stimuli in both groups. Preterm and fullterm newborns showed bilateral activations of the STG in the forward>silence and backward>silence contrasts. Furthermore, differential neural activity for forward>backward speech resulted in activation of the left STG and AG but only in single preterm and fullterm infants. Subsequently, when considering the preterm and fullterm group separately, more pronounced neural activation for backward>forward speech was found in both groups. For the fullterm group neural activation of the bilateral OFC was seen for the general backward>forward contrast. No significant activations were found in the backward>forward contrast in the mother’s voice only. The preterm group showed differential neural activations in the bilateral PCun, HC, OFC and the left PCC in response to general backward>forward speech. Moreover, while listening to their mother’s speech backward>forward, differential neural activations were found in the right IFG, bilateral SMG, anterior STS, left HC and a small part of the amygdala. No significant differential neural activations were found in the contrast forward>backward speech in either voice or group. When performing a between group comparison analysis, significant neural activations in the bilateral PCC, left MTG and anterior STG for the preterm group were found in response to backward>forward speech. Finally, activation in
the left PCC showed a significant positive correlation with weeks post birth, whereas the right IFG was negatively correlated with weeks post birth in the PT group when listening to backward>forward speech in their mother’s voice.

**Conclusion:** This neuroimaging study reveals that both preterm and fullterm newborns show novelty detection when listening to backward speech. Premature infants however show additional activations in emotional and attentional processing areas when the contrasts are presented by their mother’s voice. Thus, we can conclude that auditory stimulations experienced in the extra-uterine environment may have a positive effect on the maturation of functional networks involved in speech processing.
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TABLE OF CONTENTS

INTRODUCTION .................................................................................................................. 1

1. BACKGROUND .............................................................................................................. 2
   1.1 Perception .................................................................................................................. 2
       1.1.1 Development of the auditory system ................................................................. 2
       1.1.2 Neonatal auditory perception ............................................................................. 2
   1.2 Language processing ................................................................................................. 4
       1.2.1 Neural substrates ............................................................................................... 4
       1.2.2 Neural networks .................................................................................................. 6
   1.3 Preterm birth ............................................................................................................. 7
       1.3.1 Definition ........................................................................................................... 7
       1.3.2 Early extra-uterine exposure ............................................................................. 7
   1.4 Neuroimaging Technique ......................................................................................... 12
       1.4.1 Functional Magnetic Resonance Imaging ........................................................ 12
       1.4.2 Imaging in the newborn .................................................................................... 13

2. HYPOTHESES ............................................................................................................. 15

3. METHODS .................................................................................................................... 16
   3.1 Subjects ................................................................................................................... 16
   3.2 Study Design .......................................................................................................... 16
   3.3 Experiment .............................................................................................................. 17
       3.3.1 Stimuli ................................................................................................................ 17
       3.3.2 Procedure ......................................................................................................... 17
   3.4 Data analysis .......................................................................................................... 18
       3.4.1 Preprocessing ................................................................................................... 18
       3.4.2 fMRI analysis .................................................................................................. 18

4. RESULTS ...................................................................................................................... 22
   4.1 Listening to sound .................................................................................................... 22
   4.2 Listening to forward and backward speech stimuli ................................................. 23
       4.2.1 First Level Analysis ......................................................................................... 24
       4.2.2 Second Level Analysis ..................................................................................... 25
   4.3 Exposure duration analysis ..................................................................................... 30

5. DISCUSSION ............................................................................................................... 32
   5.1 Listening to sound ................................................................................................... 33
   5.2 Listening to forward and backward speech stimuli ................................................... 33
   5.3 Effect of exposure duration ..................................................................................... 36
5.4 Limitation of the study .................................................................................................................. 37
CONCLUSION....................................................................................................................................... 38
REFERENCES
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AG</td>
<td>angular gyrus</td>
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<td>BOLD</td>
<td>blood oxygenation level dependent</td>
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<td>CBF</td>
<td>cerebral blood flow</td>
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<td>FT</td>
<td>fullterm</td>
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<td>GA</td>
<td>gestational age</td>
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<td>hippocampus</td>
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<td>HRF</td>
<td>hemodynamic response function</td>
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<td>IFG</td>
<td>inferior frontal gyrus</td>
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<td>M1</td>
<td>primary motor cortex</td>
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<td>mGA</td>
<td>mean gestational age</td>
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<td>MTG</td>
<td>middle temporal gyrus</td>
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<td>NICU</td>
<td>neonatal intensive care unit</td>
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<td>OFC</td>
<td>orbitofrontal gyrus</td>
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<td>PCC</td>
<td>posterior cingulate cortex</td>
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<td>PCun</td>
<td>precuneus</td>
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<td>PoG</td>
<td>postcentral gyrus</td>
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<td>PT</td>
<td>preterm</td>
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<td>PTe</td>
<td>planum temporale</td>
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<td>SD</td>
<td>standard deviation</td>
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<td>SMG</td>
<td>supramarginal gyrus</td>
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<td>STG</td>
<td>superior temporal gyrus</td>
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<td>STS</td>
<td>superior temporal sulcus</td>
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<td>TEA</td>
<td>term equivalent age</td>
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<td>WHO</td>
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INTRODUCTION

Accumulating evidence has shown that preterm birth, a birth before 37 weeks of gestation, impacts neurodevelopmental outcomes (Bos & Roze, 2011; Pierrat et al., 2017). In the literature, premature birth has been linked with complications such as motor delays, global cognitive impairment, visual perception problems, executive functioning deficits and atypical language development (Carter & Msall, 2017; Delobel-Ayoub et al., 2009; Johnson & Marlow, 2017; Leung, Thompson, Black, Dai, & Alsweiler, 2018).

During pregnancy, the third trimester marks a critical period of fetal brain maturation in which brain development becomes sensitive to endogenous activity and environmental stimuli. Dramatic changes in the environment of the fetus, such as prematurity may have an impact on this maturation and therefore one’s neurodevelopment. It has been described that early exposure to the extra-uterine environment can either be detrimental or advantageous for neurodevelopment in the preterm newborn. However, the emphasis mostly lies on the fact that preterm birth is associated with delay in neurodevelopment and later deficits in cognition and behavior and leads to an atypical language development in this population.

In this Master’s thesis, we investigate early speech and language perception in newborns. Fullterm (FT) infants were tested during their first days of life and the preterm (PT) group was tested at term equivalent age (TEA) using functional magnetic resonance imaging (fMRI) in a 3T scanner. The aim of this study was to assess brain activity underlying language perception in newborns and to investigate whether preterm newborns, who were exposed to language in their environment earlier, process speech and language stimuli differently from FT newborns. We hypothesized that, following premature birth and early extra-uterine exposure, PT infants at TEA may have an enhanced language processing and differentiate forward from backward speech in comparison to their FT peers. In addition, we wanted to evaluate the effect of duration exposure on discrimination abilities in the PT group.
1. BACKGROUND

1.1 Perception

1.1.1 Development of the auditory system

The ability to perceive sounds and discriminate between acoustic signals is fundamental for the development of receptive and expressive language skills. Already very early in gestation, the fetus’s auditory system develops. Between the 23\textsuperscript{rd} and 25\textsuperscript{th} week of gestational age (GA), major structures of the auditory system (e.g. cochlea) are already developed. As of 26 weeks GA, hair cells in the cochlea become fine-tuned for specific frequency bands, converting acoustic signals into electrical stimuli and forwarding them through the auditory nerve to the auditory cortex in the brain (McMahon, Wintermark, & Lahav, 2012). Between 28-30 weeks of gestation, these neural connections to the temporal lobe are functional (Graven & Browne, 2008). Quickly after birth (1-4 months postnatal age), the arcuate fasciculus, a bundle of nerve fibers connecting Wernicke’s area (upper/posterior part of the temporal lobe) with the center of Broca (lower/posterior part of the frontal lobe) two areas important for understanding and producing language, is already mature and left lateralized. This early asymmetry of language related networks shows that functional lateralization is related to early structural maturation taking place in the immature brain (Dubois et al., 2009). This maturation may allow for the development of perceptual processes required to correctly process all environmental sounds.

1.1.2 Neonatal auditory perception

During intra-uterine life, the fetus is mainly exposed to internal sounds i.e. sounds from the mother, which have an important role in shaping the fetal brain’s auditory system (Webb, Heller, Benson, & Lahav, 2015). These sounds can either be rhythmic in nature (heartbeat, breathing, speech patterns etc.), or partly non-rhythmic (swallowing, isolated speech sounds, etc.). Sounds from the outside may also penetrate the womb but are largely attenuated by maternal tissue and the amniotic fluid. Inside the womb, the fetus is able to perceive sounds by means of bone conduction, meaning that sounds are conducted to the inner ear through the skull. The observed frequencies are distributed tonotopically as on the basilar membrane in the cochlea, making the uterus the ideal place for auditory maturation as it acts as a low-pass filter, protecting newly developed hair cells from potentially harmful high pitch tones. As of
approximately 27 weeks of GA, the fetus is able to perceive sounds. Firstly, those in the low frequency range can be perceived and later (around 33-35 weeks GA) sounds in the high-frequency range (+1kHz). Allowing the basilar membrane to develop and enabling the fetus to perceive human speech (e.g. intonation, pitch, intensity) and establish later language processing (Hepper & Shahidullah, 1994; Shahidullah & Hepper, 1994).

Hence, the fetus is able to process auditory stimuli such as tones and sounds very early on and becomes attuned to features of the surrounding auditory environment. For example, fetuses habituate to familiar sounds (Granier-Deferre, Bassereau, Ribeiro, Jacquet, & DeCasper, 2011). However, in the prenatal and primarily in the extra-uterine environment, human voices are the most important auditory stimuli and additionally play an important role in social interactions. They not only carry speech, but also convey important affective and identity information (Belin, Fecteau, & Bédard, 2004). Voice sensitivity has been described during the fetal period using behavioral observations. Fetuses in the third trimester, exposed to the mother voice, become familiar with maternal speech sounds and the mother’s voice and showed orientation responses (DeCasper, Lecanuet, Busnel, Granier-Deferre, & Maugeais, 1994; Kisilevsky et al., 2003; Voegtline, Costigan, Pater, & DiPietro, 2013). Repetitive prosody and rhythm of the mother’s voice helps shape early auditory learning and recognition of the native language (Moon, Lagercrantz, & Kuhl, 2013). Furthermore, in a study performed by Partanen et al., (2013), fetuses were systematically exposed to selected speech stimuli (e.g. syllables: ‘tatata’) during the prenatal period. After birth, they were exposed to the same syllables but with a change in vowel or pitch. It was found that, fetuses who were exposed in the prenatal period, showed a greater neural activity and discrimination ability than the newborns who had not been exposed to these speech materials. Hence, it can be concluded that speech sounds experienced during the fetal period can form neural memory traces and induce neural processing.
1.2 Language processing

1.2.1 Neural substrates

Neural substrates in adults

The system involved in perceiving auditory information comprises of interconnected neural substrates that allows humans to effortlessly distinguish between sounds (noise, voices etc.) in the auditory environment. It was found that humans activate voice-selective regions in response to hearing human speech in comparison to other sounds. The more activated regions were the bilateral superior temporal gyrus (STG) and superior temporal sulcus (STS) which seems to be even more activated in the right hemisphere (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000). Furthermore, the STS was found to be more involved in processing paralinguistic aspects (e.g. tone of voice) of voice perception and seem to be more activated in response to human voices when compared to other non-vocal stimuli (Belin, Zatorre, & Ahad, 2002).

Since voices trigger specialized neural substrates in the brain, it enables them to process spoken language. Studies performed on aphasia patients revealed early on that there is a functional asymmetry in the left hemisphere for language processing. Comprehension of spoken language is placed in the posterior STG (Wernicke’s area) and productive language is based in the inferior frontal regions of the brain, also known as Broca’s area (Damasio & Geschwind, 1984). Later, neuroimaging studies on language processing have suggested a more distributed cortical activation while comparing non-speech stimuli with speech stimuli. Firstly, stronger activation was found in multiple left hemisphere areas, including the STS, middle temporal gyrus (MTG), angular gyrus (AG) and lateral frontal lobe while listening to speech stimuli in comparison to non-speech stimuli (e.g. noise burst) (Binder, Frost, Hammeke, Rao, & Cox, 1996). However, non-speech stimuli such as short tone bursts are nothing alike speech and thus can be argued to be imperfect control stimuli. Thus, stimuli more closely matched to real speech in terms of spectral and temporal properties are preferred. For example, backward speech (in time-reversed) matched to normal speech in terms of duration, spectral properties and amplitude (Binder, 2000). The advantage of this type of stimuli is that it has the same acoustic properties as normal speech stimuli but without the linguistic properties. Vocal quality and global acoustic characteristics are preserved but the prosodic structure is broken making it unintelligible. When backward speech was
compared to silence in a positron emission tomography imaging study, similar brain areas (such as the STS and inferior frontal gyrus (IFG)) as with normal speech stimuli are activated. So, although the stimuli are lacking semantic content, they are perceived as speech-like by activating prefrontal regions used in lexicosemantic processing (Wong et al., 2002). However, when speech is compared to a stimuli that is matched in both spectral and temporal properties (e.g. sine-wave analogue) during an event related fMRI study, it was found that speech elicits greater activations in typical receptive language areas; the left posterior STG and bilateral MTG (Vouloumanos, Kiehl, Werker, & Liddle, 2001).

**Neural substrates in newborns**

In newborns, behavioral studies performed during the postnatal period have shown a preference for human voices with a predilection for the mother voice (Lee & Kisilevsky, 2014; Shultz & Vouloumanos, 2010; Vouloumanos & Werker, 2007). In addition, a clear difference was reported in response to familiar versus unfamiliar language offers, showing that even before birth, the brain is being tuned to its language environment and infants prefer their native language (May, Byers-heinlein, Gervain, & Werker, 2011; Moon et al., 1993). Furthermore, after only a few hours of postnatal exposure, neonates respond specifically to speech offerings (Dehaene-Lambertz et al., 2006), and are able to discriminate between different prosodic patterns (Saito et al., 2007). Newborns are able to discriminate between 2 languages by relying on prosodic cues but fail to do so when played backwards. This may depend on the specific properties of speech that disappear when language is played backwards (Ramus, 2000). In backward speech, global characteristics of sound (intensity, duration) and familiarity of the speaker are preserved but the prosodic structure of the sentence is broken.

Brain networks sensitive to phonemes and voices are present at the very onset of cortical organization allowing the brain to already discriminate between small differences in speech syllables. Furthermore, brain activation during discrimination is not limited to primary auditory areas but also involved more inferior frontal regions (Mahmoudzadeh et al., 2013). Using non-invasive neuroimaging studies, speech processing right after birth can be assessed. Pena et al. (2003) reported stronger responses in the left temporal areas for sentences in the mother language than for the same stimuli played backwards (Pena et al., 2003). Moreover, in a study performed by Dehaene-Lambertz (2002), 20 healthy FT newborns (2-3-month-olds) were tested using fMRI while listening to forward and backward speech samples. Results
showed more significant brain activations in the left-lateralized STS, AG and precuneus (Pcun) while listening to forward speech (Dehaene-Lambertz, 2002). Furthermore, Minagawa-Kawai et al. (2011) also described a clear left lateralized cerebral basis for speech processing in 4 month-olds (Minagawa-Kawai et al., 2011). Hence it can be concluded that even early in infancy, there is a neural precursor of functional organization in the brain.

1.2.2 Neural networks

Comprehending spoken language requires the activation of more than just the auditory cortex. Multiple brain areas surrounding the primary auditory cortex are involved in processing speech. In humans, the primary auditory cortex is located in the transverse temporal gyrus, also known as Heschl’s gyrus, in both hemispheres. When processing language, primary acoustic analysis is performed in the auditory cortex from which information is then sent in two directions: (1) in the posterior direction to the planum temporale (PTe) and posterior STG extending to the STS and (2) to the planum polare and the anterior STG/STS (Friederici, 2011). In the posterior direction, the PTe is located within the Sylvian fissure and makes up the posterior superior surface of the STG. A structural difference can be found in both hemispheres, with a larger PTe in the left, language dominating hemisphere. However, it was found that the PTe and posterior STG/STS respond equally to both words and tones/non-speech (Binder et al., 1996; Démonet et al., 1992). Thus, activations in the posterior areas in response to sound are not speech specific. Nonetheless, they have an important function for speech comprehension. Lesions in this area reveal deficits in the perception of (non) speech sounds and can lead to word deafness (Pinard, Chertkow, Black, & Peretz, 2002). Thus, they are more likely to be involved in early language processing. It was even proposed to be a “computational hub” from which information is sent to higher-cortical areas (Griffiths & Warren, 2002). Conversely, in the anterolateral regions, the STG/STS are activated during speech perception of phonemes enabling one to differentiate between speech and non-speech stimuli. In addition, they are more activated when perceiving intelligible sounds (Obleser, Zimmermann, Van Meter, & Rauschecker, 2007).

An additional brain region which can be associated with language processing is the inferior parietal lobule near the edge of the temporal lobe. Consisting of the AG and supramarginal gyrus (SMG), it has an integrative role in comprehension (Seghier, 2013). Greater activations
in this area were found when listening to words versus non words (Binder, 2000; Démonet et al., 1992) or when perceiving forward speech (Dehaene-Lambertz, 2002). The region is connected to the auditory, somatosensory and visual cortices making it a multimodal region responsible for integrating different types of stimuli. Alongside this, the area is connected to both the inferior frontal lobe and Wernicke’s area with a large bundle of fibers, providing a second important language route for language production parallel to the arcuate fasciculus.

1.3 Preterm birth

1.3.1 Definition

Preterm birth can be described as a birth prior to 37 weeks of gestation. As proposed by the World Health Organization (WHO), this can be further sub-divided based on GA (Blencowe et al., 2012):

- Extremely preterm: < 28 weeks GA
- Very preterm: 28 - 32 weeks GA
- Moderate to late preterm: 32 - 37 weeks GA

According to a 2010 estimation by the WHO, about 15 million babies are born PT each year, which is more than one in ten births worldwide. Globally, PT birth is the second most common cause of death in children under the age of 5 (Liu et al., 2016). Unfortunately, in most countries, PT birth rates keep rising. Additional to the high mortality risk, prematurity affects neurodevelopmental functioning and survivors can face a lifetime of disability.

1.3.2 Early extra-uterine exposure

Considering brain development is mostly shaped by early sensory experiences, exposure to language in the infant’s environment is of utmost importance (Webb et al., 2015). Since PT born infants are exposed earlier to the environment outside of the uterus, one can wonder what the impact of this early exposure to the auditory environment has on the developing brain.
When born prematurely, infants spend the first weeks or even months of their life in the Neonatal Intensive Care Unit (NICU). During this critical period for development, they are deprived of the sounds they would otherwise be hearing in utero (e.g. maternal sounds). As discussed earlier, the intra-uterine environment allows the fetus to perceive low-frequency sounds in an attenuated fashion, ensuring the development of the auditory system (Lahav & Skoe, 2014). However, once born PT, this safe haven vanishes and the infant ends up in a (high-frequency) environment which can have profound effects on the auditory brain maturation and subsequent speech and language acquisition (McMahon et al., 2012).

Although PT infants residing in the NICU are deprived of maternal sounds, they are not necessarily deprived of all auditory stimulation. Unlike in utero, the auditory stimulation available to the infant depends on the NICU environment they are residing in. Two different scenarios can be distinguished to cause language deprivation in this environment. Firstly, the NICU environment may be too loud for the infant to reside in. While being placed in an open room, they are exposed to unpredictable multiple high-frequency sounds (electronic/machines) and voices (e.g. parents, nurses, doctors etc.) which may prevent them from being exposed to meaningful and infant-directed language inputs. In addition, it was shown that excessive exposure to loud ambient noises can negatively affect the infant’s physiological stability (e.g. affect the cardiovascular and respiratory systems), which in turn may cause a risk for neurodevelopment (Wachman & Lahav, 2011). Secondly, the environment can be too quiet when the infant is placed in an incubator that does not allow them to perceive language stimuli (Rand & Lahav, 2014).

It was found that early exposure to the maternal voice through bone conduction can support neurobehavioral outcome and auditory development (Picciolini et al., 2014). The study by Caskey, Stephens, Tucker and Vohr (2014) shows that a larger range of language exposure in PT babies can have a positive effect on later language development in the first weeks after birth. They hypothesized that PT born babies residing in the NICU would have higher cognitive and language scores if they were exposed more to adult talk. At 7 and 18 months corrected age, infants scored less than average on the language tests with great inter-individual differences, whereas no differences were found on cognitive scales (BSID-III language and cognitive scales). In addition, a positive correlation was found between the
number of words heard during the first weeks and BSID-III scores (Caskey, Stephens, Tucker, & Vohr, 2014). Similar results were found by Montirosso et al. (2016) when comparing very PT born infants residing in 19 different NICU’s to FT controls. Infants residing in a high-quality developmental care unit (better infant pain management, improved control of external stimuli, more parental involvement) showed better receptive language skills than those residing in low-quality developmental care (Montirosso et al., 2016). Hence, these studies support the view that exposure to adult talk in the NICU is associated with better language, cognitive and communicative development at an older age (Caskey et al., 2014). It can be concluded that early adequate exposure to language and sensory stimulation is of great importance.

**Dysfunctional early caregiver-infant relationship**

For infants residing in the NICU, full time parental presence is not the case. Dysfunctions in early social communication, due to long periods of separation in the NICU, can have negative consequences on an infant’s behavior and emotional- and physiological well-being. An early intervention found to be effective is interaction through maternal speech and singing, showing favorable effects on an infant’s physiological state such as heart rate, oxygen saturation levels and respiration rate (Filippa, Devouche, Arioni, Imberty, & Gratier, 2013). Furthermore, a meta-analysis performed by Filippa et al. (2017) evaluating 15 maternal voice interventions in 512 PT infants, showed that maternal speech has a supporting role in clinical outcomes such as physiological state, behavior and neurological development (Filippa et al., 2017).

Moreover, an important aspect affecting language development in PT born children, is the quality of the infant-caregiver relationship. Multiple studies show that when a child and their caregiver participate in quality interactions, language development will improve. PT birth may represent a challenge for early bonding and interactions between a baby and his or her family. The increased psychological stress experienced by mothers of preterm infants has been linked to differences in the mother-infant interactions in this population (Forcada-Guex, 2011; Muller-Nix et al., 2004). On the Care Index, a measurement index that assesses mother-infant interactions, mothers of PT infants who are affected by maternal depression and anxiety have been found to be more controlling or unresponsive when interacting with their child, compared to mothers of FT infants (Forcada-Guex, 2011; Muller-Nix et al., 2004). On the other hand, it was found that maternal anxiety may lead to more intrusive behavior, in which
mothers provide less sensitive and a more controlling style of parenting. Zelkowitz et al. studied whether anxiety affects maternal interaction and leads to less optimal communication into the pre-school years. During their stay in the NICU, mothers were tested using the self-report State-Trait Anxiety Questionnaire, a measure of trait and state anxiety which is commonly used to indicate caregiver distress. Later, in a 24-month follow-up period, free play between the mother and child was observed. Results showed that anxiety during the period in the NICU, leads to less sensitive and responsive interaction between mother and child. In return, children involved their mothers less during play time (Zelkowitz, Papageorgiou, Bardin, & Wang, 2009). In light of the importance parent-infant interaction plays in language development, early intervention targeting these disordered dyads in the preterm population could be beneficial. Meijssen and colleagues investigated the effect of PT birth on the quality of mother-child bonding and the consequences on child development. PT born infants were divided into two groups: a control group (standard care) and an intervention group who participated in a post-discharge intervention program and attended regular visits to a pediatric hospital. It was hypothesized that the intervention group would display more positive interactions with their caregiver, improving development. At 6 months, both groups were tested using an extensive assessment battery consisting of the BSID, physical examination and a still-face procedure. Results showed better scores for the intervention group on the BSID. Moreover, mothers in the intervention group showed more positive and sensitive interaction behavior towards their child (Meijssen et al., 2010).

*Can infants benefit from early exposure?*

Although most abovementioned findings suggest a negative impact of PT birth, some studies suggest that PT infants can also benefit from early auditory exposure. At 29 weeks of GA, PT infants already possess the ability to process subtle changes in phonemes and voices (Mahmoudzadeh et al., 2013). Hence, they are able to encode acoustic properties in order to perceive and process speech offerings in their environment. Furthermore, Nishida et al (2008) demonstrated that the duration of extra-uterine exposure is correlated with enhanced brain responses. A shorter latency of oxyhemoglobin measures, using near-infrared optical tomography, was found in the PT group in response to verbal stimulation (Nishida et al., 2008). Moreover, despite immature auditory pathways, early auditory interventions may have a positive influence on the PT infant’s brain development. For example, PT infants residing in
an environment in which they are exposed more to maternal sounds (mother voice) show larger auditory cortices (Webb et al., 2015). Also, differences in activation for the discrimination of two voices (mother vs. nurse) was found (Saito et al., 2007). In addition, several auditory evoked potential studies showed no differences in central auditory pathway maturation (Jiang, 1995; Jo & Kim, 2015; Porto, Azevedo, & Gil, 2011) or even reported that exposure of PT infants to the extra-uterine environment is associated with advances in development compared to FT’s (Hafner, Pratt, Blazer, & Sujov, 1994). Hence, it can be concluded that PT birth may not always result in negative repercussions.

**Voice perception in preterm born infants**

In the study performed by Adam-Darque and colleagues, prior to this study, brain activity following auditory stimulation with the maternal voice and a female stranger’s voice were assessed in FT infants during their first days of life and PT infants at TEA using both fMRI and high-density EEG. Both groups were tested for responses to specific vocal stimulations (mother’s voice/stranger’s voice vs. silence) and voice discrimination abilities (mother’s voice vs. stranger’s voice). Results showed that, in the FT group, there was a difference in discrimination between both voices. The stranger’s voice elicited increased activations in the anterior STG, bilateral insula, middle cingular cortex and the hippocampus (HC) which may be due to an overall raise in attention, stimulated by this unfamiliar and novel stimulus, which may have led to a global increase in brain activity. The PT infants on the other hand, processed each voice equally. Furthermore, they demonstrated activity in brain areas associated with attentional and emotional processing. This may be explained by the fact that they have encountered multiple voices during their stay in the hospital, decreasing their processing of novelty. Hence, it was concluded that early postnatal exposure to the extra-uterine environment leads to enhanced processing abilities of voices in PT newborns (Adam-Darque et al., n.d.).
1.4 Neuroimaging Technique

1.4.1 Functional Magnetic Resonance Imaging

fMRI is a MRI based technique used to measure vascular perfusion changes occurring in higher activated brain areas (Kwong et al., 1992). These changes occur due to task-induced cognitive state changes, or as a result of a resting state. It is a widely used method in clinical and cognitive studies due to its non-invasive nature, high spatial resolution and widespread availability (Glover, 2011; Seghier, Lazeyras, & Hüppi, 2006).

fMRI is based on the blood oxygenation level-dependent (BOLD) contrast and allows us to study local changes in deoxyhemoglobin concentration in the brain (Uluda, Dubowitz, & Buxton, 2005). The different parameters influencing the BOLD are: (1) cerebral blood flow (CBF), (2) metabolic rate of oxygen consumption and (3) cerebral blood volume. When neurons in the brain become active, they consume more oxygen and nutrition (glucose) provided through the CBF. When the rate of oxygen consumption increases, so will the CBF and cerebral blood volume (Glover, 2011). This process leads to increased oxyhemoglobin levels in the CBF in comparison to deoxyhemoglobin, creating an increased oxyhemoglobin/deoxyhemoglobin ratio. In order to fully understand how this signal can be measured, it is important to know that deoxyhemoglobin is paramagnetic and disturbs the magnetic field, thereby decreasing the signal. Oxyhemoglobin on the other hand, is diamagnetic and does not possess this characteristic. The decrease in deoxyhemoglobin leads to a signal change in the MRI.

The initial goal of using fMRI is to extract information out of the BOLD signal in order to make assumptions about the underlying neuronal activation. In order to do this, an accurate model of the evoked hemodynamic response has to be formed. Following a period of neural activity, a temporal waveform of the observed time-course of the BOLD contrast is formed and referred to as the hemodynamic response function (HRF). A normal BOLD response to a brief physiological stimulus is known as the canonical HRF and can be illustrated in several steps (Glover, 1999). Firstly, at the onset of brain activity, the BOLD signal is at baseline since the brain is in a resting state. Secondly, only seconds after the onset of the task (± 5-8s), a positive spike indicating a brief intense period of neuron stimulation can be distinguished. This process requires an increased blood and nutrient flow. Thirdly, after the initial peak, the
BOLD signal decreases due to the reduced oxyhemoglobin/deoxyhemoglobin ratio and the signal becomes negative since deoxyhemoglobin is accumulated in the veins. This negative period is called the “undershoot”. Finally, the BOLD response reaches its baseline again. The whole canonical HRF takes approximatively 20 seconds. When analyzing the canonical HRF, measures of psychological interest such as duration and amplitude can be extracted, and used to deduce information regarding the intensity, onset latency, and duration of the underlying brain metabolic activity (Lindquist, Loh, Atlas, & Wager, 2009).

1.4.2 Imaging in the newborn

fMRI is a useful technique for early prognostic evaluations of the infant during the neonatal period. Imaging the infant’s brain can give new insights into the maturational processes that take place during the postnatal period. A clear advantage of fMRI is its good spatial resolution, allowing us to study brain activity in specific locations at the millimeter level. As described earlier, the BOLD contrast measured in fMRI is non-invasive and can identify patterns of activity across the whole brain (Kwong et al., 1992).

When studying the newborn brain however, questions may arise about the use of the canonical HRF. In several studies, it has been suggested that the infant’s HRF resembles that of an adult response (Dehaene-Lambertz, 2002; Dehaene-Lambertz et al., 2010). Namely that of a positive BOLD response resulting from an increased oxyhemoglobin/deoxyhemoglobin ratio in the CBF. Others described a smaller positive peak in infants (Harris, Reynell, & Attwell, 2011) or even a positive trend with a later peak (± 6-12s), in which the peak increased in relation to increasing age (Arichi et al., 2012), suggesting that the HRF depends on developmental changes in the infant (Cusack, McCuaig, & Linke, 2017; Harris et al., 2011). In contrast, during early stages of development, it was described that in comparison to the adult HRF response, sensory stimulation induces a negative BOLD (decreased BOLD) response (Seghier et al., 2004). This response can become even greater due to the use of sedatives frequently used to keep newborns calm (less motion artifacts) during testing (Seghier, Lazeysras, & Hüppi, 2006). Supporting these findings are Kozberg et al. (2013), who even describe the response to be biphasic as a result of immature neurovascular coupling (Kozberg, Chen, DeLeo, Bouchard, & Hillman, 2013).
Hence, the shape of the HRF in infants is still debated and several parameters (e.g. neurovascular maturation) should be taken into account when interpreting fMRI BOLD measures in newborns.
2. HYPOTHESES

The aim of this research project is to assess the difference in brain activation while listening to forward and backward (in time reversed) speech in PT born in comparison to FT born infants.

This objective can be divided into three individual aims:

1. To evaluate the functional brain activation while perceiving forward versus backward speech in PT infants at TEA.
2. To evaluate whether FT infants, only a few days old, show neural activity in language areas while perceiving forward versus backward speech.
3. To evaluate the effect of exposure duration on discrimination abilities in PT infants at TEA.

The general hypotheses are:

1. We expect to find more enhanced language processing in PT infants at TEA, who were exposed to language earlier in the extra-uterine environment, while listening to forward speech stimuli.
2. We do not expect to find enhanced language processing in the FT group who were only exposed to language for a few days.
3. We believe to find an effect of exposure duration on the discrimination abilities of PT infants at TEA.

Taking into account earlier research, this first hypotheses can be specified:

1. We expect to find more activations in the PT group in the STS and extending more posteriorly to the AG and PCun lateralized in the left hemisphere while listening to forward speech.
3. METHODS

In this section, the protocol, measurement techniques and data analysis of the current study will be described. All data acquisition was performed by Alexandra Adam-Darque at the University Hospital of Geneva.

3.1 Subjects

In this study, 39 infants were tested: 19 FT newborns (9 boys, 10 girls; mean gestational age (mGA) = 40 weeks, standard deviation (SD) = 1.1), tested between their 2nd and 6th day after birth and 20 PT infants (9 boys, 11 girls; mGA at birth = 28.7 weeks, SD = 2.5) tested at their TEA (mGA at TEA = 40.4 weeks, SD = 0.7). Data from 3 infants was excluded from the study because of excessive motion (2 FT) and developmental problems (1 FT). All subsequent fMRI analyses were performed on 36 infants (16 FT and 20 PT).

3.2 Study Design

Functional MRI was performed on FT and PT newborns while listening to their mother’s and a stranger’s voice, each played forward and backward (in time-reversed). The stimuli were natural human voice auditory stimuli, spoken by the mother of each newborn and a female stranger’s voice. The stranger’s voice varied for each infant and was the maternal voice from a previous infant in the study. Prior to data acquisition, the speech samples were recorded in a soundproof room (background noise <25dBA sound recording parameters: Wave PCM signed 16 bit, 44100 Hz, 705 kbps, mono), and acquired and edited with the Goldwave Inc. software program. Sentences were normalized to have the same intensity level. The amplitude envelope of each sound was kept intact in order to keep the specificity of each voice and the natural rising envelope of the sound to ensure the voice to remain as natural and identifiable as possible. The same manipulations were done in backward sentences which are only time-reversed using Matlab software program (MathWorks Inc.). Backward speech is a good acoustic control condition, because it keeps global characteristics of the sound (spectral contents, intensity, acoustic complexity, duration) but is unintelligible and breaks the prosodic structure of the sentence in preserving the familiarity of the speaker.
3.3 Experiment

3.3.1 Stimuli

Four auditory stimuli were presented to the newborns, namely the mother’s and stranger’s voices, played forward and backwards. The stimulus consisted of free speech from each mother lasting approximately 5 minutes. The mother was told to speak as if she was speaking to her child, to stay as close as possible to infant-directed speech. These 5 minute sound records were cut and edited to 10 fragments of 24 seconds (Goldwave Inc. software program) and presented to each infant using a MR-compatible headphone (MR Confon GmbH, Magdeburg, Germany) during MRI acquisition. The 5 auditory conditions (4 auditory stimuli and a silence condition) were presented in a block paradigm for 24 seconds and each condition was repeated 5 times per run in a pseudo-randomized order. The level of sound presentation during MRI acquisition was adjusted to a comfortable level, to be easily understandable above the residual scanning noise by a normal adult.

3.3.2 Procedure

After being fed, the infants were swaddled in a blanket, headphones placed on their ears and set up in a vacuum pillow, longer than the baby’s body and surrounding the head, to prevent them from moving. The infant’s well-being and behaviour during the experiments was monitored using pulse oxymetry, a camera, a microphone and by the presence of a nurse during the entire MRI acquisition. Scanning was interrupted immediately if the infants became restless.

Figure 3-1. A FT born infant prepped for the fMRI recording.
MR images were acquired on a Siemens 3 Tesla scanner (Siemens Magnetom Trio, Erlangen, Germany) using a 32-channel head coil. Two runs of 310 functional images were acquired during auditory stimulation using a single-shot T2*-weighted gradient-echo Echo-Planar Imaging (EPI) sequence for each run (TR=2000ms, TE=30ms, 30 slices, voxel size=1.56x1.56x3mm³). A T2-weighted structural image was acquired for anatomical reference (TR=4990ms, TE=160ms, 113 coronal slices, voxel size=0.78x0.78x1.2mm³) and was reviewed by a paediatric neuroradiologist to exclude any pathology.

### 3.4 Data analysis

#### 3.4.1 Preprocessing

The pre-processing of the functional images was performed using SPM8 (Wellcome Department of Imaging Neuroscience, UCL, London, UK) and included: (1) realignment, (2) slice timing, (3) rigid-body coregistration of functional images on a T2 structural image, (4) normalization of subject’s anatomical T2 image (1x1x1mm³) and EPI (2x2x2mm³) to a T2 template of the newborn brain, (5) spatial smoothing (FWHM 6mm). The T2 template of the newborn brain used in this study was created from 20 infant’s anatomical T2 image and is composed by an average of 10 PT infants at TEA and 10 FT newborns, to provide the best brain template as possible to study both preterm and FT born infants in our experiment. To accommodate the high level of motion in infants, images with framewise displacement superior to 1mm as well as one previous and two following images were excluded. Sessions without motion superior to 1mm and including a minimum of one repetition of each condition were used for the analysis.

#### 3.4.2 fMRI analysis

After pre-processing the fMRI images, we modelled the BOLD stimulus-response relation in order to determine which stimulus influenced that positive BOLD effect during testing. This was done by using a general linear model in SPM8. Here, time series of each voxel in the brain were analysed by fitting them into an experimental design matrix. All the different conditions are described and modelled by the adult HRF through the correct parameters. Afterwards, in order to identify cortical brain regions showing an activation in response to forward and backward speech stimuli, different contrasts were formed through subtraction
Hereafter, multiple statistical analyses were performed at both the individual and group level. Like this, functional activations could be evaluated for language perception and the effect of premature birth. The threshold of significance was set at p<0.005 with an extent threshold of 10 voxels.

**Table 1. Forward and backward speech contrasts in SPM.**

<table>
<thead>
<tr>
<th>Contrasts</th>
<th>C2 Forward&gt;backward</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C3 Mother voice forward&gt;backward</td>
</tr>
<tr>
<td></td>
<td>C4 Stranger voice forward&gt;backward</td>
</tr>
<tr>
<td></td>
<td>C5 Forward&gt;silence</td>
</tr>
<tr>
<td>Backward</td>
<td>C9 Backward &gt;forward</td>
</tr>
<tr>
<td></td>
<td>C10 Mother voice backward&gt;forward</td>
</tr>
<tr>
<td></td>
<td>C11 Stranger voice backward&gt;forward</td>
</tr>
<tr>
<td></td>
<td>C12 Backward&gt;silence</td>
</tr>
</tbody>
</table>

**First Level analysis**

First, we performed our analysis at the first level in which we were concerned with single subject data. Activations evoked by language presentations were investigated in each baby separately for each of the 6 forward>backward and backward>forward contrasts. After establishing activations in each baby separately, they were grouped per condition to perform further analysis.

**Second Level analysis**

In the next phase, second level analysis was performed. The second level incorporates information from a group of subjects making it possible to examine differences between our two groups (between-subjects). The first test we performed before any other analysis, was to evaluate the cortical activation to all (vocal) sound stimulations (sound vs. silence) at the group level using a one-sample t-test in both the FT- and PT group. Secondly, we assessed the activations evoked by forward and backward speech with the speech versus silence conditions (C5,C12) using a one-sample t-test in both groups. Furthermore, in order to investigate
whether perceiving language in the different forward>backward and backward>forward contrasts evokes activations in language associated areas in the newborn brain, we performed a one-sample t-test to check for activations per group and per contrast. Hereafter, a group comparison (two-sample t-test) was performed for each forward>backward and backward>forward contrast to compare between the two groups and assess the effect of postnatal exposure between them.

In addition to these analyses, correction was performed for multiple comparison at cluster level for all the contrasts in which we previously found significant activations (C9,C10 and C11). The individual threshold was set at p<0.005 and the corresponding threshold of cluster size was set based in the Random Field Theory (RFT). In order to correct for a univariate setting, in which it is assumed that each neighboring voxel is independent, spatial relations were accounted for by smoothing the data prior to voxel-wise analysis during pre-processing. However, by smoothing the data through kernels, working out independent observations is harder. Therefore, RFT is applied to determine statistical significance for the entire set of voxels. Here, the smoothness of the data in an image is calculated, giving a threshold more closely to the observed value for a sequence of smoothed images. In detail, the corresponding thresholds we found, defined by the RFT corrections were: for the one-sample t-test in the preterm group: FWEc: 2025 for the general backward>forward contrast (C9), FWEc: 1876 for the mother’s voice backward>forward contrast (C10) and FWEc: 1003 for the stranger’s voice backward >forward contrast (C11). However, when performing the one-sample t-test in the FT group and the two-sample t-test, the corresponding thresholds defined by the RFT corrections were: FWEc: inf. Meaning that no supra-threshold activations remained when correcting for multiple comparison at cluster level for all the backward>forward contrasts (C9,C10,C11) in these tests.

After performing the t-tests and correcting for multiple comparison, a F-test (2x2 ANOVA) was conducted using a flexible factorial design in SPM. We have taken into account three factors i.e. subject, group (PT/FT) and a within-subject condition with two levels (forward/backward) in which the mother and stranger voice were combined. We included two main- (group and condition) and one interaction effect (group x condition) in the design matrix and performed an F-contrast to probe for the effects (p<0.005 (uncorrected)). Nonetheless, no supra-threshold activations were found in this test.
Finally, a multiple regression analysis was conducted to check for an effect of duration exposure in the PT group. Each infant was exposed to the extra-uterine environment, with a mean exposure of 11 weeks and 6 days or 81.5 days (Table 2). We wanted to learn more about the possible relationship between the explanatory variable (exposure duration in days) on functional cortical activation in this group.

Table 2. Duration extra-uterine exposure in preterm group.

<table>
<thead>
<tr>
<th>ID</th>
<th>GA (Birth)</th>
<th>GA (fMRI)</th>
<th>Exposure (w = weeks)</th>
<th>Exposure (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby002</td>
<td>26 6/7</td>
<td>40 3/7</td>
<td>13w 4</td>
<td>95</td>
</tr>
<tr>
<td>Baby006</td>
<td>30 4/7</td>
<td>40 3/7</td>
<td>9w 6</td>
<td>69</td>
</tr>
<tr>
<td>Baby007</td>
<td>29 5/7</td>
<td>41 2/7</td>
<td>11w 4</td>
<td>81</td>
</tr>
<tr>
<td>Baby008</td>
<td>28 5/7</td>
<td>40</td>
<td>11w 2</td>
<td>79</td>
</tr>
<tr>
<td>Baby009</td>
<td>28 5/7</td>
<td>41</td>
<td>12w 2</td>
<td>86</td>
</tr>
<tr>
<td>Baby010</td>
<td>26</td>
<td>39 5/7</td>
<td>13w 2</td>
<td>93</td>
</tr>
<tr>
<td>Baby011</td>
<td>27 3/7</td>
<td>40</td>
<td>12w 4</td>
<td>88</td>
</tr>
<tr>
<td>Baby012</td>
<td>31 4/7</td>
<td>41 2/7</td>
<td>9w 5</td>
<td>68</td>
</tr>
<tr>
<td>Baby013</td>
<td>30 5/7</td>
<td>40 2/7</td>
<td>9w 4</td>
<td>67</td>
</tr>
<tr>
<td>Baby014</td>
<td>30 5/7</td>
<td>41 2/7</td>
<td>10w 4</td>
<td>74</td>
</tr>
<tr>
<td>Baby015</td>
<td>27 2/7</td>
<td>40 2/7</td>
<td>13w</td>
<td>91</td>
</tr>
<tr>
<td>Baby017</td>
<td>31 4/7</td>
<td>41</td>
<td>9w 3</td>
<td>66</td>
</tr>
<tr>
<td>Baby021</td>
<td>32 6/7</td>
<td>39</td>
<td>6w 1</td>
<td>43</td>
</tr>
<tr>
<td>Baby022</td>
<td>32 6/7</td>
<td>39 3/7</td>
<td>6w 4</td>
<td>46</td>
</tr>
<tr>
<td>Baby023</td>
<td>25</td>
<td>39 5/7</td>
<td>14w 5</td>
<td>103</td>
</tr>
<tr>
<td>Baby024</td>
<td>25</td>
<td>39 5/7</td>
<td>14w 5</td>
<td>103</td>
</tr>
<tr>
<td>Baby027</td>
<td>26 1/7</td>
<td>41</td>
<td>14w 6</td>
<td>104</td>
</tr>
<tr>
<td>Baby030</td>
<td>27</td>
<td>40 2/7</td>
<td>13w 2</td>
<td>93</td>
</tr>
<tr>
<td>Baby034</td>
<td>28 2/7</td>
<td>40 4/7</td>
<td>12w 2</td>
<td>86</td>
</tr>
<tr>
<td>Baby035</td>
<td>27 3/7</td>
<td>41</td>
<td>13w 4</td>
<td>95</td>
</tr>
</tbody>
</table>

n= 20

Mean 28.7 40.4 11w 6 81.5
4. RESULTS

4.1 Listening to sound

Our first result presents neural activations evoked by all vocal presentations (sound vs. silence) in both groups (PT n=20; FT n=16). As shown in Figure 4-1, significant activations were found in the left STG and PTe in both groups when using a p-value of p<0.005 and a threshold extent of 10 voxels. Symmetrical areas of the right temporal lobe also showed significant activations in both groups. However, only in the PT group, they remained significant after correction for multiple comparison (FWE p<0.05).

Considering a similar threshold of significance (p<0.005), the STG in the FT group showed an activation of 161 voxels on the left hemisphere and 176 voxels on the right hemisphere; in the PT group, 292 voxels on the left hemisphere and 238 voxels on the right hemisphere were activated.

![Figure 4-1](image-url.png)

**Figure 4-1.** Activations to all vocal sounds. One sample t-test on the two groups (PT n=20; FT n=16) showing activation of the bilateral STG during the overall sound vs. silence contrast, with a display threshold: p<0.005, uncorrected and the p-value for each condition. Activations are overlaid on the T2-weighted newborn’s template. Color bars indicate t-values.

When performing a two-sample t-test, the group comparison for the contrast PT>FT revealed small significant activations in the PT group when hearing speech stimuli. A greater activation was found in the left mesial parietal lobe (PCun) and SMG. Conversely, for the contrast FT>PT no significant activations were found.
4.2 Listening to forward and backward speech stimuli

Firstly, we present cerebral activations evoked by forward speech (forward>silence (C5)) and backward speech (backward>silence (C12)) in both groups (PT n=20; FT n=16). As shown in Figure 4-2, significant activations were found in the bilateral STG in both groups when using a p-value of p<0.005 and a threshold extent of 10 voxels. In the PT group, additional activations were found in the left AG and SMG in the backward>silence contrast. However, none of the activations remained significant after correction for multiple comparison (FWE p<0.05).

![Activation maps for forward and backward speech contrasts](image_url)

**Figure 4-2.** Activations in response to the forward and backward speech versus silence contrasts (C5/C12) in both groups. One-sample t-test in both groups (PT n=20; FT n=16) shows activations in the left STG for the forward>silence condition in both groups (upper panel). The lower panel shows activations in the left STG for the backward>silence contrast. In the PT group (lower right panel) additional activations are shown in the left AG and SMG. Activations are overlaid on the T2-weighted newborn’s template with a display threshold: p<0.005, uncorrected. Color bars indicate t-values. (See appendix table 4 for group space activations.)
4.2.1 First Level Analysis

Firstly, we evaluated the ability to differentiate forward versus backward speech in each individual infant. We attempted to identify specific cortical brain activities during the processing of language stimuli by checking activations in the 6 forward>backward and backward>forward contrasts in each infant separately. We were able to observe activations in language associated areas in both PT and FT babies. However, these were not consistent across all tested contrasts and infants (Table 3). Single patient fMRI being variable.

Table 3. Number of infants in each group showing an activation in the different contrasts.

<table>
<thead>
<tr>
<th></th>
<th>PT (n=20)</th>
<th>FT (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>C3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>C9</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>C10</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>C11</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Activations in response to the stimuli were found in at least one of these areas in the left hemisphere: STG, PTe, AG, SMG, post-central gyrus (PoG) and primary motor cortex (M1) (Figure 4-3).
4.2.2 Second Level Analysis

One-Sample t-test

To evaluate the ability to differentiate forward from backward speech and to study the effect of premature birth on language perception, we compared forward versus backward speech in both the mother’s and stranger’s voice with a one-sample t-test in each group. For the one-sample t-test, the contrast (forward>backward (C2)) in both voices (mother (C10)/stranger (C11)) did not show significant activations, neither in the FT, nor in the PT group. Nonetheless, significantly increased cortical activations were found in the backward>forward contrasts in both groups. In the PT group, the general backward>forward (C9) contrast elicited activations in the PCun, orbitofrontal cortex (OFC) and HC bilaterally and the left PCC (Figure 4-4). For both the mother and stranger voice, activations were significantly greater in the bilateral PCun and left orbitofrontal cortex (OFC). However, for the mother’s voice backward>forward contrast (C10), the PT group showed additional significant activations in the right IFG, left HC and bilateral SMG (Figure 4-5). Plus, in the same contrast (C10), activations in the left inferior parietal lobe, anterior STS bilaterally and a small part of
the amygdala were found. An overview of the significant activations can be found in table 1 in the appendix.

**PRETERM**

![Figure 4-4](image1)

**Figure 4-4.** Activations in the general backward>forward contrast (C9) in the PT group (n=20). One-sample t-test shows activations in the left PCun, left OFC and left PCC (left panel) and the HC bilaterally (right panel). Activations are overlaid on the T2-weighted newborn’s template with a display threshold: p<0.005, uncorrected. Color bars indicate t-values. (See appendix table 5 for group space activations).

**PRETERM**

![Figure 4-5](image2)

**Figure 4-5.** Activations in the mother’s voice backward>forward contrast (C10) in the PT group (n=20). One-sample t-test shows activations in the right IFG and SMG (left panel) and the left HC, PCun and OFC (right panel). Activations are overlaid on the T2-weighted newborn’s template with a display threshold: p<0.005, uncorrected. Color bars indicate t-values. (See appendix table 5 for group space activations).
When performing correction for multiple comparison at cluster level (FWE p<0.05) in the PT group for these backward>forward contrasts, several voxels survived and remained significant. The individual threshold was set at p<0.005. Our fMRI data show neural activations in the PCun and posterior cingulate cortex (PCC) bilaterally in the backward>forward contrast (C9), plus the left PoG and MFG in the mother’s voice backward>forward contrast (C10) (Figure 4-6). In addition, activation in the left PCun remained significant in the stranger’s voice backward>forward contrast (C11).

**Figure 4-6.** Activations in the (mother’s voice) backward>forward contrast (C9/C10) in the PT group (n=20) with correction for multiple comparison at cluster level. For the left panel, activations are shown in the general backward>forward contrast (C9): left PCun and PCC. In the right panel, activations are shown in the mother’s voice backward>forward contrast (C10): left PoG and MFG. Activations are overlaid on the T2-weighted newborn’s template and corrected at cluster level with p<0.05 FWE. With a voxel extent of 2052 for the left panel and 1876 for the right panel. Color bars indicate t-values.

In the FT group, general backward>forward speech (C9) elicited a significant activation in the bilateral OFC only. The same activation in the OFC was found in the stranger’s voice backward>forward contrast (C11) (Figure 4-7). No activation was found in the mother’s voice backward>forward contrast (C10). An overview of the significant activations can be found in table 1 in the appendix.
Figure 4-7. Activations in the stranger’s voice backward>forward contrast (C11) in the FT group (n=16). One-sample t-test shows activations bilaterally in the OFC. Activations are overlaid on the T2-weighted newborn’s template with a display threshold: p<0.005, uncorrected. Color bars indicate t-values. (See appendix table 6 for group space activations).

Two-sample t-test

Afterwards, a between group comparison (two-sample t-test) was performed to differentiate between both groups. No significant activations were found in forward>backward speech (C2,C3,C4) for the PT>FT contrast. When testing backward>forward speech (C9), the group comparison for the contrast PT>FT revealed more cerebral activations in the PT group than in the FT group. As shown in Figure 4-8, the PT newborns showed a greater activation of the bilateral PCC, left MTG and anterior STG in comparison to the FT group in this contrast (C9). For both voices, an activation was found in the PCC (Figure 4-9): left PCC in the mother’s voice backward>forward contrast (C10) and in the right hemisphere for the stranger’s voice backward>forward contrast (C11). For the group comparison in the FT>PT contrast, no significant activations were found for any of the contrasts (C2,3,4,9,10,11). An overview of all the significant activations can be found in table 2 in the appendix.
Figure 4-8. Activations in the general backward>forward contrast (C9) in the between group comparison for the PT>FT contrast. Two-sample t-test shows activations in the bilateral PCC (upper panel), left MTG and anterior STG (lower panel). Activations are overlaid on the T2-weighted newborn’s template with a display threshold: p<0.005, uncorrected. Color bars indicate t-values. (See appendix table 7 for group space activations).

Figure 4-9. Activations in the mother’s and stranger’s voice backward>forward contrasts (C10/C11) in the between group comparison for the PT>FT contrast. Two-sample t-test shows activations in the left PCC (upper panel) and in the right PCC (lower panel). Activations are overlaid on the T2-weighted newborn’s template with a display threshold: p<0.005, uncorrected. Color bars indicate t-values. (See appendix table 7 for group space activations).
4.3 Exposure duration analysis

Finally, using multiple linear regression analysis, we were able to investigate the effect of exposure duration on functional cortical activation in response to language stimuli. For the mother’s voice backward>forward contrast (C10), we found a significant activation in the left PCC which increased in correlation ($r = 0.62$) with exposure duration (Figure 4-10). On the other hand, longer exposure to the extra-uterine environment seems to correlate ($r = -0.51$) with an inferior activity in the right IFG in response to backward speech in the mother’s voice (C10) (Figure 4-11). An overview of all significant activations can be found in table 3 in the appendix.

![Image of brain with PCC highlighted and fitted line showing correlation between response in PCC and exposure duration.](image)

**Figure 4-10.** Fitted responses for the mother’s voice backward>forward contrast (C10) in relation to exposure duration (in days) in PT infants only. A. Activations are found in the left PCC. Activations are overlaid on the T2-weighted newborn’s template with a display threshold: $p<0.005$, uncorrected. Color bars indicate t-values. B. A positive correlation ($r = 0.62$) is shown between the response in the PCC and the amount of exposure (in days). (See appendix table 8 for group space activation).
Figure 4-11. Fitted responses for the mother’s voice backward>forward contrast (C10) in relation to exposure duration (in days) in PT infants only. A. Activations are found in the right IFG. Activations are overlaid on the T2-weighted newborn’s template with a display threshold: p<0.005, uncorrected. Color bars indicate t-values. B. A negative correlation ($r = -0.51$) is shown between the response in the right IFG and the amount of exposure (in days). (See appendix table 8 for group space activations).
5. DISCUSSION

Spoken language can be described as a whole of linguistic sounds consisting of different segments (vowels/consonants) following each other. An important aspect of spoken language is prosody. Prosody cannot be reduced to the succession of vowels and consonants but provides additional information based on intonation, rhythm and stress. Hence, prosodic units transcend the level of segments. As described in the introduction, newborns already have the ability to perceive language stimuli and prefer speech over complex non-speech sounds (Vouloumanos & Werker, 2007). More specifically, studies have shown that newborns are sensitive to the prosodic properties of their native language. For example, 4 day-old infants already have the ability to discriminate their native language from an unfamiliar one (Mehler et al., 1998; Ramus, 2000). Backward speech however, violates the segmental and supra-segmental phonological properties of speech (Dehaene-Lambertz, 2002). Hence, studies have demonstrated that newborns showed left-lateralized specialization when listening to forward speech, but not backward speech (Dehaene-Lambertz, 2002; Pena et al., 2003).

In this study, we aimed to assess whether PT born infants at TEA, who were exposed to the extra-uterine environment for several weeks, show significant brain activations in language associated areas while listening to speech stimuli in comparison to their FT peers. fMRI was used to detect cortical activations while listening to forward and backward speech stimuli. We evaluated images of 36 newborns, 20 PT and 16 FT, who were born at the University Hospital of Geneva. Hence, some hypotheses were formed. First, we expected to find cortical activations in language areas in the PT born group while listening to forward speech. More specifically, taking into account previous research, we anticipated in finding left-lateralized activations in the STS and extending more posteriorly to the AG and PCun. Second, we did not expect to find similar activations in the FT group while listening to forward speech. And thirdly, we assumed to find an effect of exposure duration in the extra-uterine environment on discrimination abilities in PT infants at TEA.
5.1 Listening to sound

Firstly, cortical activations in response to all auditory stimuli (sound vs. silence) were studied. As expected, we were able to successfully record bilateral STG activations in response to all vocal sounds in both the FT and PT group. This result corresponds to previously described results in newborns, showing similar brain activations in response to auditory stimulations (Dehaene-Lambertz, 2002). Furthermore, when performing a group comparison for the PT>FT sound vs. silence contrast, additional clusters of activation were found in the PT group while listening to speech sounds, namely in the left PCun and SMG. In adults, it has been described that auditory sound stimuli are first processed in Heschl’s gyrus and then proceed to more posterior areas such as the SMG and PCun. Here, rough auditory information is decoded and sent to other cortical areas for further processing. In addition, these cortical areas have also been described in the literature as being part of a larger auditory “where” pathway in which they play a role in localization and recognition of sound stimuli (Brunetti et al., 2005; Maeder et al., 2001). An explanation for these supplementary activations can be the early extra-uterine exposure of these infants during their postnatal stay in the NICU in which they were exposed to different types of sound stimuli.

5.2 Listening to forward and backward speech stimuli

Firstly, functional brain activations in response to the forward>silence and backward>silence contrasts were studied. We recorded bilateral STG activity in both the PT and FT group for both conditions. Showing us that the newborns in both groups are responding to the auditory speech stimulations. Secondly, first level analysis was performed for all the forward>backward and backward>forward contrasts in each individual baby. We were able to observe activations in language associated areas in all contrasts in both groups. Despite the fact that they were not consistent across all tested contrasts and infants, we were able to detect activations across the left hemisphere in the STG, PTe, AG, SMG, PoG and M1 while listening to forward speech (C2,C3,C4). So, some individuals showed processing abilities of forward speech with increased left-lateralized activations in the language associated areas. Since we were able to find an activation in at least one contrast in each subject, it was decided to retain the data of each newborn for further analysis.
Thirdly, a one-sample t-test was performed to check for between-subject activations in both the PT and FT group. Our findings do not correspond with previous results showing cortical activations in 3 month-old infants in the STS, AG and PCun while listening to forward speech stimuli (Dehaene-Lambertz, 2002). Conversely, after performing group analyses, none of the groups showed any significant activations in the forward>backward contrasts. A reason for this may be the large variability between the tested newborns. For instance, we were not able to check for an effect of wakefulness on speech-induced activations. It is possible that many of the babies were asleep during testing, which may have influenced their responses to the stimuli.

However, when considering the backward>forward contrasts (C9,C10,C11), functional brain activations were present. Our findings report a significant activation of the OFC bilaterally when FT infants listened to the stranger’s voice backwards (C11) rather than forward. No significantly different activations were found when listening to the mother’s voice backwards (C10) compared to forward. The OFC is known to play a role in attentional and emotional processing and the encoding of novel stimuli (Petrides, 2007), which can explain its activation in this backward>forward contrast (C11). Next, imaging results in the PT group showed that both voices activate the bilateral PCun and left OFC in the backward>forward contrast. In adults, the PCun is activated, mostly right-lateralized, when retrieving (verbal) information from memory (Bonni et al., 2015; Shallice et al., 1994). The activation of the PCun here may indicate that PT newborns engage in early memory retrieval. Moreover, the differential activation of additional brain areas were found when listening to backward speech in the mother’s voice (C10), namely in multiple language associated areas i.e. the right IFG, bilateral SMG and left anterior STS. As found in adult fMRI studies, the anterior STS is involved in semantic and syntactic processing and becomes active when syntactic structures have to be processed (Friederici, 2011). Alongside, the anterior STS is also a voice specific area and is involved in processing speaker identity (Belin & Zatorre, 2003; Kriegstein & Giraud, 2004). Furthermore, the PT group demonstrated additional significant activations in the left HC and a small portion of the amygdala in the mother’s voice backward>forward contrast (C10). Although the HC is mostly known to be involved in storing new memories that relate to certain facts or events, its activation can also be linked to the detection of novelty in response to auditory stimuli (Knight, 1996; Rutishauser, Mamelak, & Schuman, 2006). The amygdala on the other hand is known to play a role in processing emotional
(auditory) stimuli. It is involved in the emotional labelling of vocal stimuli (Fecteau, Belin, Joanette, & Armony, 2007) and the detection of a relevant stimulus in the environment (Sander, Grafman, & Zalla, 2003). These activations may show that PT infants respond to the mother’s voice and put in more effort to focus on this familiar voice.

Subsequently, between group comparison was conducted to investigate the differences between both groups while listening to forward and backward speech stimuli using a two-sample t-test. To test whether PT infants, who have been exposed to the extra-uterine environment for several weeks, show different cortical activations in comparison to the FT group, we tested the PT>FT contrast for all the forward>backward and backward>forward contrasts. Precedent results in 2-3 month-old infants had shown forward speech processing in left-lateralized regions such as the STS, AG and PCun in comparison to listening to backward speech (Dehaene-Lambertz, 2002). In our study activations were found for the general backward>forward (C9) contrast in the bilateral PCC, left MTG and anterior STG. Each voice separately for the PT>FT comparison showed activations in the PCC for backward speech (C10/C11). The role of the PCC is mostly known as that of an auditory association area, incorporating information of different modalities and forming an auditory memory (Démonet et al., 1992). In addition, in adult neuroimaging studies, the PCC was found to be an area closely related with other brain regions, forming functional connectivity interactions with i.a. the prefrontal cortex. As such, providing a mechanism for attentional focus (Leech & Sharp, 2014). This present study suggests that the role of this area in the backward>forward contrast might be related to an increased focus of attention conveyed by an unknown stimulus such as backward speech.

Our findings report that both groups involve more cortical regions in processing backward speech than forward speech. This was demonstrated by the enhanced activation of brain areas in the backward>forward contrasts. This effect can be attributed to the detection of novelty. In the FT group, detection of backward speech in a stranger’s voice might be perceived as a relevant and novel stimulus in the environment since they have mainly been hearing their mother’s voice at this age. In contrast, PT newborns have been exposed to forward speech and many different voices longer in the extra-uterine environment. Thus, they might be more surprised when hearing backward speech instead of forward speech. Their effort to process
this unusual stimulus mobilizes more cognitive processing which can explain the activation of multiple brain areas such as the PCun, OFC and PCC. In addition, our results show that the group of PT newborns exhibit more activations in emotional processing areas when listening to their mother’s voice backwards. This may be due to the fact that they have become more familiar to the mother’s voice and already assigned an emotional value to it. Furthermore, it is important to note that all the vocal stimuli used in this study are from mothers addressing their infants. This type of infant-directed speech, which is high in pitch and has exaggerated pitch contours, conveys a positive emotional prosody. It was found to play a role in attracting an infant’s attention and aiding emotional communication (Trainor & Desjardins, 2002) which could explain the activation of the emotional areas we found in our study. Hence, we can conclude that both the FT group as the PT group are able to differentiate backward from forward speech. This may be explained by the fact that both the FT group and the PT group are already familiar with the prosodic rules of their native language. Which corresponds to previously found data stating that even newborns of only a few days old are already familiar with the prosody of their mother tongue (Mehler et al., 1998). A new (unknown) stimulus, such as backward speech, which breaks down the rules of this prosody, can lead to an increased attention and impulse to be processed. Thus, we may assume that both groups are able to differentiate prosody.

5.3 Effect of exposure duration

Finally, we determined the correlation between extra-uterine exposure duration and language processing abilities in the PT group. Our fMRI results showed a positive correlation between exposure duration and activity in the PCC for the mother’s voice backward-forward contrast (C10). Thus, while exposure duration increased, so did the activity in this area. In adult neuroimaging studies, the PCC has been found to be a key area in recognizing familiarity such as familiar faces and voices (Shah et al., 2001) and also gets activated by emotional stimuli (Maddock, Garrett, & Buonocore, 2003). The activation of this area may be explained by the fact that the PT newborns are already more familiarized with the voice of their mother after prolonged extra-uterine exposure. Additional results showed a negative correlation between exposure duration and activity in the right IFG for this contrast (C10). Activations in the right IFG became weaker with the increase in exposure duration. This may be the result of
their stay in the extra-uterine environment in which they get more familiarized with normal speech stimuli and thus stop to try and process backward speech as a relevant stimulus.

5.4 Limitation of the study

A limitation of this study is that the study was initially performed to assess voice perception in PT and FT newborns and not language perception. Therefore, we were not able to control for auditory activations. It would be interesting to conduct future research in which a noise condition (e.g. white noise) is added to correct for this. Furthermore, we did not assess the newborns state of wakefulness during the fMRI experiment, which could have further influenced their neural processing of stimuli as well as the BOLD response itself.
CONCLUSION

The aim of this Master’s thesis was to assess differences in brain activations while listening to forward and backward speech stimuli in PT born in comparison to FT born infants. More specifically, we aimed to assess whether PT newborns at TEA show functional brain activations in language associated areas while listening to forward speech and if there was an effect of exposure duration to the environment on discrimination abilities.

It was hypothesized that PT newborns, who were exposed to the extra-uterine environment earlier, show activations in brain areas such as the STS, AG and PCun in the left hemisphere while listening to forward speech and are able to differentiate between forward and backward speech. However, unlike we hypothesized, our findings only reported significant activations while listening to backward speech in both the PT and FT group. As a result, it can be confirmed that both PT and FT newborns show novelty detection when listening to backward speech. The PT group however showed additional activations in emotional and attentional processing areas while listening to their mother’s voice. Hence, we may conclude that prolonged exposure to the mother’s voice in the extra-uterine environment mobilizes more emotional and cognitive processes in response to the mother’s voice backwards.

Finally, it can be concluded that auditory stimulations experienced in the extra-uterine environment may have a positive effect on the maturation of functional networks involved in speech processing.
REFERENCES


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LIST OF TABLES

Table 1. Forward and backward speech contrasts in SPM ................................................................. 19
Table 2. Duration extra-uterine exposure in preterm group ............................................................... 21
Table 3. Number of infants in each group showing an activation in the different contrasts .. 24
LIST OF FIGURES

Figure 3-1. A FT born infant prepped for the fMRI recording ........................................... 17

Figure 4-1. Activations to all vocal sounds ............................................................................. 22

Figure 4-2. Activations in response to the forward and backward speech versus silence contrasts (C5/C12) in both groups .................................................................................. 23

Figure 4-3. First level activations in the mother’s and stranger’s voice forward>backward (C3,C4) and backward>forward (C10,C11) contrasts in both groups ........................................ 25

Figure 4-4. Activations in the general backward>forward contrast (C9) in the PT group (n=20) ........................................................................................................................................ 26

Figure 4-5. Activations in the mother’s voice backward>forward contrast (C10) in the PT group (n=20) ........................................................................................................................................ 26

Figure 4-6. Activations in the (mother’s voice) backward>forward contrast (C9/C10) in the PT group (n=20) with correction for multiple comparison at cluster level................................. 27

Figure 4-7. Activations in the stranger’s voice backward>forward contrast (C11) in the FT group (n=16) ........................................................................................................................................ 28

Figure 4-8. Activations in the general backward>forward contrast (C9) in the between group comparison for the PT>FT contrast .......................................................................................... 29

Figure 4-9. Activations in the mother’s and stranger’s voice backward>forward contrasts (C10/C11) in the between group comparison for the PT>FT contrast ........................................... 29

Figure 4-10. Fitted responses for the mother’s voice backward>forward contrast (C10) in relation to exposure duration (in days) in PT infants only ............................................................ 30

Figure 4-11. Fitted responses for the mother’s voice backward>forward contrast (C10) in relation to exposure duration (in days) in PT infants only ............................................................ 31
APPENDIX

Table 1. Significant activations found in the one-sample t-test for each group.

<table>
<thead>
<tr>
<th>Significant activations</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-sample t-test</td>
</tr>
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<td><strong>Backward&gt;Forward contrast</strong></td>
</tr>
<tr>
<td>PT group</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>FT group</td>
</tr>
<tr>
<td><strong>Mother's voice Backward&gt;Forward contrast</strong></td>
</tr>
<tr>
<td>PT group</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>FT group</td>
</tr>
<tr>
<td><strong>Stranger's voice Backward&gt;Forward contrast</strong></td>
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Table 2. Significant activations found in the two-sample t-test for the PT>FT contrast.

<table>
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Table 3. Significant activations found with multiple regression analysis in the PT group.

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<td>[0 -1] PT</td>
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<tr>
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<tr>
<td>[0 -1] PT</td>
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[0 1] defines positive correlation; [0 -1] defines negative correlation
Table 4. One-sample t-test: Significant activations in the forward>silence (C5) and backward>silence (C12) contrasts for each group.

<table>
<thead>
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<th>Group</th>
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<th>Peak Z</th>
<th>T</th>
<th>N° voxels</th>
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<td>PT</td>
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<td>3.88</td>
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<td></td>
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<td>4.4</td>
<td>71</td>
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<tr>
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<td>FT</td>
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<td>7</td>
<td>4.22</td>
<td>113</td>
</tr>
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<td>-26</td>
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</table>

Table 5. One-sample t-test: Significant activations for the backward>forward (C9) and mother’s voice backward>forward (C10) contrasts in the PT group.

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<th>Peak Z</th>
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<th>N° voxels</th>
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<td>C9</td>
<td>L/R Precuneus</td>
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<td>32</td>
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<td>4</td>
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<td>L Posterior Cingulate cortex</td>
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<td>4.92</td>
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<td>R Hippocampus</td>
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<td>-23</td>
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<td>4.06</td>
<td>36</td>
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<td>R Supramarginal gyrus</td>
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<td>-38</td>
<td>16</td>
<td>3.41</td>
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<td>L/R Precuneus</td>
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Table 6. One-sample t-test: Significant activations for the stranger’s voice backward>forward contrast (C11) in the FT group.

<table>
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<th>Peak Y</th>
<th>Peak Z</th>
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Table 7. Two-sample t-test: Significant activations for the backward>forward contrasts (C9,C10,C11) for the PT>FT contrast.

<table>
<thead>
<tr>
<th>Site</th>
<th>Area</th>
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<th>Peak Y</th>
<th>Peak Z</th>
<th>T</th>
<th>Nº voxels</th>
</tr>
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<tbody>
<tr>
<td>C9</td>
<td>R  Posterior Cingulate cortex</td>
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<td>-44</td>
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<tr>
<td></td>
<td>L  Posterior Cingulate cortex</td>
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<td>20</td>
</tr>
<tr>
<td></td>
<td>L  Middle temporal gyrus</td>
<td>-25</td>
<td>-8</td>
<td>-17</td>
<td>3.75</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>L  Anterior superior temporal gyrus</td>
<td>-31</td>
<td>8</td>
<td>-14</td>
<td>3.17</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>L  Posterior Cingulate cortex</td>
<td>-13</td>
<td>-46</td>
<td>19</td>
<td>3.14</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>R  Posterior Cingulate cortex</td>
<td>12</td>
<td>-44</td>
<td>13</td>
<td>3.22</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 8. Multiple Linear Regression: Significant activations for the mother’s voice backward>forward contrast (C10) in the PT group while testing for the effect of exposure duration.

<table>
<thead>
<tr>
<th>Site</th>
<th>Area</th>
<th>Peak X</th>
<th>Peak Y</th>
<th>Peak Z</th>
<th>T</th>
<th>Nº voxels</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10</td>
<td>L  Posterior cingulate cortex</td>
<td>-9</td>
<td>-36</td>
<td>19</td>
<td>3.83</td>
<td>56</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>R  Inferior frontal gyrus</td>
<td>33</td>
<td>24</td>
<td>4</td>
<td>4.01</td>
<td>19</td>
<td>-0.51</td>
</tr>
</tbody>
</table>