RESEARCH ARTICLE

Auditory structural connectivity in preterm and healthy term infants during the first postnatal year

Leire Zubiaurre-Elorza[1,2] [ID] | Annika C. Linke[1] | Charlotte Herzmann[1] | Conor J. Wild[1] | Hester Duffy[1] | David S.C. Lee[3] | Victor K. Han[3] | Rhodri Cusack[1,3]

[1] Brain and Mind Institute, Western University, London, Canada

[2] Faculty of Psychology and Education, Department of Methods and Experimental Psychology, University of Deusto, Bilbao, Spain

[3] Children's Health Research Institute, London, Canada

Correspondence
Leire Zubiaurre Elorza, Faculty of Psychology and Education, Department of Methods and Experimental Psychology, University of Deusto, Bilbao, Basque Country, Spain.
Email: leire.zubiaurre@deusto.es

Abstract

Assessing language development in the first postnatal year is difficult, as receptive and expressive skills are rudimentary. Although outward manifestations of change are limited, the auditory language system is thought to undergo critical development at this age, as the foundations are laid for the rapid onset of spoken language in the second and third years. We recruited 11 infants, 7 healthy controls (gestational age = 40.69 ± 0.56; range from 40 to 41.43) and preterm babies (gestational age = 28.04 ± 0.95; range from 27.43 to 29.43) who underwent a Magnetic Resonance Imaging study during the first postnatal year (age at scan = 194.18 ± 97.98). We assessed white matter tracts using diffusion-weighted magnetic resonance imaging with probabilistic tractography. Fractional anisotropy was found to be largely mature even at one month, although there was a little further increase during the first postnatal year in both the acoustic radiation and the direct brainstem-Heschl's pathway.

KEYWORDS

acoustic radiation, auditory development, brainstem-heschl's pathway, first postnatal year, tractography

1 | INTRODUCTION

The first postnatal year is a critical period for language development, since it is the time when the bases of language processing are established (Bates, Thal, Finlay, & Clancy, 2002). Fundamental to this is the auditory system, which plays an important role in spoken language understanding in adults (Davis & Johnsrude, 2003), and is critical to language learning in non-deaf infants. Behavioral and electrophysiological studies have shown that aspects of auditory processing measured during the first postnatal year predict language development in childhood (Guzzetta, Conti, & Mercuri, 2011; Tallal & Gaab, 2006). Any disruption to the auditory language system during the first postnatal year may have a cascading effect on language development.

It has been proposed that functional maturation is substantially driven by the development of connectivity in the brain (Johnson, 2001). Auditory pathways play a critical role in language acquisition and are thought to become progressively more mature and functionally efficient in the first postnatal year. One proposal is that at birth, auditory function relies on a direct pathway from the reticular activating system in the brainstem into layer I of auditory cortex, which at this age is the only layer into which mature myelinated fibers project (Eggermont & Moore, 2012; Marin-Padilla & Marin-Padilla, 1982; Moore & Linthicum, 2007). According to this proposal, around the seventh month auditory processes become dominated by the acoustic radiation, which develops projections to the thalamo-cortical recipient layer IV, and projections to layer I reduce (Eggermont & Moore, 2012; Marin-Padilla & Marin-Padilla, 1982). However, others have reported

that fibers from the thalamus penetrate the auditory cortex by as early as 22–28 weeks of gestational age (GA) (Huttenlocher & Dabholkar, 1997; Kostović, Judas, Rados, & Hrabac, 2002; Krmpotić-Nemanić, Kostović, Kelović, Nemanić, & Mrzljak, 1983). Furthermore, the reticular activating system can only convey crude auditory information, but there is evidence of sophisticated auditory function within the first few postnatal months, suggesting cortical engagement that would require rich acoustic representations delivered from the thalamus (Wild et al., 2017). For example, infants less than 3 months of age can recognize their mother's voice (Mills & Melhuish, 1974) and discriminate syllables within 400 ms of presentation (Dehaene-lamberetz & Dehaene, 1994). This sophisticated behavior might reflect processing in one of the many subcortical auditory structures, or alternatively the auditory thalamic route might be present early in development. These two proposals differ in the stipulated white matter tracts that carry information to auditory cortex. The brainstem is connected with the auditory cortex (Heschl's gyrus) through the brainstem-auditory pathway and the thalamus is connected to auditory cortex by the acoustic radiation. The structural development and maturation of these pathways during the first postnatal year still remains to be investigated. Thus, our goal was to measure, using state-of-the-art neuroimaging techniques, the organization of these auditory pathways in the first postnatal months, and to study the maturation of auditory structural connectivity during the first postnatal year.

Diffusion-weighted magnetic resonance imaging is a method that allows quantification of the microstructure of white matter with a number of indices: fractional anisotropy (FA, degree of directionality within the fibers), mean diffusivity (MD, average of water diffusion), radial diffusivity (RD, perpendicular diffusivity) and axial diffusivity (AD, parallel diffusivity). The analysis method of tractography additionally makes it possible to identify connecting tracts non-invasively. A number of studies have used diffusion-weighted magnetic resonance imaging to investigate early white matter development (Ball et al., 2013; Dubois et al., 2014; Van Den Heuvel et al., 2015). To the extent of our knowledge, this is the first study that attempts to differentiate hypotheses of the development of auditory pathways and quantify their microstructure in the first postnatal year.

Specifically, we investigated structural connectivity to the auditory cortex in infants during the first postnatal year by mapping the connections using diffusion tensor imaging: (1) from the brainstem to Heschl's gyri in the auditory cortex; (2) from the thalamus to Heschl's gyri. Given the sophistication of infants' auditory processing, we hypothesized that the early organization of both the acoustic radiation and the brainstem-Heschl's gyrus pathway will be present early after birth. Moreover, taking into account the immaturity of myelin at birth (Deoni et al., 2011) we predicted that there would still be maturation in the microstructure of these pathways with age.

2 | METHODS

2.1 | Participants

The participants (n = 51 infants) were recruited between March 2013 and March 2015 for Magnetic Resonance Imaging (MRI) scanning at Robarts Research Institute (University of Western Ontario, London, Canada). Infants were recruited from two sources: the University Department of Psychology's Child Development Participation Pool, or following a previous MRI at the neonatal intensive care unit of London Health Sciences Centre. The following inclusion criteria were applied: (1) no congenital abnormalities; (2) no contraindications for MRI; (3) an age at MRI of 1, 3, or 9 postnatal months (corrected for prematurity). From the initial 51, 27 were successfully coaxed to sleep and scanning data were acquired. However, as diffusion-weighted imaging was conducted at the end of a 30-min protocol, it was only successfully acquired in 14. We excluded infants for whom brain injury was apparent on the MRI. On this basis, three babies with substantial brain injury (intraventricular haemorrhage grades III/IV) were excluded. The final sample comprised 11 participants, 7 of them were healthy controls and four babies were born preterm, all without a diagnosis of brain injury. Clinical information was retrieved from medical records. Parental education was classified into low, intermediate and high categories (Weisglas-Kuperus et al., 2008). Approval for the study was granted by the Health Sciences Research Ethics Board of Western University (London, Canada), and informed consent was obtained from parents prior to participation.

2.2 | Magnetic resonance imaging

All participants were scanned in a three Tesla Siemens MRI system, the MAGNETOM Prisma. A highly accelerated multiband echo-planar imaging sequence (acceleration factor = 4, integrated parallel acquisition technique = 0, reaction time/echo time = 1980/71, voxel size $2 \times 2 \times 2$ mm^3, matrix 96×96) comprising 128 directions with diffusion encoding (b = 1500 s/mm^2) and 10 volumes with b = 0 s/mm^2, distributed through the acquisition was used for diffusion weighted imaging. Like the Human Connectome Project (Sotiropoulos et al., 2013), we used monopolar diffusion encoding, which allows a shorter echo time and reaction time, giving more signal. However, the eddy currents induced lead to distortion, so we used two sequences with opposite phase-encoding polarities (right-left and left-right subsequently), resulting in pairs of images with distortions going in opposite directions. With high acceleration and short reaction time, the total acquisition time for both diffusion sequences was kept to just 9 min 18 sec. To control motion during imaging, younger infants were snugly swaddled and comforted in a vacuum cushion (MedVac Infant Vacuum Immobilization Bag, Contour Fabricators, Inc, Fenton, Michigan). Moreover, earplugs (MiniMuffs, Natus, 7 decibels of attenuation) and ear defenders (29 decibels of attenuation, http://www.scansound.com/index.php/mri-noise-reduction-headphone.html) were used for noise attenuation. After the MRI session, an expert clinical neuroradiologist evaluated each MRI scan for the presence of brain abnormalities.

2.3 | Image processing

Diffusion image processing was performed using the *FSL* software (Smith et al., 2004). First, in order to remove the opposing distortions

generated by the reversed phase-encode acquisition, the *TOPUP* toolbox was used to estimate the susceptibility-induced off-resonance field (Andersson, Skare, & Ashburner, 2003) and combine each corresponding pair in the two acquisitions of 138 images into a single distortion-corrected one. Second, the data were corrected for eddy current-induced distortions and participant movement using *EDDY*. Third, non-brain tissue was removed from each image with the brain extraction tool (Smith, 2002), and fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps were generated by using *DTIFIT* (Figure 1). Fourth, seed masks and waypoint masks were generated on color-coded FA maps. Bidirectional tract tracing (i.e., seed to target and target to seed) was performed and the two directions averaged. The whole thalamus, the brainstem, and Heschl's gyri were manually drawn in each participant (Figure 2). For the thalamic-Heschl's gyrus pathway (the acoustic radiation), the thalamus was selected as seed and the Heschl's gyri as a waypoint and termination mask. Exclusion masks were generated to restrict the pathway to the region ipsilateral to the seed mask. For the brainstem-Heschl's gyrus pathway, the whole brainstem was used as a starting seed and Heschl's gyri as waypoint and termination mask. To identify the thalamic route, the thalamus was included as a waypoint, and to identify the direct pathway, the thalamus was used as an exclusion mask. Default parameters (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007) were used for the *bedpostX* (i.e., fibers per voxel = 2, weight factor = 1 and burn in factor = 1000) and *probtrackX* toolboxes (i.e., number of samples = 5000, curvature

threshold = 0.2). Probabilistic connectivity distributions were generated from every voxel in the seed masks, and only those paths that went through the waypoint masks and stopped there were taken into account for the analysis (Figure 3). Motion parameters were estimated in each participant by calculating the estimated root-mean square displacement between diffusion volumes to the b0 reference image (in millimeters, https://www.fmrib.ox.ac.uk/datasets/techrep/tr99mj1/tr99mj1.pdf, spherical approximation to head used with radius = 7 cm).

2.4 | Statistical analyses

Correlation was used to investigate the relationship between age and the strength of connectivity as well as the white matter integrity in each pathway of interest from the first to the ninth postnatal month with gestational age (GA) as covariate. Age at MRI as used for correlations was corrected for prematurity in those who were born preterm ($n = 4$).

All statistical analyses were computed using IBM SPSS 22 (SPSS Inc., Chicago, IL). All white matter tracts were normalized by dividing by the number of streamlines that went through the waypoint masks, and then thresholded at 5%. Overall and tract-specific white matter indices (FA, MD, AD, RD) were obtained in all participants. Strength of connectivity in every tract was calculated as the number of streamlines going through the waypoint, divided by the number of voxels in the seed, multiplied by the number of streamlines per run (5000).
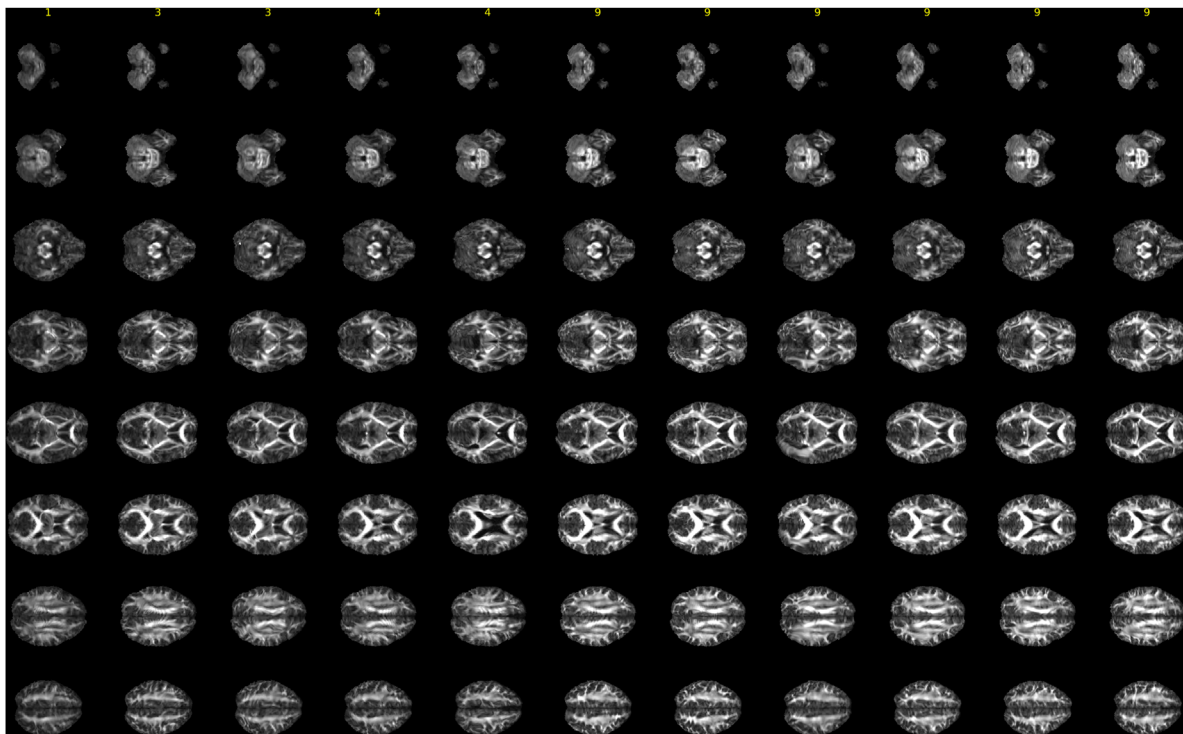

FIGURE 1 Axial slices through normalized FA for each subject during the first postnatal year. Each column represents a subject of the study. Age at scan for each participant is described with a yellow number as column headings (1 = 1 month; 3 = 3 months; 9 = 9 months). Each row represents *z* planes selected for visualization in MNI space: −42, −30, −18, −6, 6, 18, 30, 42 mm
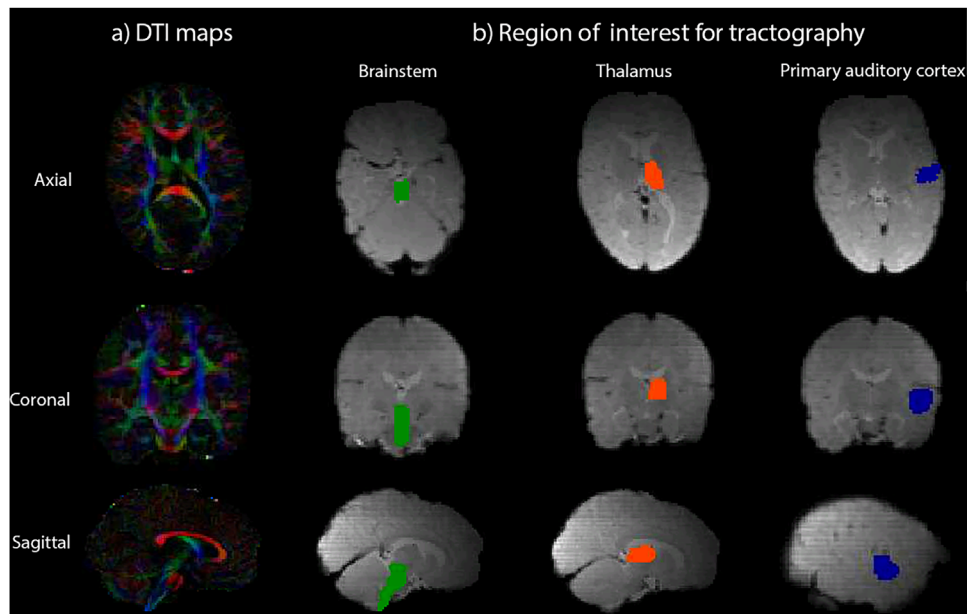
FIGURE 2 Representation in a male infant (9 months) of a) diffusion tensor imaging (DTI) maps; the direction of the fibers is represented in blue (up-down), red (left-right) and green (front-back), b) Regions of interest manually drawn and used for tractography analyses between the brainstem or the thalamus and the primary auditory cortex

3 | RESULTS

3.1 | Demographics and basic clinical measurements

Eleven infants (gender: females = 6/11, males = 5/11; socioeconomic status: high = 3/9, medium = 4/9, low = 2/9, 2 unavailable) were examined at term-equivalent age (gestational age (GA) at delivery = 36.09 ± 6.42 weeks, Min = 27.43, Max = 41.43). Seven participants were born at term age (GA at delivery = 40.69 ± 0.56; range from 40 to 41.43) and four were born preterm (GA at delivery = 28.04 ± 0.95; range from 27.43 to 29.43). Moreover, the preterm participants showed a birth weight of 1,032.50 ± 159.45 grams, head circumference of 27.05 ± 2.19 cm and length of 34.63 ± 1.11 cm at birth. Table 1 describes the perinatal characteristics and neonatal morbidity of the preterm infants included in the study. Age at magnetic resonance imaging (MRI) corrected for prematurity
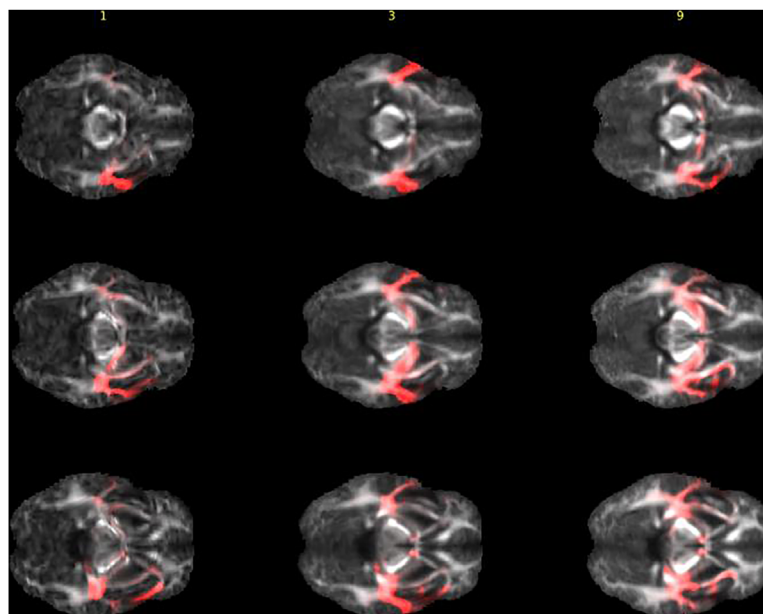

FIGURE 3 Acoustic radiation normalized FA means by age group through the first postnatal year. Each column represents axial slices for a specific group whose age at scan is described with a yellow number as column headings (1 = 1 month; 3 = 3 months; 9 = 9 months). Each row shows an MNI z plane: −13, −9, −5 mm

TABLE 1 Perinatal characteristics and neonatal morbidity of the preterm infants included in the study

Perinatal variables	Preterm sample (n)
Chorioamnionitis	(0/4)
Antenatal steroids	(2/4)
Apgar score <6 at 5 min	(1/4)
Mechanical ventilation >14 day	(1/4)
Vaginal delivery	(1/4)
Seizures	(0/4)
IUGR	(0/4)
SGA	(1/4)
Neonatal brain lesions (US)	(0/4)
Respiratory distress syndrome	(4/4)
Bronchopulmonary dysplasia	(2/4)
Patent ductus arteriosus	(2/4)
Neonatal jaundice	(3/4)
Necrotizing enterocolitis	(0/4)
Retinopathy of prematurity	(2/4)

was 194.18 ± 97.99 days (range 38–285 days). The distribution of the participants included in the study according to their age along the three time points recruited (1st, 3rd, and 9th months) showed an age at MRI (in months and corrected for prematurity) of 1.27 (n = 1), 3.27–3.97 (n = 4), and 9.00–9.50 (n = 6).

No evidence of brain abnormalities was reported in a blinded assessment by an experienced neuroradiologist. Mean root-mean square displacement in the sample ($\bar{X}$ = 1.30 ± 1.12) was not affected by age at scan (1 month: $\bar{X}$ = 0.88 mm; 3 months: $\bar{X}$ = 1.58 ± 1.88 mm; 9 months: 1.18 ± 0.51 mm; F = 0.20; p = 0.82) or prematurity (preterm group: $\bar{X}$ = 0.94 ± 0.63 mm; term group: $\bar{X}$ = 1.50 ± 1.32; t = 0.77; p = 0.46).

3.2 | Auditory connectivity through development

The correlation between overall and tract-specific white matter indices' with age at MRI are detailed in Table 2. Overall white matter indices showed a significant increase of fractional anisotropy (FA) during development, whereas all the diffusivities decreased through the first postnatal year. Next, we examined specific auditory tracts. First, age at MRI (corrected for preterms) showed a positive correlation with FA in the acoustic radiation, but a negative correlation with radial diffusivity (RD), and no significant changes for mean diffusivity (MD) and axial diffusivity (AD) were observed through the first postnatal year. Second, the brainstem-Heschl's gyrus pathway, going through the thalamus, showed a significant negative correlation between age at MRI (corrected for preterms) and MD, AD and RD, respectively. Correlation between age at MRI (corrected for preterms) and FA did show a positive trend, although it did not reach significance (p = 0.06). Figure 4 depicts the development of FA in the auditory language tracts during the first postnatal year. Finally, the results related to the

brainstem auditory pathway that excluded the thalamus found a positive significant correlation between age at MRI (corrected for preterms) and FA and negative correlations with all diffusivities (MD, AD and RD). Figure 5 shows the proportion of streamlines that reached the auditory cortex from the brainstem through the thalamus versus when excluding the thalamus [1-(streamlines excluding thalamus/streamlines going through thalamus].

A visual 3D representation of the different pathways at different time points through the first postnatal year is depicted in Figure 6. The strength of connectivity (5000 * number of streamlines going through the waypoint/the number of voxels in the seed) was not found to increase significantly during the first postnatal year in any studied tract.

4 | DISCUSSION

Our results show that the thalamic route can be traced soon after birth, specifically as early as at 1 month, and that its fractional anisotropy (FA) is largely similar to the value at 9 months. This does not lend support to the idea that the thalamic route undergoes dramatic maturation around the 7th month (Eggermont & Moore, 2012; Marin-Padilla & Marin-Padilla, 1982), and suggests the sophisticated auditory behavior shown by infants in the first few months could be cortical. However, as would be expected from the myelination through the first year (Rice, Sell, & Hadley, 1991), there was evidence of continuing maturation of the pathway: FA showed a significant increment in the acoustic radiation and brainstem-Heschl's gyrus pathway (excluding the thalamus), and all diffusivities (mean diffusivity [MD], axial diffusivity [AD], and radial diffusivity [RD]) were found to decrease with age in the thalamic and brainstem routes. We believe that this is the first work that studies auditory structural development and maturation of these pathways in infants during the first postnatal year by means of diffusion weighted imaging.

In the contrary, in adults auditory structures involved in auditory processing are well established; in fact, it is known that auditory structures in the brainstem, the superior olivary complex and the inferior colliculus, transmit information to the medial geniculate nucleus in the posterior thalamus. The acoustic radiation then connects this thalamic structure with the auditory cortex in the temporal lobe. However, in infants, it has been proposed that there is another pathway directly connecting the brainstem to the auditory cortex, without passing through the medial geniculate nucleus that might transmit basic auditory information in the first postnatal months. Eggermont and Moore (2012), proposed an alternate pathway consisting of collaterals form lemniscal axons running into the reticular core of the brainstem, from which arises the reticular activating system pathway to layer I of the auditory cortex. Layer I axons consist mainly of Cajal-Retzius cells which reduce significantly from month 4.5 (Moore & Guan, 2001). According to this model, the reticular-auditory pathway is the only existing path to the auditory cortex at birth until around month 7, when thalamic projections from the medial geniculate nucleus reach layer I. This

TABLE 2 Group correlations (*n* = 11) between corrected age at magnetic resonance imaging and overall or specific white matter indexes controlled by gestational age at birth

|	Through development (age at MRI)		
Variables	White matter index[a]	Statistics (Spearman's rho)	*p* corrected
Overall white matter			
	FA	0.81	**<0.01**
	MD	−0.91	**<0.01**
	AD	−0.91	**<0.01**
	RD	−0.91	**<0.01**
Specific white matter tracts			
Thalamic-HG (acoustic radiation)	FA	0.64	**0.05**
	MD	−0.60	0.07
	AD	−0.49	0.15
	RD	−0.70	**0.02**
Brainstem-HG-through the thalamus	FA	0.61	0.06
	MD	−0.94	**<0.01**
	AD	−0.82	**<0.01**
	RD	−0.97	**<0.01**
Brainstem-HG-excluding the thalamus	FA	0.77	**<0.01**
	MD	−0.94	**<0.01**
	AD	−0.82	**<0.01**
	RD	−0.98	**<0.01**

[a]Diffusivity units are mm^2/s.
AD, axial diffusivity; HG, Heschl's gyrus; FA, fractional anisotropy; MRI, magnetic resonance imaging; RD, radial diffusivity.
Bold values indicate a *p*-value less than 0.05.

reflects an anatomical turning point, when the acoustic radiation becomes more dominant for auditory processing. In fact, auditory detection has been attributed to the reticular activating system pathway whereas fine auditory perception, such as native language phoneme discrimination, is dependent on the auditory radiation (Moore & Linthicum, 2007; Moore, Perazzo, & Braun, 1995).

In order to evaluate empirically the above mentioned hypotheses related to the development of structural auditory pathways in infants, in this study we investigated the topography of auditory pathways using tractography (Ramnani, Behrens, Penny, & Matthews, 2004). Both the acoustic radiation and the brainstem-Heschl's gyrus pathway were found already in the first month of postnatal life. These findings
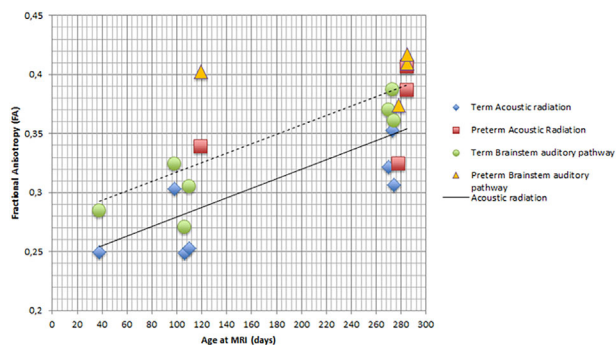
FIGURE 4 Fractional anisotropy development in the two pathways of interest: the acoustic radiation and brainstem-HG (including the thalamus) in the preterm group (red and orange colors represent the acoustic radiation and the brainstem auditory pathway respectively) and in the term group (blue and green colors depict the acoustic radiation and the brainstem-HG pathway respectively). Age at MRI has been corrected for prematurity
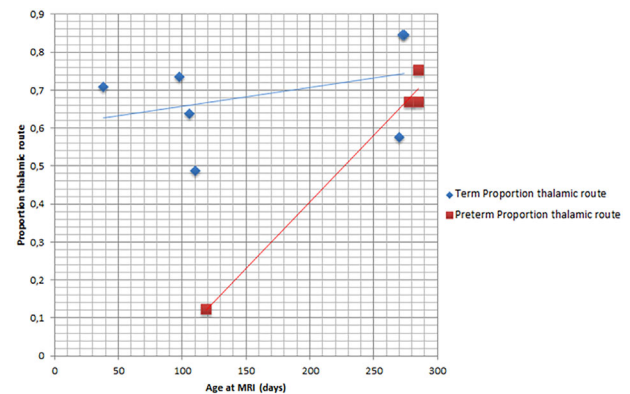
FIGURE 5 Proportion of streamlines from the brainstem to auditory cortex that passed through the thalamus, as a function of age in the preterm group (red color) and in the term group (blue color). Age at MRI is corrected for prematurity
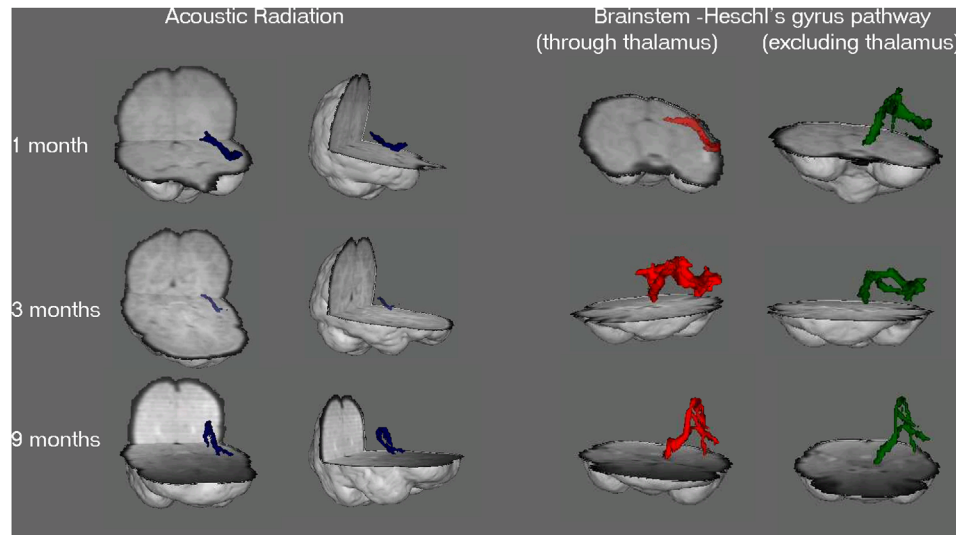
FIGURE 6 Probabilistic tractography results in a 1 month, 3 month, and 9 month old infant (only left hemisphere tractography is shown). The acoustic radiation is represented in blue whereas the brainstem pathway is depicted in red (through the thalamus) and green (excluding the thalamus)

are consistent with previous histochemical studies that have found evidence of thalamo-cortical afferents reaching the cortical plate after the 24th postconceptional week (Kostović & Judas, 2010; Kostović et al., 2002).

Early organization of these pathways precedes myelination. These structural connections to auditory cortex become progressively mature and functionally efficient throughout the myelination process. The sequence of postnatal myelination in the human central nervous system follows a specific pattern: (1) from the central sulcus outwards to the poles, with the posterior sites preceding anterior fronto-temporal regions, (2) proximal component earlier than distal one, (3) primary sensory pathways earlier than motor pathways and (4) projection pathways before association pathways (Kinney, Brody, Kloman, & Gilles, 1988). Thus, brainstem auditory pathways mature earlier than the acoustic radiation around the 27–29th postconceptional week. In our study, the structural connectivity of the brainstem to the auditory cortex was found to strengthen in the first postnatal year, not showing any downward trend as was expected following what other authors have reported (Eggermont & Moore, 2012). The acoustic radiation shows a later and slower myelination starting after the 5th month and reaching maturity by the 18th month, which coincides with vocabulary growth in infants (Pujol et al., 2006). However, we found evidence of primary organization as early as 1 month and an FA increment during the first postnatal year—in agreement with other influential findings (Huttenlocher & Dabholkar, 1997; Kostović et al., 2002; Krmpotić-Nemanić et al., 1983). Those FA increments observed, could imply changes in the organization of this tract, changes in myelination, or both. We found significant decreases of RD along the first postnatal year, thus, our results might suggest changes in myelination since RD changes have been related to

myelination alterations (Song et al., 2005). Further studies, using diffusion-weighted magnetic resonance imaging, are needed to elucidate the developmental trends of both pathways through childhood.

To our knowledge this is the first diffusion-weighted magnetic resonance imaging study using a diffusion sequence with 128 directions in neonates to provide insight into the structural auditory pathways during the first postnatal months (Heemskerk et al., 2013). Our discovery that auditory tracts are mature fits well with the evidence that auditory function is in many ways quite mature in the first postnatal year. For example, it has been demonstrated by means of event-related potentials that newborns are able to discriminate wide frequency spectrum sounds and novelty in acoustic stimulation (Kushnerenko et al., 2007), as well as repeated auditory feature conjunctions (Ruusuvirta, Huotilainen, Fellman, & Naatanen, 2004). Moreover, the correct development of these auditory processing skills will predict a proper language development (Guzzetta et al., 2011). Regarding functional magnetic resonance imaging (MRI) studies, it has been reported that the sensorimotor/auditory networks mature early showing low inter-subject variability during the first year and are among the first to evidence an adult-like pattern (Gao et al., 2014, 2015; Gao, Lin, Grewen, & Gilmore, 2016). In fact, our group (Wild et al., 2017) found complex adult-like features represented in auditory cortex during the first postnatal month. However, although the function of auditory cortex shows adult-like features it is unlikely to be completely mature; specifically, the acoustic radiation, which receives input early in life but continues maturing until the third postnatal year (Dubois et al., 2014). Therefore, further studies should be carried out in order to investigate the structural and functional development of the auditory pathways beyond the first postnatal year.

One limitation of the present study is the small sample size, but it should be noted that the data obtained were of extremely high quality (Figure 1), and represent an existence proof of the maturity of the thalamo-cortical pathway at 1 month. Another limitation is that we only measured the structure of the pathways, and not auditory function. Other studies have focused on the association between white matter maturation in the auditory cortex and single-cell electrophysiology in animal models, or used other techniques (i.e., Magnetoencephalography, Electroencephalography) to examine the development of human auditory cortex function during both typical and atypical development (Edgar et al., 2015; Kikuchi, Yoshimura, & Minabe, 2015; Roberts et al., 2009; Roberts, Lanza, Dell, Qasmieh, & Hines, 2014). Future multimodal studies, therefore, are needed in order to follow the specific development of these pathways and relate them with the development of auditory processing abilities. Moreover, in this study both very preterm (according to their mean gestational age) and term infants were included. It is worth noting that all the correlations included age at MRI corrected for prematurity and gestational age (GA) as covariate. However, perinatal variables associated to prematurity could have influenced the maturation of the central auditory pathway as previously reported (Stipdonk et al., 2016). Finally, in the current study we did not consider the possible influence of gray matter maturation on auditory processes' development, which is known to show rapid growth during the first postnatal year (Gilmore et al., 2012) coinciding with a rapid postnatal development of dendritic trees, dendritic branching, spines and synapsis (Elston & Fujita, 2014). Further studies will be needed aiming to understand the gray matter and white matter processes underlying development of auditory pathways, as well as, the possible effects of auditory development on language acquisition in larger samples.

In summary, our study has yielded valuable insight into the development of auditory pathways in infants. We found early organization of both the acoustic radiation and brainstem-Heschl's gyrus pathway as early as 1 month, but continued maturation as indexed by FA during the first postnatal year. We found no evidence of decreasing FA in the brainstem auditory pathway during the first postnatal year.

ACKNOWLEDGMENTS

CONFLICTS OF INTEREST

None.

ORCID

Leire Zubiaurre-Elorza http://orcid.org/0000-0001-9830-3939

REFERENCES

Andersson, J. L. R., Skare, S., & Ashburner, J. (2003). How to correct susceptibility distortions in spin-echo echo-planar images: Application to diffusion tensor imaging. *NeuroImage*, 20(2), 870–888. https://doi.org/10.1016/S1053-8119(03)00336-7

Ball, G., Srinivasan, L., Aljabar, P., Counsell, S. J., Durighel, G., & Hajnal, J. V. (2013). Development of cortical microstructure in the preterm human brain. *Proceedings of the National Academy of Sciences of the United States of America*, 110(23), 9541–9546. https://doi.org/10.1073/pnas.1301652110

Bates, E., Thal, D., Finlay, B., & Clancy, B. (2002). Early language development and its neural correlates. In F. Boller, J. Grafman, S. J. Segalowitz, & I. Rapin (Eds.), *Handbook of neuropsychology*, *Vol. 8: Child neurology* (pp. 109–176). Amsterdam: Elsevier Science B. V.

Behrens, T. E. J., Berg, H. J., Jbabdi, S., Rushworth, M. F. S., & Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *NeuroImage*, 34(1), 144–155. https://doi.org/10.1016/j.neuroimage.2006.09.018

Davis, M. H., & Johnsrude, I. S. (2003). Hierarchical processing in spoken language comprehension. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 23(8), 3423–3431. https://doi.org/10.23/8/3423 [pii]

Dehaene-lambertz, G., & Dehaene, S. (1994). Speed and cerebral correlates of syllable discrimination in infants. *Nature*, 370(6487), 292–295.

Deoni, S. C. L., Mercure, E., Blasi, A., Gasston, D., Thomson, A., Johnson, M., . . . Murphy, D. G. M. (2011). Mapping infant brain myelination with magnetic resonance imaging. *Journal of Neuroscience*, 31(2), 784–791. https://doi.org/10.1523/JNEUROSCI. 2106–10.2011

Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., Hüppi, P. S., & Hertz-Pannier, L. (2014). The early development of brain white matter: A review of imaging studies in fetuses, newborns and infants. *Neuroscience (v Tisku), Dostupné Z*, 1–24. https://doi.org/10.1016/j.neuroscience.2013.12.044

Edgar, J. C., Murray, R., Kuschner, E. S., Pratt, K., Paulson, D. N., Dell, J., . . . Elston, G. (2015). The maturation of auditory responses in infants and young children: A cross-sectional study from 6 to 59 months. *Front Neuroanat*, 9, 131. https://doi.org/10.3389/fnana.2015.00131

Eggermont, J. J., & Moore, J. K., (2012). Morphological and functional development of the auditory nervous system. In L. A. Werner, R. R. Fay, & A. N. Popper (Eds.), *Human auditory development*. (pp. 61–105).New York, NY: Springer Handbook 61 of Auditory Research, Springer Science + Business Media, https://doi.org/10.1007/978-1-4614-1421-63

Elston, G. N., & Fujita, I. (2014). Pyramidal cell development: Postnatal spinogenesis, dendritic growth, axon growth, and electrophysiology. *Front Neuroanat*, 8, 1–20. https://doi.org/10.3389/fnana.2014.00078

Gao, W., Alcauter, S., Elton, A., Hernandez-castillo, C. R., Smith, J. K., Ramirez, J., & Lin, W. (2015). Functional network development during the first year: Relative sequence and socioeconomic correlations. *Cerebral Cortex*, 25(9), 2919–2928. https://doi.org/10.1093/cercor/bhu088

Gao, W., Elton, A., Zhu, H., Alcauter, S., Smith, J. K., Gilmore, J. H., & Lin, W. (2014). Intersubject variability of and genetic effects on the brain's functional connectivity during infancy. *The Journal of Neuroscience*, 34(34), 11288–11296. https://doi.org/10.1523/JNEUROSCI.5072–13.2014

Gao, W., Lin, W., Grewen, K., & Gilmore, J. H. (2016). Functional connectivity of the infant human brain: Plastic and modifiable. *Neuroscientist*, https://doi.org/10.1177/1073858416635986

Gilmore, J. H., Shi, F., Woolson, S. L., Knickmeyer, R. C., Short, S. J., Lin, W., . . . Shen, D. (2012). Longitudinal development of cortical and subcortical gray matter from birth to 2 years. *Cerebral Cortex*, 22(11), 2478–2485. https://doi.org/10.1093/cercor/bhr327

Guzzetta, F., Conti, G., & Mercuri, E. (2011). Auditory processing in infancy: Do early abnormalities predict disorders of language and cognitive development?. *Developmental Medicine & Child Neurology*, 53(12), 1085–1090. https://doi.org/10.1111/j.1469-8749.2011.04084.x

Heemskerk, A. M., Leemans, A., Plaisier, A., Pieterman, K., Lequin, M. H., & Dudink, J. (2013). Acquisition guidelines and quality assessment tools for analyzing neonatal diffusion tensor MRI data. *AJNR American Journal of Neuroradiology*, 34(8), 1496–1505. https://www.ncbi.nlm.nih.gov/pubmed/23518355

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology*, 387(2), 167–178.

Johnson, M. H. (2001). Functional brain development in humans. *Nature Rev Neurosci*, 2, 475–483. https://doi.org/10.1038/35081509

Kikuchi, M., Yoshimura, Y., & Minabe, Y. (2015). *Autism spectrum disorder*. (pp. 74–88). https://doi.org/10.1111/pcn.12338

Kinney, H. C., Brody, B. A., Kloman, A. S., & Gilles, F. H. (1988). Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. *Journal of Neuropathology*, 47(3), 217–234. http://journals.lww.com/jneuropath/Abstract/1988/05000/Sequence_of_Central_Nervous_System_Myelination_in.3.aspx

Kostović, I., & Judas, M. (2010). The development of the subplate and thalamocortical connections in the human foetal brain. *Acta Paediatrica (Oslo, Norway: 1992)*, 99(8), 1119–1127. https://doi.org/10.1111/j.1651-2227.2010.01811.x

Kostović, I., Judas, M., Rados, M., & Hrabac, P. (2002). Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. *Cerebral Cortex (New York, N.Y.: 1991)*, 12(5), 536–544. http://www.ncbi.nlm.nih.gov/pubmed/11950771

Krmpotić-Nemanić, J., Kostović, I., Kelović, Z., Nemanić, D., & Mrzljak, L. (1983). Development of the human fetal auditory cortex: Growth of afferent fibres. *Acta Anatomica*, 116(1), 69–73.

Kushnerenko, E., Winkler, I., Horvth, J., Ntnen, R., Pavlov, I., Fellman, V., & Huotilainen, M. (2007). Processing acoustic change and novelty in newborn infants. *European Journal of Neuroscience*, 26(1), 265–274.

Marin-Padilla, M., & Marin-Padilla, T. (1982). Origin, prenatal development and structural organization of layer I of the human cerebral (motor) cortex. *Anatomy and Embryology*, 164, 161–206.

Mills, M., & Melhuish, E. (1974). Recognition of mother's voice in early infancy. *Nature*, Retrieved from https://www.nature.com/nature/journal/v252/n5479/abs/252123a0.html

Moore, J. K., Perazzo, L. M., & Braun, A. (1995). Time course of axonal myelination in the human brainstem auditory pathway. *Hearing Research*, 87, 21–31.

Moore, J. K., & Guan, Y.-L. (2001). Cytoarchitectural and axonal maturation in human auditory cortex. *Journal of the Association for Research in Otolaryngology*, 2(4), 297–311. https://doi.org/10.1007/s101620010052

Moore, J. K., & Linthicum, F. H. (2007). The human auditory system: A timeline of development. *International Journal of Audiology*, 46(9), 460–478. https://doi.org/10.1080/14992020701383019

Pujol, J., Soriano-Mas, C., Ortiz, H., Sebastián-Gallés, N., Losilla, J. M., & Deus, J. (2006). Myelination of language-related areas in the developing brain. *Neurology*, 66(3), 339–343. https://doi.org/10.1212/01.wnl.0000201049.66073.8d

Ramnani, N., Behrens, T. E. J., Penny, W., & Matthews, P. M. (2004). New approaches for exploring anatomical and functional connectivity in the human brain. *Biological Psychiatry*, 56(9), 613–619. https://doi.org/10.1016/j.biopsych.2004.02.004

Rice, M., Sell, M., & Hadley, P. (1991). Social interactions of speech, and language-impaired children. *Journal of Speech, Language, and Hearing*, 34(6), 1299–1307. https://jslhr.pubs.asha.org/article.aspx?articleid = 1779078

Roberts, T. P. L., Khan, S. Y., Blaskey, L., Dell, J., Levy, S. E., Zarnow, D. M., & Edgar, J. C (2009). Developmental correlation of diffusion anisotropy with auditory-evoked response. *Neuroreport*, 20(18), 1586–1591. https://doi.org/10.1097/WNR.0b013e3283306854

Roberts, T. P. L., Lanza, M. R., Dell, J., Qasmieh, S., & Hines, K. (2014). NIH Public Access, 79–85. https://doi.org/10.1016/j.brainres.2013.09.011.Maturational

Ruusuvirta, T., Huotilainen, M., Fellman, V., & Naatanen, R. (2004). Newborn human brain identifies repeated auditory feature conjunctions of low sequential probability. *European Journal of Neuroscience*, 20(10), 2819–2821. https://doi.org/10.1111/j.1460-9568.2004.03734.x

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, 17(3), 143–155. https://doi.org/10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., . . . Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, 23(SUPPL. 1), 208–219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Song, S.-K., Yoshino, J., Le, T. Q., Lin, S.-J., Sun, S.-W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage*, 26(1), 132–140. https://doi.org/10.1016/j.neuroimage.2005.01.028

Sotiropoulos, S. N., Jbabdi, S., Xu, J., Andersson, J. L., Moeller, S., . . . Auerbach, E. J (2013). Advances in diffusion MRI acquisition and processing in the Human Connectome Project. *Neuroimage*, 80, 125–143.

Stipdonk, L. W, Weisglas-Kuperus, N., Franken, M. C., Nasserinejad, K., Dudink, J., & Goedegebure, A. (2016). Auditory brainstem maturation in normal-hearing infants born preterm: A meta-analysis. *Dev Med Child Neurol*, 58(10), 1009–1015. https://doi.org/10.1111/dmcn.13151

Tallal, P., & Gaab, N. (2006). Dynamic auditory processing, musical experience and language development. *Trends in Neurosciences*, 29(7), 382–390. https://doi.org/10.1016/j.tins.2006.06.003

Van Den Heuvel, M. P., Kersbergen, K. J., De Reus, M. A., Keunen, K., Kahn, R. S., Groenendaal, F., . . . Benders, M. J. N. L. (2015). The neonatal connectome during preterm brain development. *Cerebral Cortex*, https://doi.org/10.1093/cercor/bhu095

Weisglas-Kuperus, N., Hille, E. T., Duivenvoorden, H. J., Finken, M. J., Wit, J. M., . . . van Buuren, S. (2008). Intelligence of very preterm or very low birth weight infants in young adulthood. *Arch Dis Child Fetal Neonatal Ed*, 94(3), F196–F200. https://doi.org/10.1136/adc.2007.135095

Wild, C. J., Linke, A. C., Zubiaurre-Elorza, L., Herzmann, C., Duffy, H., Han, V. K., . . . Cusack, R. Adult-like processing of naturalistic sounds in auditory cortex by 3- and 9-month old infants. *Neuroimage*, 157, 623–634. https://dx.doi.org/10.1016/j.neuroimage.2017.06.038