WHEN DOES RIGHT FUNCTIONAL HEMISPHERIC LATERALIZATION ARISE? EVIDENCE FROM PRETERM INFANTS.

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In recent years, Magnetic Resonance Imaging (MRI) has allowed researchers to individuate an earlier morphological development of the right hemisphere compared to the left hemisphere before birth. Anatomical asymmetry, however, does not necessarily mean functional asymmetry and whether the anatomical differences between hemispheres at this early age are paralleled by functional specializations is still unknown. Here we show electrophysiological evidence of an early functional right lateralization for pitch processing arising by 30 gestational weeks, not before, in preterm newborns.

The presence of structural and functional hemispheric asymmetries at the early stages of life represents one of the main challenges for developmental neuroscience. Recently[1], by means of three-dimensional cortical folding reconstructions of preterm brains, it has been identified an early rightward anatomical asymmetry of the temporal lobe. Moreover, a marked transcriptional asymmetry of the *LMO4* gene was reported, with significantly higher expression levels in the right human cerebral cortex than in the left during gestation[2]. Taken together, these data suggest that the corresponding functional maturation may occur sooner in the right hemisphere (RH) than the left hemisphere (LH).

Nevertheless, although several behavioral and electrophysiological experiments have investigated the presence of functional hemispheric lateralization in infants[3-9], to date, only one study has focused on the emergence of functional lateralization before birth[10]. Schleussner *et al*. (2004) recorded brain magnetic auditory evoked fields in fetuses, reporting rightward cortical development in response to pitch stimuli (500 Hz tones) starting from the third trimester of gestation. These findings can be interpreted as proof of an anatomo-functional correlation between earlier RH development and right functional specialization of the auditory cortex. However, Schleussner and colleagues did not identify a specific time-point during the gestational development by which the RH dominance arises, since the gestational age of the fetuses was not specified in their study. Hence, a major question remains: ‘At what time do the hemispheres functionally differentiate along the ontogenetic course of human development?’

Premature birth represents a natural example allowing one to disentangle the early interaction between genetics and environmental factors in determining brain development, including the temporal relationship between structural and functional asymmetries. By investigating brain electrical activity in preterm newborns of different gestational ages it may be possible to verify whether the earlier right cortical maturation previously reported[1,11] is paralleled by a right functional lateralization when newborns are passively presented with auditory stimuli.

In this study the presence of lateralized electrical brain activity related to both pitch detection (1,000 Hz tones; p = 91%) and discrimination (2,000 Hz tones; p = 9%) was investigated using a frequency-change oddball experimental paradigm (**Fig. 1a**; more information can be found as **Supplementary Methods** on-line) in 34 healthy preterm newborns with normal hearing (23–34 gestational weeks; M = 29; S.D. = 2.9; the maturational characteristics of the newborns can be found as **Supplementary Table 1** online) recruited from the Neonatal Intensive Care Unit (NICU) of the Hospital of Padua. The families gave informed consent for these tests, which were carried out according to the local ethical committee. All the newborns were tested at the same post-conceptional age of 35 weeks; this was computed as the sum of the gestational age at birth and the period of extra-uterine life from birth to ERP recording. This age was chosen because it is usually the mean age at which newborns are discharged from the hospital. Furthermore, this allowed us to control for the confounding effects of subsequent environmental variables (i.e. the exposure to different socio-economical familiar contexts, *etc.*) on brain maturation. Two groups of 'Extremely Low Gestational Age' (ELGA, 23–29 weeks; N = 15) and 'Low Gestational Age' (LGA, 30–34 weeks; N = 19) were extracted to evaluate the effect of gestational age on the emergence of functional hemispheric asymmetries.

Group-averaged event-related potentials (ELGA versus LGA) for LH (T3 electrode) and RH (T4 electrode) are shown in **Fig. 1b** and **1c,** respectively for standard and deviant condition. In both the cases we observed a morphological complex characterized by a first positive and a second negative deflection, here defined as P1 and N2 respectively, according to their polarity and order of appearance. Furthermore, a sustained late negative response (LNR) characterized by a higher right voltage occurred about 300 ms from stimulus onset. Generally, LGA newborns showed higher ERP activity than ELGA ($F_{(1,32)} = 5.7$; $p = 0.023$) in all the time interval windows. More interestingly, the ANOVA revealed a significant group x hemisphere x time interval interaction ($F_{(4.27,136.81)} = 2.89$; $p = 0.022$). The Bonferroni *post-hoc* test confirmed that, both in standard and deviant conditions, ERP mean amplitudes were significantly higher at RH (T4) than LH (T3) and selectively in the interval windows between 350-400 ms ($p = 0.02$), 400-450 ms ($p = 0.01$), 450-500 ms ($p = 0.003$), 500-550 ms ($p = 0.002$), 550-600 ms ($p = 0.007$), 600-650 ms ($p = 0.002$) after stimulus onset. Conversely, in ELGA group (< 30 gestational weeks), there were no differences between the two hemispheres in any of the 50 ms interval windows compared. Generally, these findings confirm the results of Schleussner *et al*. (2004), showing that the earlier right functional maturation in fetal epoch[1,11] may parallel the early right structural development.

Different theories have been proposed to explain this early right lateralization. The main line of reasoning, suggests that the earlier structural asymmetry reported during fetal development[1,11] may underpin a different functional maturation of the left and the right temporal regions, presumably involved in processing different sound features. More specifically, temporal information would be dominantly processed in the LH, whereas spectral information would mainly involve the RH[12]. Starting from about 30 gestational weeks, the earlier RH maturation may bias the functional organization of the temporal cortex towards an early specialization for the non-linguistic domain (i.e., pitch processing), where spectral analysis is highly engaged. In support of this hypothesis we did not find any difference between hemispheres in infants born under 30 gestational weeks when they passively detected and discriminated non-verbal stimuli. Hence, under this age the temporal auditory neural network underlying auditory processing, even if active, does not functionally differentiate between hemispheres, since no measurable differences in electrical evoked activity are present.

An alternative interpretation of these data could be rely on the ‘right-hemisphere conservatism’ theory[13,14]. According to this view, the RH would sustain the functions necessary to the survival of the species, such as visuo-spatial or emotional processes. Consequently, earlier and faster development of the neural substrates underlying these functions would be needed in order to prevent a possible impairment during infancy and childhood. In this case, the higher RH activation would reflect a non-specific, pylogenetically-determined right dominance rather than a specific functional specialization for non-verbal processing. Further research, however, will be needed to disentangle these two hypotheses.

Whatever the model for the emergence and consolidation of structural and functional inter-hemispheric asymmetries, it is clear from our data that at a specific time-point along the course of ontogenetic development of the human being, about gestational week 30, the hemispheres start to functionally differentiate.

Finally, these data have important implications clinically, since early alteration of the normal hemispheric asymmetry in terms of both structural and functional development in extremely premature infants might be the basis of several neuro-cognitive impairments observed, especially during childhood[15].

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Author contributions

G.M and P.S.B. conceptualized, designed the experiment and wrote the paper. G.M. collected the data and performed the analyses. The neonatal neurological and neurophysiological screening was performed by A.S.

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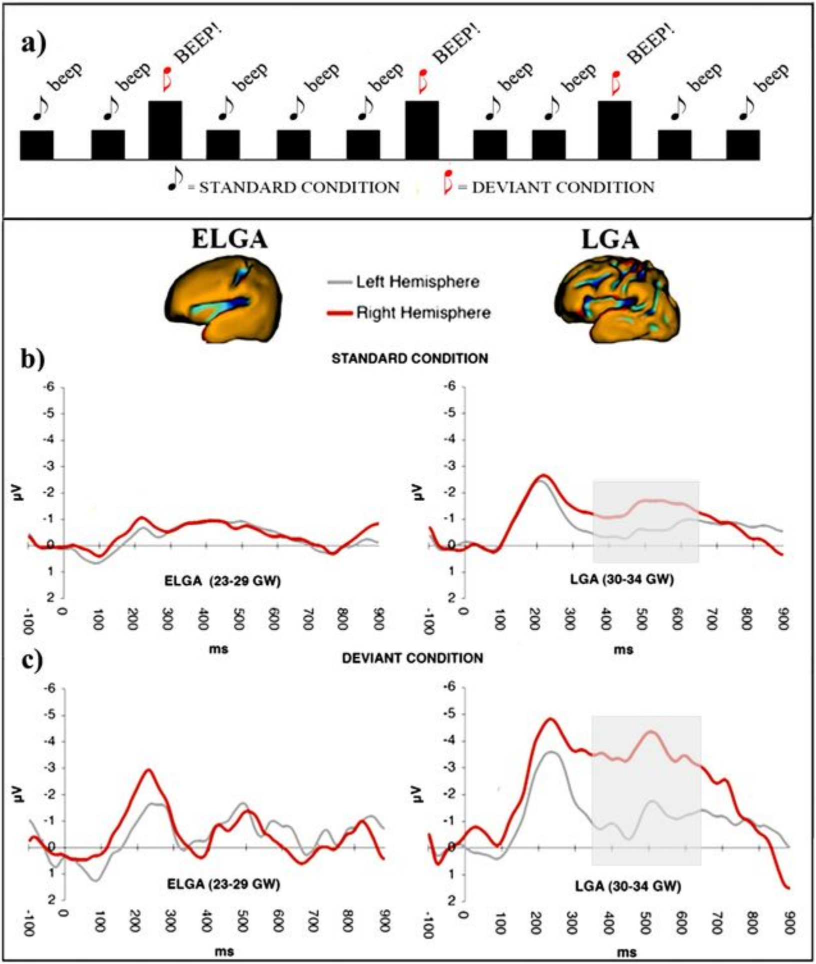
Figure 1. Experimental paradigm and ERPs.
a) Experimental paradigm: two sinusoidal tones of 1,000 Hz (standard condition; 91% of the total numbers of stimuli) and 2,000 Hz (deviant condition; 9% of the total number of stimuli) were randomly and binaurally delivered via headphones and with a random ISI between 1250-1850 ms.
b) Grand-averaged waveforms recorded from left (T3; gray line) and right (T4; red line) electrodes on standard trials in both ELGA (left panel) and LGA (right panel) newborns. The shaded area represents the time interval window significantly different between hemispheres. The upper pictures display the different degree of cortical folding in both ELGA and LGA preterm newborns (Adapted from: Dubois et al., 2007[1)].
c) Grand-averaged waveforms recorded from left (T3; gray line) and right (T4; red line) electrodes on deviant trials in both ELGA (left panel) and LGA (right panel) newborns. The shaded areas represent the time interval window significantly different between hemispheres.



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