Research Report

Sex differences in neural processing of speech in neonates

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ABSTRACT

The large majority of studies shows that girls develop their language skills faster than boys in the first few years of life. Are girls born with this advantage in language development? The present study used fNIRS in neonates to investigate sex differences in neural processing of speech within the first days of life. We found that speech stimuli elicited significantly more brain activity than non-speech stimuli in both groups of male and female neonates. However, whereas girls showed significant HbO changes to speech stimuli only within the left hemisphere, boys exhibited simultaneous neural activations in both hemispheres, with a larger and more significant fronto-temporal cluster in the right hemisphere. Furthermore, in boys, the variation in time-to-peak latencies was considerably greater than in girls. These findings suggest an earlier maturation of language-related brain areas in girls and highlight the importance of sex-specific investigations of neural language networks in infants.

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1. Introduction

In the first years after birth, girls show a well-documented advantage in language development compared to boys. Between the age of 8–30 months, girls are better than boys in word comprehension and word production, and sex differences in these skills increase up to the age of two years (Fenson et al., 1994; Galsworthy, Dionne, Dale, & Plomin, 2000). Two-to-six-year old girls have larger vocabularies, produce word combinations earlier, and perform better on pragmatic communication skills, including gestures, imitation, and eye contact (Bornstein, Hahn, & Haynes, 2004; Chipman & Hampson, 2007; Lutchmaya, Baron-Cohen, & Raggatt, 2002;
Ozcaliskan & Goldin-Meadow, 2010). These differences can be found across various languages, countries, and in urban as well as in rural areas (Bornstein & Cote, 2005; Eriksson et al., 2012). Even the social background does not affect language development of boys and girls equally: a low socio-economic status generally has a negative impact on children’s language skills, but more so in boys than in girls, suggesting that the boys’ language development may also be more vulnerable (Barbu et al., 2015).

It is well known that already infants and toddlers show left lateralized neural activations during language processing (Bortfeld, Fava, & Boas, 2009; Dehaene-Lambertz et al., 2006). During childhood, age-related increases in left lateralization of semantic and syntactic processing (Holland et al., 2007; Nunez et al., 2011; Szafiarski et al., 2012), of language production (Kadis et al., 2011), and of pitch perception (Y.Sato, Bortfeld, Fava, & Boas, 2009) have been described, while right hemisphere contributions to language processing seem to decrease over age (Olulade et al., 2020). This is also true for the lateralization of the arcuate fasciculus connecting relevant language areas, where a more leftward lateralization in children is associated with better verbal performance (Lebel & Beaulieu, 2009). These observations have led to the hypothesis that the functional lateralization increase reflects underlying maturation processes of language-associated brain areas (Herve, Zago, Petit, Mazoyer, 2013; Plante, Almyryde, Patterson, Vance, & Asbjornsen, 2015).

Correspondingly, several neuroimaging studies in healthy children have found more left language lateralization being associated with better language functioning in most (Berl et al., 2010, 2014; Everts et al., 2009; Groen, Whitehouse, Badcock, & Bishop, 2012), though not all studies (Lidzba, Schwiling, Grodd, Krageloh-Mann, & Wilke, 2011). Atypical functional symmetry or even right-ward asymmetry of language-associated areas has been furthermore described in various neurodevelopmental diseases associated with language deficits, including autism (Postema et al., 2019), specific language impairment (Badcock, Bishop, Hardiman, Barry, & Watkins, 2012), and dyslexia (Xu, Yang, Siok, & Tan, 2015). These findings support the hypothesis of a relationship between language lateralization and language functioning.

It remains, however, unclear from these studies if there are sex differences in functional language localization during childhood. A comprehensive literature review on sex differences in brain and language development (Etchell et al., 2018) shows contradictory findings and limited evidence for sex differences in brain structures and functions associated with language processing. However, few of these reviewed studies included language proficiency in their analyses (e.g., Blanton et al., 2004; Preis, Jancke, Schmitz-Hillebrecht, & Steinmetz, 1999; Tanaka-Arakawa et al., 2015), or more importantly, tested children under 30 months of age (Su, Kuan, Kaga, Sano, & Mima, 2008). Considering the fact that language related differences between girls and boys mainly occur before the age of 30 months, it appears necessary to include children under this age when examining sex-specific differences in language-related brain structures.

This raises the question: Are sex-related differences in language processing and language-associated areas already present at the very early beginning of language development? Identifying sex differences in speech discrimination as early as possible in life, where the influence of cultural factors is still limited, would shed light on very early differences in language processing and maturation processes of language-associated brain areas in girls and boys, and would underline the hypothesis that biological factors rather than environmental factors are responsible for these early differences.

While still in the womb, fetuses can already identify their mothers’ voices (Kislevsky et al., 2003). Using fNIRS, it is possible to measure the neonate’s brain activity during the processing of speech stimuli right after birth in a natural setting, i.e. in the crib. One of the pioneering fNIRS studies has shown that the infant’s brain responds with a stronger left-lateralized activity to forward stimuli (Peña et al., 2003). An fMRI study measuring speech processing in three-month old infants obtained similar results (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002). While further fNIRS studies in neonates also confirmed a left-lateralized processing of speech stimuli (Bartha-Doering et al., 2019; H. Sato et al., 2012), others suggested more bilateral language processes at this early stage of development, or different localization for different linguistic aspects (May, Byers-Heinlein, Gervain, & Werker, 2011; Telkemeyer et al., 2009). However, none of these studies took into account sex differences, and sometimes even the number of boys and girls included was not balanced or mentioned. In adults, EEG studies exhibit consistent sex differences in latency of auditory processing during speech perception and production, with earlier latency of auditory evoked responses for female compared to male participants (Li et al., 2018; Scheerer, Liu, & Jones, 2013; Swink & Stuart, 2012). Neuroimaging studies in adults show, however, inconsistent findings of sex differences in brain areas involved in language processing (for a comprehensive review, please see (M. Sato, 2020). Yet, as most sex effects in language development are only obvious during early childhood, sex differences in lateralization and localization of language-associated brain areas may only be present in the first years of life.

This study therefore used fNIRS to investigate sex differences in the localization, lateralization, and dynamics of brain areas underlying speech discrimination in a large sample of neonates within the first days after delivery. Since earlier studies (Gervain et al., 2011; Lloyd-Fox, Blasi, & Elwell, 2010) have shown that the concentration of oxyhemoglobin (HbO) is the strongest indicator for neural responses in the neonatal fNIRS, we focused our analyses on HbO signal changes. We perform cluster-based and mean response analyses to investigate group differences, and we evaluated latencies of hemo-dynamic changes to investigate sex differences in the dynamics of cognitive processing. In the light of some studies revealing better language abilities in young girls compared to boys and others pointing to an association of left hemisphere lateralization with better language functioning, we hypothesized to find an earlier and stronger left lateralized activity during speech discrimination in female compared to male neonates.
2. Methods

2.1. Participants

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

We collected fNIRS data in 52 (27 female) neonates born at the Division of Neonatology, Pediatric Intensive Care and Neuropediatrics of the Medical University of Vienna. Seven subjects had to be excluded from further analyses due to excessive movement during fNIRS data collection (i.e., if more than half of the trials were objectively determined to be affected by motion artifact). All infants met the following inclusion criteria: 1) normal auditory evaluation as measured by auditory brainstem response; 2) normal neurological findings including normal clinical examination and normal head ultrasound scan; 3) gestational age (GA) at birth >32 weeks; 4) birth weight >1.5 kg; 5) both parents native speakers of German; 6) normal language and reading development in both parents as evaluated by questionnaire; 7) no chromosomal or congenital anomalies. The study was conducted in accordance with the Declaration of Helsinki (1973, revised in 1983) and approved by the Ethics Committee of the Medical University of Vienna. Written informed consent was obtained prior to the experiment from one parent in all children.

The remaining 22 male and 23 female infants did not differ in terms of GA at birth, weight, length, and head circumference (for all $p > 0.60$). Time between birth and measurement, i.e. the age of the female (mean = 2.83 days, SD = 4.57) and male infants (mean = 2.77 days, SD = 2.58), did also not differ between the two groups ($t = .061, p = .952$). All infants had an Apgar score at 5 min of ≥9 (for details see Table 1). In addition, type of delivery (Cesarean vs vaginal) was not different between male and female neonates ($U = 249.00, p = .917$).

2.2. fNIRS paradigm

A well-known speech discrimination paradigm using backward and forward speech segments was used. This paradigm has proven speech discrimination abilities in neonates, infants, and adults and has shown robust activations in temporal and frontal brain areas (Bartha-Doering et al., 2019; Dehaene-Lambertz et al., 2002; Peña et al., 2003; Perani et al., 1996; H. Sato et al., 2012).

Auditory stimuli consisted of speech samples collected by recording a female speaker reciting a children’s story using infant-direct speech (Lobe & Weigel, 1972). The speech samples were edited into 15 sec sequences with well-formed prosodic units (mean pitch 233 Hz, mean intensity 70 dB) and each sequence was then reversed, resulting in a total of 10 native (forward) speech stimuli and 10 backward speech stimuli with the same phonetic features, but with distorted semantic and prosodic information. The presentation of backward and forward speech stimuli was counterbalanced, and each sequence was followed by silence with randomized length (15–30 sec). The total stimulation was 600–900 sec or a maximum of 15 min. A detailed description of the fNIRS paradigm was given previously (Bartha-Doering et al., 2019).

2.3. fNIRS data acquisition

Hemodynamic responses were acquired using an ETG-4000 optical topography system (Hitachi Medical Corporation, Japan) with 10 fibers for emission and 8 fibers for detection, resulting in a total of 24 channels at a sampling rate of 10Hz. The separation between emitters and detectors was 2 mm. The laser diodes emitted near infrared light at two different wavelengths, 695 and 830 nm respectively, and total laser power was set at .75 mW. The optical fibers were embedded in soft silicon cushions designed for use in neonates (Hitachi Neonate Probes). The optical fibers were placed on the head of the neonate and positioned directly above the ear. The bilateral preauricular points were used as the reference to align the bottom finger of the probe (channels 3, 6, 8, and 11 in the left hemisphere; channels 17, 19, 22, and 24 in the right hemisphere) with the temporal areas (T3 to T5 and T4 to T6 lines in the left and right hemispheres, respectively).

Infants were tested in a quiet, dimly lit room within the neonatal ward and were lying in their cribs in a state of regular or irregular sleep. One parent attended the measurement standing or sitting next to the cribs. The position of the head was supported with a gauze diaper to ensure a straight posture of head and neck. The stimuli were presented using two loudspeakers positioned at a distance of approximately 2m in front of the baby and an angle of 30° from the infant’s head.

Table 1 – Study participants.

|                        | Female (N = 23) |                  | Male (N = 22) |                  | T     | p     |
|------------------------|----------------|-----------------|---------------|-----------------|-------|-------|
|                        | Median Mean*   | SD               | Range         | Median Mean     | SD    | Range |
| GA at birth, weeks     | 38.28          | 1.89             | 34.14–40.86   | 38.02           | 1.91  | 34.43–41.29 |
| GA at test, weeks      | 38.80          | 1.64             | 36.00–41.01   | 38.61           | 1.52  | 36.00–41.43 |
| HC at birth, mm        | 33.96          | 1.68             | 30.5–37       | 34.18           | 1.77  | 31–38   |
| Birth weight, g        | 2972.26        | 565.49           | 1950–3940     | 2911.50         | 591.58| 1840–3940 |
| Birth height, mm       | 49.61          | 2.66             | 44–54         | 49.41           | 3.11  | 44–56   |
| Apgar score at 1 min   | 9              | 8–10             |               | 9               | 7–10  | –278   |
| Apgar score at 5 min   | 10             | 8–10             |               | 10              | 8–10  | .055   |
| Apgar score at 10 min  | 10             | 9–10             |               | 10              | 9–10  | .626   |

* Mean is given in metric data, median in ordinal data; GA = gestational age; HC = head circumference.
2.4. Data processing

FNIRS data were pre-processed using open source software HOMER2 on MATLAB (R2013b, Mathworks, Natick, MA) (Huppert, Diamond, Franceschini, & Boas, 2009). Raw signals were first converted into optical density. Channels with very high or very low optical density and channels with low signal to noise ratio were removed from individual participants’ datasets. Motion artifacts were corrected using targeted principal component analysis (PCA), where PCA was applied on segments of data identified as motion artifacts (Yucel, Selb, Cooper, & Boas, 2014). Components accounting for 97% of covariance of data were filtered out. Remaining artifact segments that could not be corrected were automatically identified and corresponding trials were rejected. On average we excluded .58 (± 1.10) forward sequences and 6.2 (± 1.10) out of 10 backward sequences. There was no significant difference in the number of sequences excluded between the two conditions (t = −.321; p = 0.750). Next, data were low-pass filtered to .5 Hz.

Optical densities were converted into changes in the concentration of HbO and deoxyhemoglobin (HbR) using the modified Beer–Lambert law. Newborn appropriate differential path-length factor (DPF) values were calculated using a general equation relating the DPF with age and wavelength: DPF (695 nm) = 5.31, DPF (830 nm) = 4.67 (Scholkmann & Wolf, 2013). Responses were baseline corrected by removing the mean signal of the 5 sec preceding the stimulus. The hemodynamic response function (HRF) was extracted for each subject, channel, and condition by calculating the mean response from 5 preceding the stimulus to 25 sec post stimulus onset. Averaged HRF were subjected to further analysis.

2.5. Data analysis

2.5.1. Cluster based permutation analysis

The Nonparametric cluster-based permutation on the hemodynamic response of the HbO signal was performed to examine whether male and female neonates responded differently to the two speech conditions over the entire time interval of 25s after stimulation and each individual channel. The nonparametric cluster-based permutation tests are an approach to deal with the multicomparison problem while preserving the multidimensional nature of spatiotemporal analysis. In a two-step process, (1) the clusters were identified to summarize the large amount of data, and (2) then the resulting cluster structure is compared to the clusters constructed under the null hypothesis which assumes that the data in the two conditions are interchangeable. Thus, to identify clusters, we ran individual t-tests between speech forward and speech backward condition for each pair of channels and for each time point (sampling rate was 10Hz), separately for each hemisphere. Samples (every channel/time pair) were considered temporally adjacent when they were consecutive and spatially adjacent when corresponding channels were adjoining and assignable to one common optode. The t-score threshold for the cluster was ± 2.36 (which corresponds to a conventional alpha = .05 p-value). All samples whose t-score exceeded this threshold were selected. Two pairs of samples were clustered when exceeding this predefined threshold and when they were temporally consecutive and spatially adjacent. Next, to calculate cluster statistics, clusters were quantified by summing the t-value of every data point included in the cluster. Clusters with a maximum t-value were then taken and a permutation test was used to calculate whether this cluster belonged significantly to one condition and not to the other. To this end, all trials of the speech forward and speech backward condition were combined and randomly assigned to subset 1 or subset 2 and test statistics was run on these random partitions. This procedure was repeated a 2000 times to estimate the p-value using the Monte Carlo method. The estimated p-value is the proportion of random partitions where the test statistics is greater than the actually observed test statistics (Maris & Oostenveld, 2007). Since the second step is only calculated with the summarized data or the cluster size, conclusions can be drawn related to differences between condition but not about the exact spatial or temporal differences in the data (Sassenhagen & Draschkw, 2019).

2.5.2. Mean response calculation

Based on visual inspection of grand-averaged activation pattern and previous studies, we calculated the mean response in the time period 5–15 sec post stimulus onset. To assess laterality effects, mean response of channels of the right and left hemisphere were compared. A repeated measure ANOVA with between-subject factor group (male/female) and within-subject factors condition (speech forward/speech backward) and hemisphere (left/right) was used to determine statistically significant differences in hemodynamic responses to speech forward and speech backward stimuli. Next, we calculated paired-sample t-test for each channel between the two conditions within each group. Benjamin-Hochberg procedure was applied to correct for multiple comparison. Kolmogorov–Smirnov and Levene inspections were employed to ensure the normality and homogeneity of variances. Simple linear regression was used to test if GA at birth had a significant influence on speech discrimination abilities, with speech discrimination being defined as the difference in HbO concentration change following speech forward versus speech backward. The significance threshold was set to p ≤ .05. Analyses were carried out with IBM SPSS Statistics 19 software (IBM Corp., Armonk, NY, USA).

2.5.3. Latency analysis

To measure hemodynamic response latency differences, a jackknife approach was applied with latency differences being estimated using a threshold-crossing method, i.e. the time when the HRF exceeds a certain threshold. The jackknife approach yields more accurate estimates of latency differences, since it is less prone to noise in the data and it has proven its superiority over the individual subject approach in ERP research and recently also in the estimation of latency differences in the hemodynamic response in FNIRS (Kiesel, Miller, Jolicoeur, & Brisson, 2008; Maheux et al., 2017). For the jackknife, we calculated n grand averages, whereas each grand average HRF is calculated with one subject being left out (n-1). Next, to estimate the differences in onset times we collected the first time point at which the HRF for both conditions increases above 70% of the peak value in each of the n-
1 (jackknifed) grand averages. The threshold of 70% was chosen based on previous research with fNIRS data (Maheux et al., 2017). We next calculated the latency differences between right and left hemisphere. To calculate appropriate t-values, the jackknife standard error of onset time was calculated using the formula suggested by Miller, Patterson, and Ulrich (1998), where $D_{-1}$ is the difference in latency onset and $J$ is the mean of these differences obtained in each of the grand averages:

$$\text{SD} = \sqrt{\frac{n-1}{n} \sum_{i=1}^{n} (D_{-1} - J)^2}$$

3. Results

3.1. Cluster based permutation analysis

The nonparametric cluster-based permutation analysis investigating hemodynamic responses over the epoch of 0–25 msec post-stimuli per group yielded significant cluster in both groups with stronger activation in the speech forward compared to the speech backward condition. In the group of female infants, we found one significant cluster comprising channels 5 and 7 ($p = .02$). This cluster covered parts of the inferior parietal lobe in the left hemisphere. Male infants exhibited a large fronto-temporal cluster within the right hemisphere comprising channels 18, 19, 21, 23, and 24 ($p = .01$).

3.2. Mean response calculation

Repeated measures ANOVA revealed a significant main effect on HbO concentration changes for the factor condition ($F\ (1,43) = 4.481, p < .04, \eta^2 = .094$), but no significant difference between hemispheres ($F\ (1,43) = 2.198, p = .145, \eta^2 = .049$) and groups ($F\ (1,43) = .165, p = .686, \eta^2 = .004$). Regardless of sex and hemisphere, speech forward stimuli (mean = .022, SD = .03) were associated with an increase in HbO concentration compared to speech backward stimuli (mean = -.005, SD = .028). Furthermore, an interaction between hemisphere and condition was observed ($F\ (1,43) = 3.87, p = .05, \eta^2 = .168$) with boys exhibiting a significantly stronger differentiation between conditions within the right hemisphere ($t = -2.195, p = .034, d = .66$), which was not observable within the left hemisphere ($t = .554, p = .583, d = -.17$; Fig. 1). In the group of female neonates, a significant difference between speech forward and speech backward stimuli was observed in the left hemisphere ($t = 2.073, p = .05, d = .60$), but not in the right hemisphere ($t = -.541, p = .594, d = .17$; Fig. 1). A comparison of the averaged response to speech forward and speech backward per channel revealed a significant difference in the left hemisphere in channels 5 and 7 (Figs. 2 and 3). Male neonates demonstrated greatest differences in the right hemisphere, nevertheless, channel-wise comparison revealed a significant difference in channels 15, 17, 18, 19, and 23 over the right hemisphere and channels 3 and 6 over the left hemisphere.

Repeated measures ANOVA on HbR concentration changes revealed no significant main effects (all $> .368, \eta^2 < .019$) nor a significant interaction effect ($F\ (1,43) = .441, p = .510, \eta^2 = .010$). Furthermore, regression analysis showed that GA at birth did not significantly predict speech discrimination, neither in the left ($R^2 = .010, b = -.059, p = .701$) nor in the right hemisphere ($R^2 = .003, b = -.79, p = .365$) hemisphere.

3.3. Latency analysis

The HRF latencies in the left hemisphere of girls (mean = 6.89 sec, SD = 1.31) were not significantly different to the left hemisphere latencies in boys ($p > .05$) nor to the right hemisphere in girls (mean = 8.40 sec, SD = 1.00). In male neonates, there was a delay of HRF peaks in the right compared to the left hemisphere, but the difference in the time-to-peak means between left (mean = 5.09 sec, SD = 3.87) and right hemisphere (mean = 7.22 sec, SD = 7.00) did not reach significance ($p > .05$). Interestingly, in boys, the HRF latencies in the right hemisphere showed considerably more variance compared to those in the left hemisphere as well as compared to HRF latencies observed in girls (Fig. 4).

4. Discussion

The present study investigated sex differences in neural processing of speech and non-speech (reversed) stimuli in infants within the first days after birth using fNIRS and a well-studied speech discrimination paradigm. We found that speech stimuli elicited significantly more brain activity than non-speech stimuli in both, male and female neonates. However, whereas girls showed significant HbO changes to speech stimuli only within the left hemisphere, boys exhibited simultaneous neural activations in both hemispheres, with a larger and more significant fronto-temporal cluster in the right hemisphere.

Our results confirm previous studies showing the newborn’s ability to discriminate speech from non-speech sounds (Mehler et al., 1988; Dehaene-Lambertz et al., 2002; Peña et al., 2003; Sato et al., 2012; Bartha-Doering et al., 2019). However, our study for the first time reveals significant sex differences in this very early language processing. These findings cannot be attributed to differences in brain volumes, as head circumferences were comparable between groups, but point to greater involvement of the right hemisphere in the processing of speech sounds in boys compared to girls. While our study offers, to the best of our knowledge, evidence of sex differences in language processing in the youngest group that has been ever tested, it is consistent with previous findings in children under the age of five years. One of the few studies in very young children recorded auditory evoked potentials in response to verbal and musical stimuli in eight girls and eight boys aged between 10 and 13 weeks (Shucard, Shucard, Cummins, & Campos, 1981). Independent of conditions, female infants responded with stronger left lateralized activation, whereas boys showed stronger responses in the right hemisphere. A further electroencephalography study investigated 16-month-old infants (9 males and 9 females) while they listened to a series of known and unknown words (Molfese, 1990). For both sexes, larger amplitudes were observed after the onset of unknown words over left temporal
Fig. 1 – Mean time course of hemodynamic response for conditions speech forward (red) and speech backward (blue) for each individual channel in female (A) and male neonates (B).

Fig. 2 – Mean group oxyhemoglobin (HbO) concentration of 24 channels during forward (red) and backward (blue) speech in female (left) and male (right) infants.
regions. Only boys, however, showed additional responses over the right hemisphere and bilateral frontal regions. Similar results were obtained in a functional magnetic resonance imaging study investigating receptive language functions in 30 children aged 3–5 years (Sroka et al., 2015). In both sex groups, increased activation was found in superior temporal cortices bilaterally as well as in the left angular and supramarginal gyri. However, boys again showed stronger activation in right frontal brain regions including the anterior cingulate cortex and superior frontal gyrus. In sum, neuroimaging studies in younger children, including the present study investigating 45 neonates, indicate that female infants have a stronger left language lateralization than their male counterparts.

How can these very early functional differences between girls and boys be explained? The more left lateralization of neural speech processing in female neonates might reflect an earlier functional maturation of language associated brain areas in girls compared to boys. Neuroimaging studies consistently show that language lateralization towards the dominant hemisphere increases throughout childhood (Szaflarski, Holland, Schmithorst, & Byars, 2006). However, several studies have outlined that brain development follows different pathways over time in boys and girls (Choe et al., 2013). Female neonates show a trend towards a more rapid growth rate in unmyelinated white matter tracts (Gilmore et al., 2007). Preterm born female neonates furthermore exhibit a lower diffusion in the left superior longitudinal fasciculus than their male counterparts, suggesting an early established difference in favor of female neonates in the number or size of axons that transmit auditory information from the superior temporal gyrus to the inferior parietal lobe (Liu et al., 2011). In line with this, sex differences in the processing of auditory stimuli have been described in neonates (Lundqvist & Sabel, 2000). Female newborns hear more sensitively, especially in the higher frequency range, than boys (Cassidy & Ditty, 2001). These auditory differences between boys and girls are, however, only apparent when the stimuli contain human voice, whereas no differences are observed when a rattle produces the sounds (Boatella-Costa, Costas, Botet, Fornies Deu, & Cáceres-Zurita, 2007). Zhang, Li, Zheng, Dong, and Tu (2017) examined the development of auditory perception using event-related potentials with a special focus on N2, a component associated with higher cognitive processes. Female newborns revealed shortened N2 latency and increased N2 areas compared to male newborns. These data, together with our results, suggest that female infants show more mature abilities to process auditory language stimuli.

The female neonates in the present study did not only show differences in the lateralization of language activity, but also in the localization of language-associated areas. Only girls exhibited a significant cluster in the left inferior parietal lobe, which is very much in line with above-mentioned early sex differences in fibers connecting temporal and inferior parietal language areas (Liu et al., 2011). Boys, on the contrary, showed more involvement of right fronto-temporal areas in language processing. We assume that boys need this additional recruitment of right hemisphere areas to process speech stimuli. Previous studies have shown that increasing
workload during cognitive processing is associated with additional involvement of the right hemisphere, and fNIRS has been proven to be sensitive to variations of task difficulty (Causse, Chua, Peysakhovich, Del Campo, & Matton, 2017; Drager et al., 2004). We thus postulate that the simultaneous, bilateral HbO changes to speech sounds in male neonates mirror the greater neural immaturity and the less neural specialization of language-related brain areas of male infants shortly after birth.

The sex differences in the lateralization and localization of neural activation found in the present study may also reflect different neural processing strategies in boys and girls. It may be hypothesized that girls might focus on left-hemisphere phonetic and phonological processing (Turkeltaub & Coslett, 2004).
male variability in regional brain structure across the whole brain may include sex chromosomes and sex steroids. Genetic differences in the temporal dynamics of different linguistic processes (Angrilli, Elbert, Cusumano, Stegagno, & Rockstroh, 2003; Friederici, 2002). The present study shows comparable latency measures of left and right hemisphere responses to speech stimuli in male neonates and thus points to simultaneous bilateral processing of speech. The results of the present study may contribute to the understanding of early differences in language abilities in girls and boys. In the first few years of life, language development is faster in girls than in boys, with girls outperforming boys in most aspects of language perception and production (Fenson et al., 1994; Galsworthy et al., 2000). It is well-known that during the last trimester of pregnancy, fetuses increasingly perceive sounds and increasingly recognize recurrent speech stimuli (Kisilevsky et al., 2003). Earlier maturation of language-associated brain areas and white matter pathways may improve the ability of the fetus to process speech sounds and support the formation of auditory memory traces. Hence, girls may already be born with a developmental advantage for neural language processing that is reflected in their subsequent language development.

It is, however, interesting that the variation in time-to-peak latencies in boys is considerably greater in their right compared to their left hemisphere, and also greater compared to the HRF latency in girls. This finding may point to a greater variation in brain maturation within the group of boys and is in accordance with studies that report greater male than female variability in regional brain structure across the whole lifespan (Forde et al., 2020; Ritchie et al., 2018; Wierenga et al., 2022). Factors underlying these early sex differences in the brain may include sex chromosomes and sex steroids. Genetic studies suppose that single X-chromosome expression in males compared to the mosaic pattern of X-inactivation in females may lead to increased male vulnerability, as is also seen for a number of rare X-linked genetic mutations (Reinhold & Engqvist, 2013; Wierenga et al., 2022). In our sample of full-term and preterm born neonates where all infants were born after the GA of 32nd week, GA at birth did not significantly predict speech discrimination at term. This is in line with our two previous studies that examined altered language processing in preterm born infants and investigated the effect of GA at birth on speech discrimination (Alexopoulos et al., 2021; Bartha-Doering et al., 2019). In these studies, we identified a critical threshold at the 32nd week of GA, with only infants born after this threshold showing speech discrimination abilities comparable to full-term born neonates. We thus conclude that the GA at birth did not significantly influence our study results on very early sex differences in neural processing of speech.

5. Limitations

Results of different brain regions involved in speech discrimination in girls versus boys were derived mainly from the t-test results for each channel within each sex group. Although interaction effects on the grand means across all channels were conducted, no such analyses were performed in every channel to directly confirm the sex difference in specific locations. Therefore, the different localizations of the language effects between females and males should be interpreted with caution. Furthermore, the present study only included neonates whose parents’ were native German speakers. Furthermore, all of the families lived in Vienna. We cannot, however, exclude that some fetuses were exposed to another language aside from German during the last trimester of pregnancy. Yet, we think that the influence of infrequent non-native language stimuli by other speakers than the parents on the development of language areas would be negligible in the present study. However, previous studies have shown an influence of the socioeconomic status on neural brain development and function in infants, with an increasing effect throughout early childhood (Olson, Chen, & Fishman, 2021). The present study did not collect information on the socioeconomic background, the educational level, and the linguistic environment. Thus, we cannot exclude possible group differences in this regard. This is a limitation of the present study, and future studies should include these variables in their analyses.

6. Conclusion

In conclusion, the present study demonstrates in a large sample of newborns that language-related sex differences are already present in the neonatal period. Female newborns show more left lateralized brain activity to speech stimuli, whereas boys exhibit bilateral, simultaneous neural activations. These findings suggest an earlier maturation of language-related brain areas in girls, explain the sex differences in early language developmental abilities, and highlight the importance of sex-specific investigations of neural language networks in infants.

Significance

Are girls born with an advantage in language development? The present study used fNIRS in neonates to investigate sex differences in neural processing of speech within the first days of life. We found more lateralized neural activations in girls who showed significant hemodynamic changes to speech stimuli only within the left hemisphere, whereas boys exhibited simultaneous neural activations in both hemispheres with greater variations in latencies. These findings suggest an earlier maturation of language-related brain areas in girls.

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J. Alexopoulos, V. Giordano, A. Berger, R. Seidl, S. Doering, S. Benavides-Varela, and L. Bartha-Doering designed the study. J. Alexopoulos, V. Giordano, M. Russwurm, S. Greenwood, and L. Bartha-Doering conducted the experiments and analysed the data. All authors contributed to the writing of the manuscript.
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Open practices
The study in this article earned Open Data and Open Materials badges for transparent practices. Materials and data for the study are available at https://osf.io/wx3rt/

Data availability
Data will be made available on request.

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