scientific reports

Check for updates

OPEN

Prenatal brain connectivity and postnatal language: how familial risk and prenatal speech exposure shape early language skills

Cristina Cara[1,2], Matteo Canini[3]✉, Claudia Oprandi[3], Nicolò Pecco[3], Paolo Ivo Cavoretto[4], Massimo Candiani[4,6], Andrea Falini[3,6], Cristina Baldoli[3], Marco Tettamanti[5,7]✉ & Pasquale Anthony Della Rosa[3,7]✉

The maturation of the auditory-language brain network begins before birth, driven by gene-environment interactions. We investigated the association between familial and environmental factors and the foetal development of this network, as well as the predictive value of this association for postnatal language outcomes. Using prenatal resting-state fMRI, we examined 25 foetuses to identify functional connectivity within the auditory-language network. Postnatal language was assessed longitudinally between 1 and 3 years using the Bayley-III scale. Familial risk for language disorders and prenatal speech exposure were quantified using a newly developed questionnaire. First, hierarchical clustering on foetal functional connectivity confirmed that an auditory-language network can be identified in the foetal brain. In this network, foetuses with higher speech exposure exhibited increased connectivity between left-hemisphere regions and decreased connectivity between homologous right-hemisphere regions. Higher familial risk was linked to reduced connectivity within the left language network. Regression analyses revealed that prenatal functional connectivity between insula, caudate nucleus, and rolandic operculum significantly predicted postnatal language. These findings underscore the critical role of genetic and environmental influences in functionally shaping the foetal auditory-language network, with lasting impacts on early language development. By integrating prenatal brain connectivity, familial risk, and speech exposure, this study provides new insights into prenatal language neurodevelopment, highlighting its importance for future language capabilities.

Keywords Foetal neurodevelopment, Early language acquisition, Functional connectivity, Auditory and language networks, Familial risk, Language disorders

Language developmental trajectories are influenced by both genetic and environmental factors[1–3]. Familial clustering and twin studies provided evidence that developmental language and reading disorders are highly heritable[1,4]. Genetic influences extend beyond pathological conditions, as inheritability has also been observed in normotypical language development for various abilities encompassing reading, spelling, phonology, syntax, and articulation[5–7]. The amount of environmental linguistic stimulation and exposure in childhood has also been shown to influence language skills development[8].

Genes and environment likely impact language development indirectly, by shaping the structural and functional brain network, which in turn shapes cognitive and behavioural profiles in early infancy and childhood. Language-related genes, as well as environmental factors, participate in early neurodevelopmental processes including axonal growth, neural migration, and myelination[9,10] as well as functional connectivity[11]. As for environmental factors, a recent study has shown that functional connectivity in the language network in infancy is affected by the amount of adult-infant conversations[12].

[1]CIMeC - Center for Mind/Brain Sciences, University of Trento, Trento, Italy. [2]Faculty of Mathematics and Natural Sciences, Heinrich Heine University Düsseldorf, Düsseldorf, Germany. [3]Department of Neuroradiology, IRCCS San Raffaele Scientific Institute, Milan, Italy. [4]Department of Obstetrics and Gynecology, IRCCS San Raffaele Scientific Institute, Milan, Italy. [5]Department of Psychology, University of Milano-Bicocca, Milan, Italy. [6]Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy. [7]Marco Tettamanti and Pasquale Anthony Della Rosa contributed equally to this work. ✉email: canini.matteo@hsr.it; marcodante.tettamanti@unimib.it; dellarosa.pasquale@hsr.it

Multiple lines of evidence indicate that the impact of genetic and environmental factors on functional connectivity within the auditory and language network begins as early as the foetal stage[9,13]. Behavioural observations and neuroimaging studies in newborns have suggested that prenatal exposure to auditory and speech stimuli could shape the infants' postnatal brain and behavioural responses, including speech perception and language acquisition abilities[13–15]. However, evidence gained from observations in newborns has only indirect pertinence to infer prenatal neurodevelopmental processes.

Recent advancements in foetal multimodal neuroimaging have greatly enhanced our opportunities to directly investigate prenatal brain development. In a recent review, we described the structural and functional maturation trajectories of the auditory and primordial language brain networks in foetuses[15]. The development of peripheral and subcortical brain structures forming the auditory pathways begins in the first trimester of gestation and approaches maturation in foetuses at term[16]. Foetal brain response to sounds has been recorded in the auditory cortex through magnetoencephalography as early as 27 gestational weeks (GW) and throughout the third trimester of gestation[15,17]. Cortical folding and gyrification of perisylvian regions start around 20 GW and undergo significant growth between 24 and 36 GW[15,18,19]. Structural connections between auditory and perisylvian regions, also involving subcortical relay nuclei (e.g., thalamus, basal ganglia), can be detected as early as 26 GW, with full maturation only occurring in the early years after birth[20,21]. Concurrently, functional brain networks start to emerge at around 26 GW, with a spurt in their maturation occurring throughout the late foetal period, between 26 and 36 GW[22]. This functional development has been shown particularly by resting-state fMRI (rs-fMRI) evidence, indicating that the foetal brain already exhibits a modular functional connectivity architecture[23]. Primary sensorimotor (i.e., visual, somatosensory, auditory, and motor) networks emerge during the third trimester and reach substantial functional stability already by the beginning of the late preterm phase (i.e., around 32 GW). Brain regions within the primary sensory network were also shown to interact with higher-order regions[24,25]. This crucial functional maturation in the late stages of foetal brain development establishes a blueprint for subsequent cognitive development[26]. Of particular relevance for shaping language developmental trajectories is the emergence of functional connectivity between the primary auditory network and a primordial higher-order network involving perisylvian and sensorimotor brain regions - a connectivity pattern thought to support later language acquisition[15]; for the sake of simplicity, in the current manuscript we will refer to this functional connectivity pattern as the "auditory-language network", while acknowledging that the involved systems are distinct and present different developmental timelines.

Thus, the late foetal period represents a critical window to study the maturation of foetal functional networks, to assess potential genetic and environmental modulatory influences on connectivity patterns, and to identify functional brain markers predictive of postnatal language development. The first aim of the current study was to spotlight clusters of foetal brain function among primary sensorimotor networks, subcortical relay nuclei, and primordial languages regions in the perisylvian cortices, in order to explore the emergence of the auditory-language network. The second aim was to examine whether foetal functional connectivity in the auditory-language network is sensitive to familial susceptibility to developmental language and learning disorders, as well as to the degree of prenatal language exposure. Indeed, language development entails both resistance to developmental perturbations, such as gene mutations that can lead to developmental disorders, and sensitivity to environmental influences such as auditory and speech input[27] in striving to achieve neurotypical homeostatic brain network states[28]. Crucially, we also investigated how prenatal functional connectivity within the foetal auditory-language network relates to early postnatal language outcomes.

To achieve these goals, we investigated a sample of 25 healthy foetuses which were scanned with rs-fMRI to collect functional connectivity measures. This sample was followed-up longitudinally with the assessment of language abilities within the first three years after birth, by means of the standardized Bayley-III test battery[29]. While no genetic data were collected in the present study, familial susceptibility to developmental disorders, estimated through a newly designed structured questionnaire administered to the parents, was used as a proxy for inherited risk for the children in this sample. Through the same questionnaire, we also retrospectively assessed the amount of environmental linguistic stimulation during gestation.

We first analyzed the foetal functional connectivity data to examine the maturation of the foetal auditory-language network in our cohort[15,23]. We then sought to determine the association of functional connectivity strength in the auditory-language network with familial susceptibility to language disorders, as well as with the amount of environmental linguistic stimulation during gestation. In the final step, we utilized a stepwise linear regression analysis on the postnatal Bayley-III language outcomes to assess which prenatal brain functional connections sensitive to familial and environmental influences can significantly predict language behaviour in early infancy.

Materials and methods

Experimental sample

Twenty-five pregnant mothers participated in the present study. They were recruited at San Raffaele Hospital, Milan, Italy during regular pregnancy monitoring. Inclusion criteria were as follow: (i) healthy foetuses in the late foetal period, which is characterized by significant structural and functional changes in the organization of cerebral connections[30] (ii) normal foetal anatomy and growth assessed through foetal ultrasound; (iii) low-risk for major chromosomal disorders by first trimester combined screening with or without non-invasive prenatal screening by means of cell-free foetal DNA testing; (iv) no sign of foetal neurodevelopmental abnormality nor brain parenchymal signal alterations acknowledged by means of structural MRI investigation; (v) healthy pregnancy, without any serious maternal medical complications, such as gestational hypertension or hyperglycemia. All foetuses were subsequently born at term, without complications, had normal neonatological assessment at birth, and showed no major health problems in the first year of postnatal life. The final sample

included 25 foetuses (13 M, 12 F). The average gestational age of the foetuses at the time of MRI session was 32.5 GW (SD = 1.8, range = 27–35; Supplementary Materials: Table S1).

This study and all its experiments were conducted in full accordance with ethical guidelines and regulations, including the World Medical Association Declaration of Helsinki and subsequent revisions. The research protocol was reviewed and approved by the Ethics Committee of the San Raffaele Hospital (protocol code: RF-2016-02364081; Register of Opinions Number: 51/INT/2018; date of approval: 04/05/2018). Accordingly, all women provided written informed consent prior to foetal MR scanning.

Family background questionnaire

The Family background questionnaire (FBQ) is a parent report instrument designed to gather comprehensive information on child's risks for developmental language and learning disorders based on familial and prenatal exposure factors. In order to fulfil this aim, the FBQ collects data related to familiar history of language and learning disorders and attempts to retrospectively quantify the amount of prenatal exposure to speech input. Information on the validation of the FBQ is provided in the Supplementary Materials (Methods S1; Figure S1). The FBQ was administered to the parents when their children were between 19 and 37 months of age (mean child age = 26.7 months, SD = 5.6).

The questionnaire consists of two main parts: the first part (FBQ1) was administered either by phone or in person (required time for administration was approximately 15 min), and included three main sections:

FBQ1 - General information

The first section was adapted from the factsheet of the MacArthur–Bates Communicative Development Inventories[31] and provides general information about the child and the nuclear family, parental educational and socioeconomic statuses, and child's postnatal exposure to mono- or multilingual contexts.

FBQ1 - Familial susceptibility for language frailties

The second section of the FBQ1 explores the child's familial susceptibility to neurodevelopmental language frailties. Parents are asked whether any first-degree family member (i.e., parents, siblings) ever had undiagnosed difficulties related to: (1) reading; (2) writing; (3) spelling and letter recognition; (4) language production and articulation; (5) speech delay.

The responses to this section were summarized by means of a binary score for each subject. A score of 1 was assigned if at least one first-degree relative had one or more frailties in the domains under investigation, while a score of 0 was assigned if no frailties were reported in the family (Supplementary Materials: Figure S2).

FBQ1 – Familial susceptibility for language impairments

The third section of the FBQ1 further explores the child's familial susceptibility to neurodevelopmental language impairments. Parents were asked whether any nuclear or extended family member (i.e., also including cousins, aunts and uncles, grandparents) ever had a diagnosis of the following disorders: (1) dyslexia; (2) language disorders; (3) articulatory or phonological disorders; (4) dysgraphia; (5) dysortographia; (6) stuttering.

The responses to this section were summarized by means of a binary score for each subject. A score of 1 was assigned if at least one family member had one or more diagnoses, while a score of 0 was assigned if no diagnoses were reported (Supplementary Materials: Figure S2).

FBQ2

The second part of the questionnaire (FBQ2) unfolded in two sections. Following an oral presentation to the parents by a designated researcher, the FBQ2 was sent via email and both parents were asked to complete both sections.

FBQ2 – Parental self-assessed language- and speech-related difficulties The first section of the FBQ2 includes self-reported questions aimed at characterizing the parents' cognitive profiles by means of three items: (i) "*I am fast at reading a book's page*", (ii) "*I have difficulties in putting sounds together during word pronunciation*", (iii) "*I make mistakes in taking notes*". Both parents were asked to rate each item on a 5-point Likert scale (0 = strongly disagree; 4 = strongly agree). The aim of this section is to explore more subtle signs of language- and speech-related difficulties without explicitly referring to language or learning disorders.

Following reverse scoring for the first item, the raw scores of the three different items were summed to compute an overall median-split score for each subject (i.e., 1 ≥ median; 0 < median; Supplementary Materials: Figure S2). Three subjects had missing data for this variable, due to failure to return the questionnaire: for these subjects, the overall median-split score was imputed based on the two familial scores for language frailties and impairments, resulting in a score equal to 0 for all three subjects.

FBQ2 – Environmental prenatal speech exposure The second section of the FBQ2 investigated the amount of speech stimulation provided by the parents to the child during pregnancy by means of two distinct items: (i) "*During pregnancy, I talked to the baby*", (ii) "*During pregnancy, I used to read story tales aloud*". Both parents were asked to rate each item on a 4-point Likert scale (0 = never; 3 = always). The aim of this section is to retrospectively quantify the child's prenatal exposure to speech (Supplementary Materials: Figure S3).

Aggregate Familial risk score

The items described above in FBQ1 - Familial susceptibility for language frailties, FBQ1 – Familial susceptibility for language impairments, and FBQ2 – Parental self-assessed language- and speech-related difficulties were combined together into an aggregate familial risk score (Supplementary Materials: Figure S2), measuring the

child familial predisposition to neurodevelopmental language and learning disorders. More specifically, the binary scores obtained from the three familial variables were summed together. The aggregate score ranged from 0 to 3, reflecting the subject's familial risk for developing language disorders. The aggregate familial risk score was used as a variable of interest in the group-level analyses.

Aggregate prenatal speech exposure score

For each subject, an aggregate score was calculated by averaging the raw data from both parents for the two items included in the second section of FBQ2 (FBQ2 – Environmental prenatal speech exposure; Supplementary Materials: Figure S3).

This aggregate prenatal speech exposure score was used as a variable of interest in the group-level analyses. Missing data for three subjects were replaced with the sample's mode.

In addition, the mother was asked to rate the noise level of her home and workplace environments at the time of pregnancy on a 4-point Likert scale ranging from 0 (very silent) to 3 (very noisy). The raw scores of these items were averaged to compute an aggregate individual score reflecting the child's prenatal exposure to noise, which was used as a nuisance covariate in group-level analyses.

Postnatal behavioural assessment

Children's linguistic skills were assessed by a developmental neuropsychologist (C.O.) with the Bayley-III scale for infant and toddler development[29]. The Bayley-III measures developmental functioning in children between 1 and 42 months across various domains, including language. Specifically for purposes of this study, we used age-corrected total language scores computed as the sum of the expressive and receptive linguistic scores obtained from the Bayley-III language scale. Children were tested between 1 and 3 years of age (mean age at time of testing = 22.2 months, SD = 7.7, range = 12–38; Supplementary Materials: Table S1).

Prenatal MRI data acquisition

Foetal MR scanning was performed on a Philips Achieva 1.5 T scanner, using a 16 channels body coil. All pregnant women were asked not to eat within 2.5 h preceding the MR scanning. Foetal rs-fMRI consisted of GE EPI scans (TR = 2000 ms, TE = 30ms, acquisition voxel size 2.81 × 2.86 × 3 mm, 25 slices, slice gap = 0). Each rs-fMRI scan consisted of 60 volumes. Four to six consecutive rs-fMRI sessions (i.e., 240–360 volumes, covering from 8 to 12 min of continuous brain activity at rest) were acquired for each subject depending on the condition of each pregnant woman during MR scanning and the quality of the scans. Foetal structural scans consisted of a T2 Single Shot Turbo Spin Echo scan on the axial, sagittal and coronal planes of the foetus (TR = 8000 ms, TE = 125 ms, voxel size 1.17 × 2.76 × 3 mm, 25 slices) for a total scanning duration time of 17s. All foetuses showed no sign of foetal neurodevelopmental abnormality nor brain parenchymal signal alterations acknowledged by a neuroradiologist (C.B.) on structural MRI scans.

Foetal rs-fMRI image pre-processing

Foetal scans were processed using the Resting-State Foetal functional MRI (RS-FetMRI) preprocessing pipeline (https://github.com/NicoloPecco/RS-FetMRI). The RS-FetMRI is divided into the following preprocessing steps: (a) rs-fMRI volume reorientation and origin set on the anterior commissure; (b) 1st-pass masking step with a GWsession-specific mask to remove the majority of the maternal abdominal tissue; (c) within-session realignment step with a binary tissue-weighting mask which binds motion estimation only to inner-brain portions of the foetal brain; (d) 1st-pass scrubbing through ART (https://www.nitrc.org/projects/artifact_detect); (e) segmentation of session-specific functional reference volumes to derive session-specific inner-brain masks in subjects anatomy space based on registration with seven "best-fit" GW-specific brain foetal tissue and structure maps; (f) between-session mean functional reference volume calculation on session-specific masked functional reference scans; (g) between-session 2nd-pass realignment of all session-specific masked functional volumes; (h) 2nd-pass between-session scrubbing procedure through ART and estimation of frame-to-frame estimation of motion (FD) and signal intensity (DVARS) changes; (i) calculation of deformation parameters through SPM's unified segmentation–normalization algorithm[32] based on spatial registration with specific brain foetal tissue and structure maps for warping the between-session mean functional reference volume to the median-sample group-based atlas space; (j) application of deformation parameters to between-session masked functional volumes in order to warp all volumes in the rs-fMRI time-series to GW median-sample group-based atlas space; k) smoothing normalized between-session masked volumes using an isotropic gaussian filter kernel with full width at half maximum (FWHM) 4 mm.

Smoothed, normalized volumes were then denoised using the CONN functional connectivity toolbox (version 22a)[33]running on Matlab. A component-based noise correction method (CompCor[34] was used to regress-out confounding effects related to white matter, cerebrospinal fluid, and global signal intensity. After nuisance regression, data were band-pass filtered at 0.01–0.08 Hz, before entering functional connectivity analysis.

Functional connectivity analysis

In order to assess the presence of a primordial auditory-language network during the late foetal period, we adopted an a-priori region of interest (ROI)-to-ROI connectivity approach. Namely, we selected 42 ROIs linked to language processing, primary sensory and motor functions, and subcortical gray matter relay nuclei (Fig. 1). Pearson's correlation coefficients were computed for each possible pair of ROI. Fisher's transformation was applied to convert Pearson's coefficients to z-score coefficients. This procedure generated a correlation matrix for each subject reflecting the ROI-to-ROI functional connectivity between each pair of ROI.

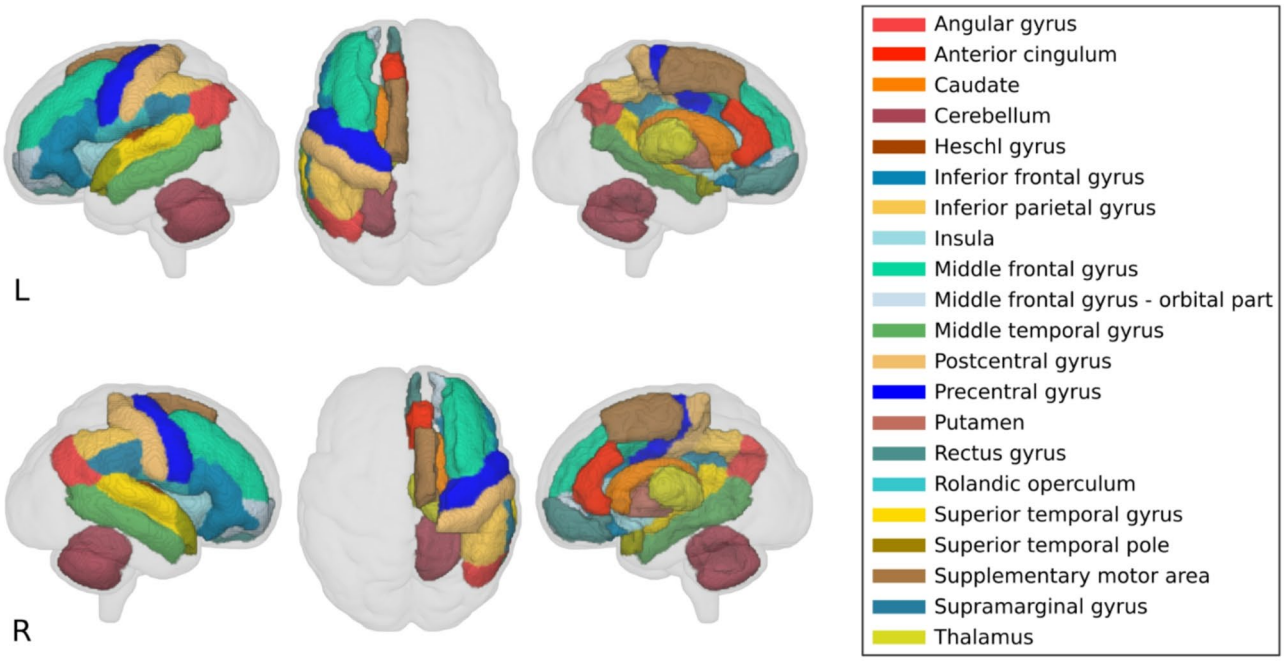

Fig. 1. Regions of interest. Regions of interest selected in the left and right hemisphere for functional connectivity analysis. All regions were taken from a 33 GW foetal brain atlas[35]. L, left; R, right.

At the second (group) level, a contrast testing for the effect of group was specified. Results were explored for patterns of spontaneous functional coupling between the included ROIs, using the data-driven hierarchical clustering (complete-linkage) algorithm implemented in CONN, with a 0.05 weighting factor to favour functional similarity over spatial proximity[36]. The multivariate pattern analysis (MVPA) inferential approach was employed to assess statistical significance between ROIs pairs, using a $p < 0.001$ threshold corrected for false discovery rate at both the connection and cluster levels. Sets of functionally-similar ROIs were deemed as functional networks (see[37] for additional details).

Familial risk and prenatal speech exposure associations with functional connectivity

We investigated the association between the FBQ variables and functional connectivity in pairs of ROIs composing the auditory-language network identified through the hierarchical clustering analysis. Before assessing the FBQ-functional connectivity associations, a linear mixed-effects model was applied to evaluate the presence of hemispheric asymmetry in the auditory-language network, while controlling for potential confounding effects of gestational age at scan and parental education. The model incorporated both fixed and random effects, allowing for repeated measurements of functional connectivity across bilateral ROI pairs within each participant. Maximum likelihood estimation was used for model fitting. The familial risk scores and the prenatal speech exposure scores were correlated with the functional connectivity values between all possible pairs of ROI within the left ($n = 45$) and the right ($n = 55$) auditory-language networks. Spearman correlations were first performed. Statistical significance was determined using a threshold of $p < 0.05$, and confidence interval were computed through bootstrapping (iterations = 10000). Significant effects at this step were used for subsequent regression analyses.

Stepwise regression model with functional connectivity proxies to predict postnatal language outcomes

From the previous step, we selected ROI-to-ROI functional connections that exhibited significant correlation with familial risk or prenatal speech exposure, surviving the bootstrapping correction (see Results). These functional connectivity values were included as explanatory variables in a stepwise multiple regression analysis to assess model significance and to identify the most significant predictors of the Bayley-III language total composite outcomes. Stepwise regression was chosen due to its ability to add or remove predictors based on statistical criteria, allowing the identification of variables that contribute the most to the model. The criteria for variable entry into the model were based on the probability of F-to-enter set at 0.05 and the probability of F-to-remove set at 0.10.

Results

FBQ - Variable distribution

The combination of the three familial risk variables (language frailties, language impairments, parental self-assessed language- and speech-related difficulties) into an aggregate score ranging from 0 to 3, with higher values indicating higher risk levels, yielded 9 subjects with a score of 0, 9 subjects with a score of 1, 4 subjects

with a score of 2, and 3 subjects with a score of 3 (Fig. 2A; see Supplementary Materials: Results S1, Figure S4 for further details on the individual familial risk scores).

The two items investigating prenatal speech exposure were combined into an aggregate score ranging from 0.5 to 2.75 (mean = 1.36, SD = 0.64), with higher values indicating a greater exposure to speech stimuli during pregnancy (Fig. 2B).

Importantly, there was no significant sample-wise association between the aggregate familial risk score and the aggregate prenatal speech exposure scores, as shown by a correlation analysis on the two FBQ variables (Spearman coefficient = – 0.19, $p = 0.37$).

Bayley-III language scale - Score distribution

The sample mean for the total score of the Bayley-III language scale was 16.96 SU (SD = 5.3, range = 4–28; Supplementary Materials: Figure S5). Data range and distribution showed a certain degree of variability, which reflects interindividual heterogeneity in children's language trajectories. This diversity renders our sample particularly suitable for studying individual differences in language development.

Functional connectivity – Hierarchical clustering identification of functional networks

The hierarchical clustering analysis revealed the presence of a unilateral auditory-language network in both hemispheres of the foetal brain (Fig. 3; Supplementary Materials: Figure S6, Figure S7). This network encompassed subcortico-cortical relay nuclei (thalamus, putamen, caudate nucleus), regions in the auditory cortices (Heschl's gyrus, superior and middle temporal gyri), sensorimotor cortices (rolandic operculum), and primordial language regions in the auditory cortices (inferior frontal gyrus, insula, superior temporal pole). In the right hemisphere, the network additionally encompassed the orbital part of the middle frontal gyrus (Fig. 3).

Effects of hemispheric asymmetry in the auditory-language network, controlling for gestational age and parental education

No fixed effects in the linear mixed-effects model reached statistical significance. The intercept was not significantly different from zero (B = −0.120, SE = 0.502, t(25.021) = −0.239, $p = 0.813$). Gestational age at scan was not a significant predictor of functional connectivity (B = 0.021, SE = 0.015, t(25) = 1.370, $p = 0.183$, 95% CI [−.011, 0.052]). Similarly, parental education did not significantly predict connectivity values (B = 0.016, SE = 0.023, t(25) = 0.686, $p = 0.499$, 95% CI [−0.031, 0.063]).

Regarding hemispheric asymmetry, no significant difference was found between left and right hemisphere connections (B = −0.025, SE = 0.020, t(875) = −1.208, $p = 0.227$, 95% CI [−0.065, 0.015]).

Familial risk and environmental score associations with functional connectivity

Familial risk was negatively correlated with functional connectivity in the "left insula - left rolandic operculum" connection (Spearman's rho = −0.5, $p = 0.01$, bootstrap 95% CI [−0.75, −0.12]), as well as in the "left insula - left caudate" connection (Spearman's rho = −0.47, $p = 0.02$, bootstrap 95% CI [−0.75, −0.03]) (Fig. 4). These effects were also significant in a partial correlation model in which prenatal speech exposure and prenatal noise exposure were entered as nuisance variables (Table 1). In turn, the prenatal speech exposure score positively correlated with functional connectivity in two connections, namely "left rolandic operculum - left middle temporal gyrus" (Spearman's rho = 0.55, $p = 0.004$, bootstrap 95% CI [0.28, 0.75]), and "left rolandic operculum - left superior temporal pole" (Spearman's rho = 0.6, $p = 0.001$, bootstrap 95% CI [0.29, 0.79]). There was also a negative correlation in the connection "right orbital middle frontal gyrus - right Heschl's gyrus" (Spearman's

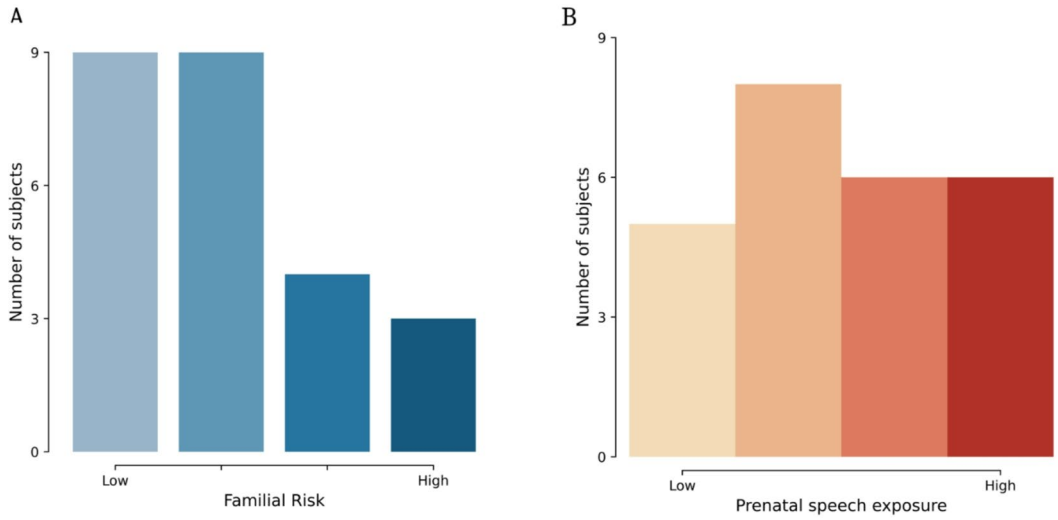

Fig. 2. Family background questionnaire (FBQ) aggregate scores. The plots show the sample distribution of, (**A**) the aggregate familial risk score; (**B**) the aggregate environmental, prenatal speech exposure score.

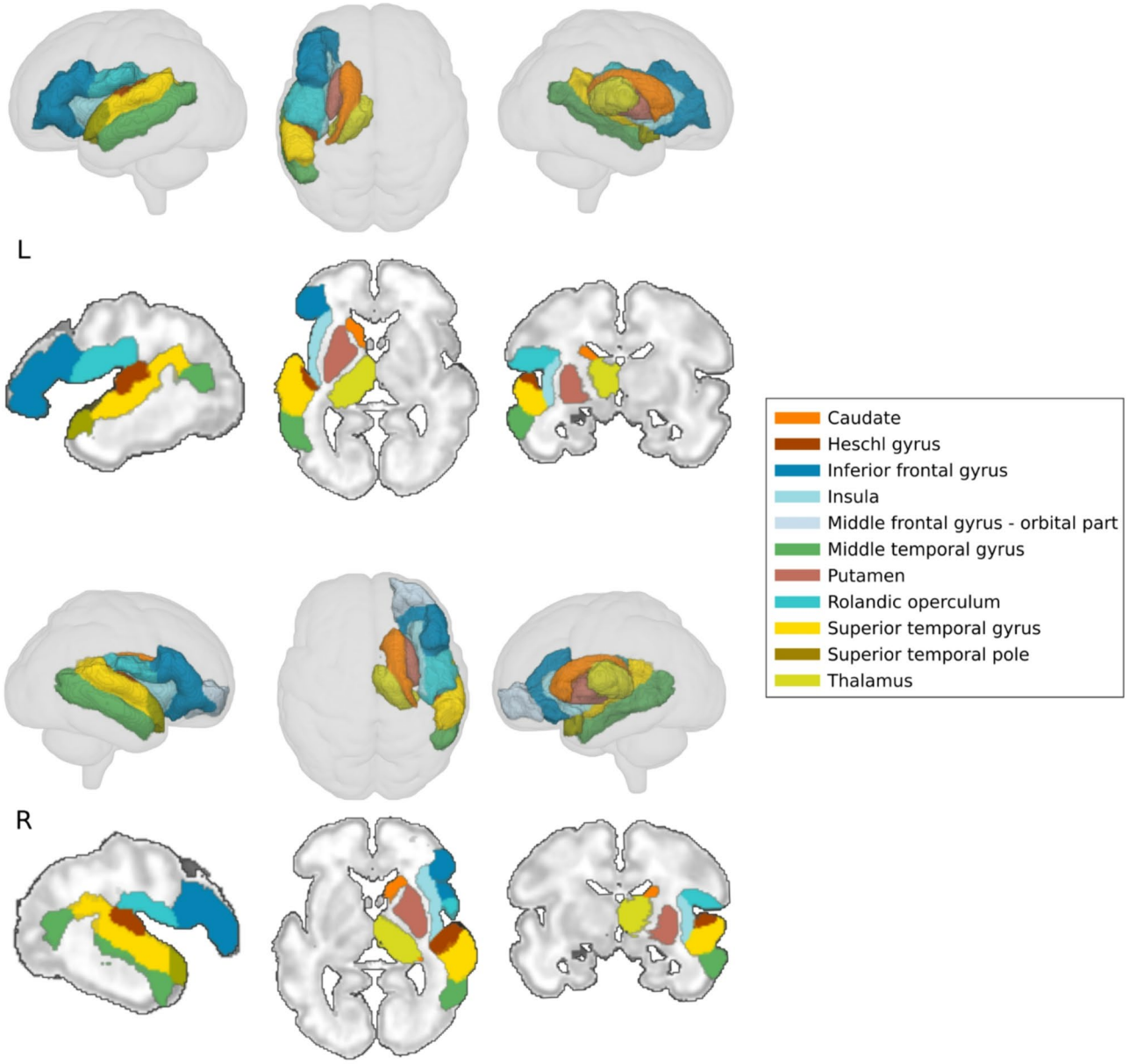

Fig. 3. Auditory-language networks in the foetal brain. Regions of the auditory-language networks in the left and right hemisphere resulting from the functional connectivity analysis. All regions were included in both hemispheres, except for the orbital part of the middle frontal gyrus, which was only present on the right. The displayed regions of interest were taken from a 33 GW foetal brain atlas[35]. L, left; R, right.

rho = −0.45, $p = 0.02$, bootstrap 95% CI [−0.74, −0.05]) (Fig. 4). These effects were also significant in a partial correlation model in which familial risk and prenatal noise exposure were entered as nuisance variables (Table 2).

Prenatal functional connectivity association with postnatal language development

The two "familial risk" and the three "prenatal speech exposure" functional connectivity proxies (Familial risk and environmental score associations with functional connectivity; Tables 1 and 2) were fed as explanatory variables into a stepwise regression model to highlight predictive relations with the postnatal Bayley-III language outcomes. Out of the five explanatory variables, two accounted for significant effects.

The first variable was the "left insula - left rolandic operculum" "familial risk" connection, which explained 16.88% of the variance in the Bayley-III language total composite outcomes ($R^2 = 0.169$, Adjusted $R^2 = 0.133$), and showed a statistically significant regression ($F(1, 23) = 4.67$, $p = 0.041$). The stepwise addition of the "left insula - left caudate" "familial risk" connection improved the model's explanatory power, accounting for 33.78% of the variance ($R^2 = 0.338$, Adjusted $R^2 = 0.278$), leading to a significant increase in the model's explanatory power, $F(2, 22) = 5.61$, $p = 0.011$. Due to the stepwise addition of the "left insula - left caudate" "familial risk"

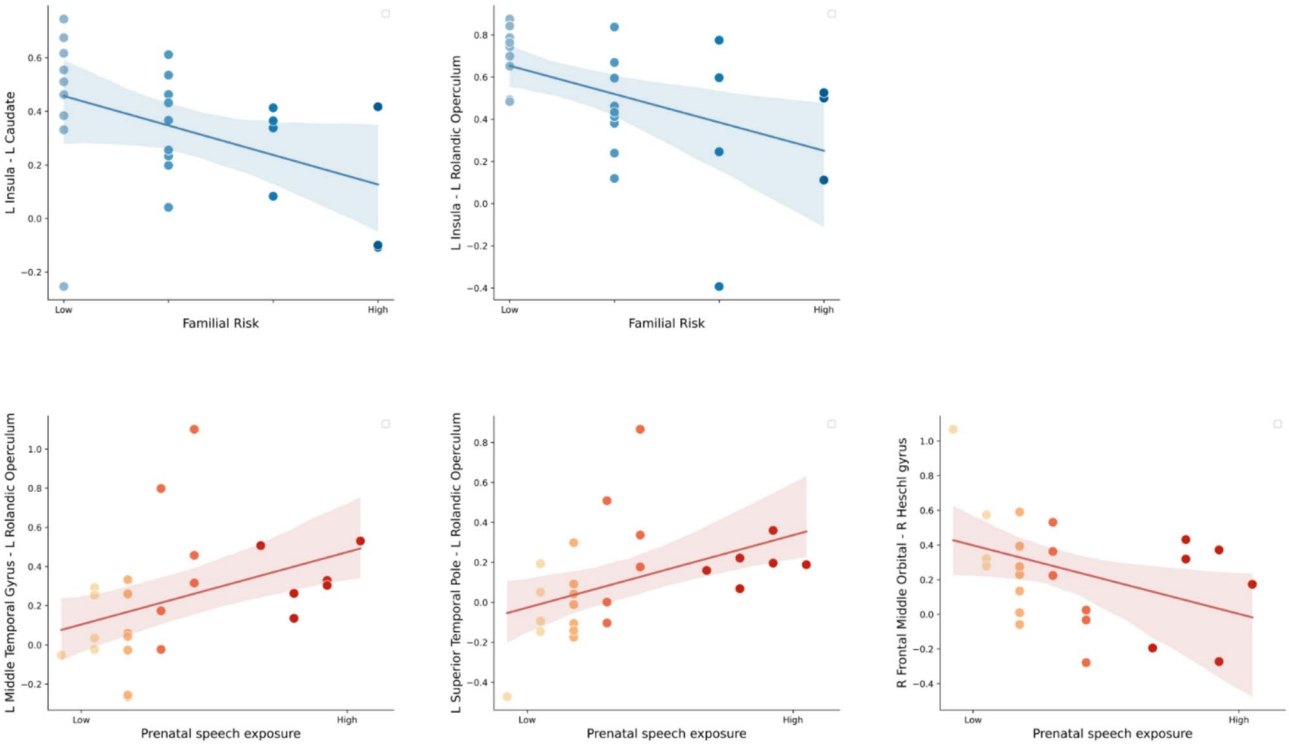

Fig. 4. Correlations between functional connectivity and FBQ variables. The scatterplots in the top row show the correlations between familial risk (x-axis) and ROI-to-ROI functional connectivity (y-axis). The scatterplots in the bottom row show the correlations between prenatal speech exposure (x-axis) and ROI-to-ROI functional connectivity (y-axis).

Functional connectivity and aggregate familial risk score					
				Partial correlation model	
Connection	rho	p	Bootstrap CI 95%	rho	p
L Insula – L Caudate	– 0.47	0.018	– 0.75 – 0.03	– 0.47	0.02
L Insula – L Rolandic Operculum	– 0.5	0.011	– –0.75 – 0.12	– 0.47	0.02

Table 1. Correlations between functional connectivity and Familial risk. Spearman's rho coefficient and the associated p-values are reported. Confidence intervals (CI) were computed using bootstrap ($n = 10000$). The two rightmost columns report rho and p for the partial correlation model with prenatal speech exposure and prenatal noise exposure as nuisance variables. L = left.

Functional connectivity and prenatal speech exposure score					
				Partial correlation model	
Connection	rho	p	Bootstrap CI 95%	rho	p
L Rolandic Operculum – L Middle Temporal	0.55	0.004	0.28 0.75	0.51	0.01
L Rolandic Operculum – L Superior Temporal Pole	0.6	0.001	0.29 0.79	0.57	0.004
R Middle Orbital Frontal - R Heschl Gyrus	– 0.45	0.02	– 0.74 – 0.05	– 0.43	0.04

Table 2. Correlations between functional connectivity and prenatal speech exposure. Spearman's rho coefficient and the associated p-values are reported. Confidence intervals (CI) were computed using bootstrap ($n = 10000$). The two rightmost columns report rho and p for the partial correlation model with famililal risk and prenatal noise exposure as nuisance variables. L = left; R = right.

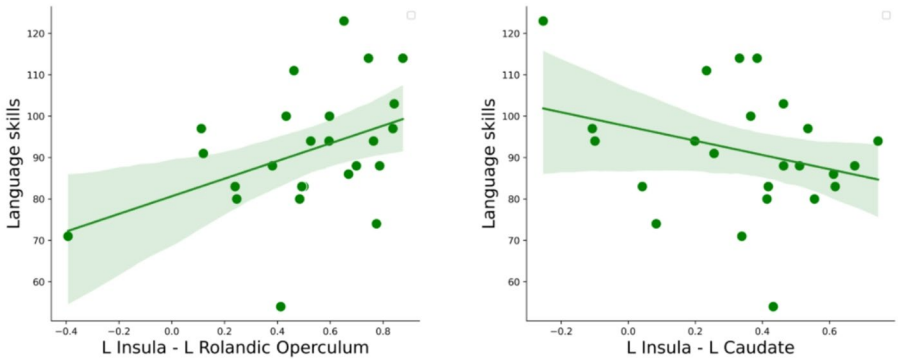

Fig. 5. Associations between foetal functional connectivity and postnatal language skills. The scatterplots show the associations between foetal ROI-to-ROI functional connectivity strength and postnatal language skills measured with the Bayley-III language scale.

connection, the standard error of the estimate decreased from 13.998 to 12.775, indicating improved accuracy of the predictions (Fig. 5).

In the final stepwise model including both connections, the "left insula - left rolandic operculum" "familial risk" connection had a significant positive association with the Bayley-III language total composite outcomes ($B = 27.09$, $SE = 9.32$, $\beta = 0.522$, $t = 2.91$, $p = 0.008$), indicating that an increase in "left insula - left rolandic operculum" connectivity is associated with an increase in postnatal language abilities. In turn, the "left insula - left caudate" "familial risk" connection had a significant negative association with the Bayley-III language total composite outcomes ($B = -25.34$, $SE = 10.69$, $\beta = -0.426$, $t = -2.37$, $p = 0.027$), suggesting that an increase in connection strength is associated with a decrease in postnatal language abilities (Fig. 5).

In order to find further support for the significant predictive relationship between familial risk and the Bayley-III language score emerged from the stepwise regression model, we tested the correlation between the two variables. A post-hoc Spearmans' correlation (bootstrapping, $n = 10000$) revealed a significant negative association (rho = −0.42, $p = 0.03$, 95% CI [−0.7, −0.003]).

Discussion

Language acquisition is one of the major achievements in early childhood and represents an essential requirement to succeed in social and educational contexts[38,39]. Early language skills are indeed reliable predictors of later literacy proficiency, academic attainments, and career outcome[38,40]. Conversely, language disorders often lead to educational struggles, including specific learning disabilities[41]. Given this context, there is a pressing need to identify biomarkers for predicting language developmental trajectories in the early stages of development. A growing body of research has demonstrated that the structural and functional brain systems underlying auditory and language processing develop prenatally[15]. Early brain development trajectories are driven by both genetic and environmental factors[11]. Understanding the multiple links between genetic and familial influences, prenatal environment, and brain maturation, and how these different variables shape individual differences in language development is one of the major challenges in cognitive neuroscience. The foetal brain, with its rapidly forming neural networks, offers a unique window to understand how early connectivity patterns can act as intermediaries linking genetic predisposition and environmental stimuli to postnatal cognitive outcome.

In the current study, we aimed to provide some insights into these issues through a longitudinal approach that involved the acquisition of prenatal rs-fMRI data, followed by postnatal language assessments by means of the Bayley-III language scale[29] within the first three years of life. The hereditary background related to familiar vulnerabilities or disorders of language and cognition, and the environmental input, that is the amount of exposure to speech during the prenatal period, were retrospectively reconstructed by means of a novel instrument that we developed ad hoc, named the Family Background Questionnaire (FBQ). The first result of our study is that the data-driven hierarchical clustering analysis of foetal resting-state functional connectivity confirmed the presence of an auditory-language network in the third trimester of foetal development. A unilateral network was present in both hemispheres encompassing subcortical relay nuclei (thalamus, putamen, caudate nucleus), sensorimotor cortices (Heschl's gyrus, middle and superior temporal gyri, and rolandic operculum) and primordial language regions in the perisylvian cortices (inferior frontal regions, insula, superior temporal pole). These results are in line with previous rs-fMRI evidence and confirm the establisment of subcortico-cortical functional connectivity between deep grey matter nuclei, sensorimotor, and perisylvian cortices. Subcortico-cortical functional connectivity along the auditory pathway[42] as well as local connectivity within temporal regions[43] start to develop around 24–25 GW. Thomason and colleagues[44] have observed functional connectivity in a left-lateralized fronto-temporal network including language-related regions in foetuses older than 31 GW. A recent study[23] conducted on a large sample of foetuses between 21 and 40 GW found functional connectivity in a left-lateralized fronto-temporal-insular network which strongly overlaps with the one we found, and included Heschl's gyrus, mid and superior temporal cortices, inferior frontal regions, insula, rolandic operculum, and the anterior cingulum. A recent study described the development of the language network from 30 GW to 1 month after birth, and in particular it reported a significant increase in functional connectivity within the language

network occurring between 31 and 35 GW[45]. Considering this body of evidence, our study clearly confirms that functional networks supporting auditory and language processing are already established between 27 and 35 GW.

The FBQ was conceived as a retrospective tool for determining which children may be at risk of developing language processing difficulties based on familial and prenatal speech exposure factors. The outcome of the expert FBQ validation by means of content and face validity assessments (Supplementary Materials: Methods S1, Figure S1) highlighted that this instrument is endowed with enough sensitivity to capture at least part of the intricate relationships between familial and environmental background and early postnatal language developmental trajectories. We correlated the familial risk and environmental exposure FBQ scores with foetal functional connectivity values across all possible ROI pairs within the identified left and right auditory-language networks. The results revealed a negative correlation between familial risk scores and strength of the two connections "left insula - left rolandic operculum" and "left insula - left caudate nucleus". Previous research has consistently demonstrated that infants and children at risk for developmental language and learning disorders exhibit abnormal functional connectivity patterns, reduced functional brain activation, and white matter disorganization compared to controls[46–52]. Our results extend and anticipate the developmental time frame of these associations to the prenatal period, by showing that they may already be present in the foetal brain. Neuroimaging genetic evidence showed that children with a risk allele for dyslexia have reduced functional and structural connectivity between fronto-temporal language regions compared to children without any risk alleles[52].

The FBQ variable related to prenatal speech exposure showed a positive correlation with foetal functional connectivity in the two region pairs "left rolandic operculum - left middle temporal gyrus" and "left rolandic operculum - left superior temporal pole", and a negative correlation in the "right orbital middle frontal gyrus - right Heschl's gyrus" pair. Thus, foetuses exposed to a greater amount of speech stimuli developed stronger functional connectivity between regions of the left auditory-language network, and weaker connectivity between regions of the right hemisphere. Recent studies demonstrated that the amount of domestic language interactions between infants and adults affects the infants' functional connectivity in posterior temporal regions of the language network[12] and predict the myelination of language-related white matter tracts measured at 2 years[53]. A review paper has recently examined the relationship between other environmental factors, such as the socio-economic status, and structural and functional brain development[54]. Children and adolescents with higher socio-economic status have thicker cortex[55] and larger surface areas[56,57] compared to their peers with lower socio-economic status[54]. These effects are observed in multiple subcortical and cortical regions, including middle temporal and inferior frontal language structures[56,57]. Functional connectivity between limbic structures and cortical regions has been found to be reduced in children with lower socio-economic status[54,58]. However, results in this field are not always consistent across studies, and some authors claimed that the influence of environmental variables on brain development may vary depending on developmental age[54].

A recent study demonstrated that morphological fingerprints in perinatal brains can predict language abilities at 18 months of age[59]. While this study focused on infants, in our study we wished to evaluate the challenging hypothesis that already in the foetal developmental stage, early brain architecture can be predictive of postnatal language outcome. We therefore tested through a stepwise regression model whether fotal functional connections showing associations with familial risk and environmental speech exposure can predict the postnatal development of linguistic skills. Our results revealed prediction of language developmental outcomes in infancy pivoted on prenatal connectivity of the insular cortex with the caudate nucleus and the rolandic operculum. This finding highlights the potential of prenatal functional connectivity as an early biomarker for postnatal language development. To this respect, it is worth highlighting that, amongst the plethora of regions of interest and connections included in our analyses, insular connectivity emerged as a consistent predictor of language outcomes. This is interesting when considering that modulation of insular functional connectivity patterns has been previously reported by studies investigating the impact of psychological[60–62]environmental[63] and lifestyle[64] factors in fetuses, as well as in neonates born preterm[65] and with a higher familial risk of developing autism[45]. Our work aligns with these findings and suggests that familial risk for language disorders may influence the functional architecture of the developing language system, ultimately impacting language outcomes in infancy.

We believe our evidence is consistent with the centrality of the insula for the development of the brain's functional architecture. In fact, the insula is a phylogenetically-old structure and has been recognized as a key neurodevelopmental hub in the maturation of the whole neocortical mantle[66]. Structurally, the insular cortex reaches maturation around 30 GW, and establishes an extensive pattern of connections with both subcortical structures (including the thalamus, putamen, and caudate nucleus), and all major neocortical processing sites related to both sensorimotor and higher-order processing[67]. Functionally, during the late foetal period, the insula, alongside the sensorimotor cortices, acts as a major functional hub triggering transient bursting activity propagation, and underlying the maturation of large scale brain networks[68]. Thus, within the conceptual framework of our study, the insular functional gridline represents a particularly sensitive proxy for detecting the influence of familial and environmental factors during the prenatal developmental stage.

Furthermore, our findings are in line with the centrality of the insular cortex for language and speech processing[69] as well as with its involvement in shaping functional networks underlying adaptive cognitive and behavioural processes. In particular, the anterior insula contributes to the regulation between task passive and task active networks[70] promoting the development of executive control[28,37]. This self-regulatory capability throughout infancy is pivotal for pre- and proto-linguistic communicative interactions and represents the groundings on which proper language development occurs[37].

More specifically, our results revealed that the prediction of language development in early childhood pivoted on prenatal functional synchronization of the insular cortex with, subcortically, the caudate nucleus and a region associated with sensorimotor processing (i.e., the parietal operculum and caudate nucleus). The parietal

operculum hosts a large portion of the secondary somatosensory cortex, and supports multimodal integration of somatosensory, auditory, visual, visceral and motor information, which is essential for the learning, consolidation and execution of complex behavioral repertoires[71]. The caudate nucleus is involved in the flexible adaptation of behavior based on internal and external feedback[72] and play a key role in temporal sequencing, initiation and monitoring of actions. The insula could thus represent an ontogenetic relay for the consolidation of subcortical-cortical and cortical-cortical sensorimotor functional loops, which in turn scaffold the emergence of functional networks underlying higher-order cognitive functions, including the development of language capabilities[37].

Another notable finding emerging from our results concerns the issue of hemispheric lateralization in early language network development. Previous evidence on young infants supports the idea that structural and functional asymmetries of the auditory-language network develop in the first year of life[73,74]. There is limited evidence regarding leftward lateralization of language in the foetal brain. In the current study, we reported the presence of unilateral FC auditory-language networks in both hemispheres of the 27–35 GW foetal brain. The hierarchical clustering analysis did not reveval any difference in functional connection strength between the left and right hemispheres. Notably, however, both familial risk and speech exposure FBQ variables were mainly linked with left-hemispheric FC. More specifically, familial risk for developing language disorders was associated with lower FC between regions of the left hemisphere. Greater prenatal speech stimulation was linked with increased FC in regions of the left hemisphere, and with decreased FC in regions of the right hemisphere. Moreover, FC in the left hemisphere significantly predicted postnatal language abilities. This evidence may indicate that, although two functional networks are specularly present in both hemispheres of the foetal brain, the left-hemispheric FC within the primordial auditory-language network is predominantly involved in the prospective development of language functions over the perinatal and postnatal periods.

Conclusions, limitations, and future directions

The current study represents a first attempt to link familial and prenatal exposure factors with foetal functional connectivity and postnatal language development trajectories. We showed that higher exposure to speech stimuli during pregnancy is associated with stronger prenatal functional connectivity between regions of the left auditory-language network. Moreover, we showed that familiarity for language disorders is associated with lower functional connectivity between the left caudate nucleus and insula, and between the left insula and rolandic operculum. Functional connectivity in these connections is in turn associated with language development outcomes in early childhood. These results are promising and support the idea that prenatal functional connectivity, prenatal speech exposure, and familial risk variables could serve as potential markers for predicting early language development trajectories and disorders. However, an important limitation of this study is the relatively small sample size. While these findings offer valuable insights into early brain and language development, the generalizability to a broader population may be limited. Future confirmative studies in larger samples will be required. Another limitation concerns the limited variability observed in the Family Background Questionnaire scores, which were relatively skewed toward lower values for both familial risk and prenatal speech exposure. This likely reflects the prevalence of these traits in the general population, as our sample was not selectively recruited based on these factors. The restricted score spread may have reduced sensitivity to detect finer associations. Future studies may benefit from stratified recruitment to ensure broader representation of these variables. Moreover, future studies may also take advantage of a more detailed characterization of prenatal environmental variables, by gathering more comprehensive data on the type, amount, and frequency of auditory and speech stimulation that reaches the foetus during pregnancy, either retrospectively and taking advantage of the FBQ as in the present study, or eventually directly in prospective longitudinal studies. Crucially, longitudinal assessments of language abilities up to school-age may evaluate whether these multimodal factors can predict the insurgence of developmental language and learning disorders, thus opening the way to more timely supportive interventions.

Data availability

The data that support the findings of this study cannot be made openly available due to confidentiality restrictions. Anonymized data will be made available upon reasonable request from Pasquale Anthony Della Rosa (dellarosa.pasquale@hsr.it), in accordance with the Ethics Committee of the San Raffaele Hospital, Milan, Italy.

Received: 26 February 2025; Accepted: 25 August 2025
Published online: 26 September 2025

References

1. Mountford, H. S. & Newbury, D. F. The Genetics of Language Acquisition. In *International Handbook of Language Acquisition* (eds. Horst, J. S. & Von Koss Torkildsen, J.) 33–50 (Routledge, New York, NY: Routledge https://doi.org/10.4324/9781315110622-3 (2019).
2. Onnis, L., Truzzi, A. & Ma, X. Language development and disorders: possible genes and environment interactions. *Res. Dev. Disabil.* **82**, 132–146 (2018).
3. Rowe, M. L. & Weisleder, A. Language development in context. *Annu. Rev. Dev. Psychol.* **2**, 201–223 (2020).
4. Grigorenko, E. L. Speaking genes or genes for speaking?? Deciphering the genetics of speech and Language. *J. Child. Psychol. Psychiatry*. **50**, 116–125 (2009).
5. Andreola, C. et al. The heritability of reading and reading-related neurocognitive components: A multi-level meta-analysis. *Neurosci. Biobehav Rev.* **121**, 175–200 (2021).
6. Kovas, Y. et al. Genetic influences in different aspects of Language development: the etiology of Language skills in 4.5-Year-Old twins. *Child. Dev.* **76**, 632–651 (2005).
7. Stromswold, K. The heritability of language: A review and metaanalysis of twin, adoption, and linkage studies. *Language* **77**, 647–723 (2001).

8. Ferjan Ramírez, N., Lytle, S. R., Fish, M. & Kuhl, P. K. Parent coaching at 6 and 10 months improves Language outcomes at 14 months: A randomized controlled trial. *Dev. Sci.* **22**, e12762 (2019).
9. Eising, E. et al. A set of regulatory genes co-expressed in embryonic human brain is implicated in disrupted speech development. *Mol. Psychiatry*. **24**, 1065–1078 (2019).
10. Galaburda, A. M., LoTurco, J., Ramus, F., Fitch, R. H. & Rosen, G. D. From genes to behavior in developmental dyslexia. *Nat. Neurosci.* **9**, 1213–1217 (2006).
11. Richmond, S., Johnson, K. A., Seal, M. L., Allen, N. B. & Whittle, S. Development of brain networks and relevance of environmental and genetic factors: A systematic review. *Neurosci. Biobehav Rev.* **71**, 215–239 (2016).
12. King, L. S., Camacho, M. C., Montez, D. F., Humphreys, K. L. & Gotlib, I. H. Naturalistic Language input is associated with Resting-State functional connectivity in infancy. *J. Neurosci.* **41**, 424–434 (2021).
13. Gervain, J. Plasticity in early Language acquisition: the effects of prenatal and early childhood experience. *Curr. Opin. Neurobiol.* **35**, 13–20 (2015).
14. Dehaene-Lambertz, G. et al. Functional organization of perisylvian activation during presentation of sentences in preverbal infants. *Proc. Natl. Acad. Sci. U. S. A.* 103, 14240–14245 (2006).
15. Ghio, M., Cara, C. & Tettamanti, M. The prenatal brain readiness for speech processing: A review on foetal development of auditory and primordial Language networks. *Neurosci. Biobehav Rev.* **128**, 709–719 (2021).
16. Granier-Deferre, C., Ribeiro, A., Jacquet, A. Y. & Bassereau, S. Near-term fetuses process Temporal features of speech. *Dev. Sci.* **14**, 336–352 (2011).
17. Schleussner, E. & Schneider, U. Developmental changes of auditory-evoked fields in fetuses. *Exp. Neurol.* **190**, 59–64 (2004).
18. Dubois, J. et al. Mapping the early cortical folding process in the preterm newborn brain. *Cereb. Cortex N Y N 1991*. **18**, 1444–1454 (2008).
19. Habas, P. A. et al. Early folding patterns and asymmetries of the normal human brain detected from in utero MRI. *Cereb. Cortex*. **22**, 13–25 (2012).
20. Khan, S. et al. Fetal brain growth portrayed by a Spatiotemporal diffusion tensor MRI atlas computed from in utero images. *NeuroImage* **185**, 593–608 (2019).
21. Martino, J. et al. Analysis of the subcomponents and cortical terminations of the Perisylvian superior longitudinal fasciculus: a fiber dissection and DTI tractography study. *Brain Struct. Funct.* **218**, 105–121 (2013).
22. Kostović, I., Sedmak, G. & Judaš, M. Neural histology and neurogenesis of the human fetal and infant brain. *NeuroImage* **188**, 743–773 (2019).
23. Turk, E. et al. Functional connectome of the fetal brain. *J. Neurosci.* **39**, 9716–9724 (2019).
24. Jakab, A. Developmental pathoconnectomics and advanced fetal MRI. *Top. Magn. Reson. Imaging.* **28**, 275–284 (2019).
25. Desrosiers, J. et al. Functional connectivity development in the prenatal and neonatal stages measured by functional magnetic resonance imaging: A systematic review. *Neurosci. Biobehav Rev.* **163**, 105778 (2024).
26. Jakab, A. et al. Fetal functional imaging portrays heterogeneous development of emerging human brain networks. *Front Hum. Neurosci.* **8**, (2014).
27. Bourguignon, N. J., Nadig, A. & Valois, D. The biolinguistics of autism: emergent perspectives. *Biolinguistics* **6**, 124–165 (2012).
28. Della Rosa, P. A. et al. The effects of the functional interplay between the default mode and executive control resting state networks on cognitive outcome in preterm born infants at 6 months of age. *Brain Cogn.* **147**, 105669 (2021).
29. Bayley, N. Bayley Scales of Infant and Toddler Development, Third Edition. (2012). https://doi.org/10.1037/t14978-000
30. Kostović, I., Radoš, M., Kostović-Srzentić, M. & Krsnik, Ž. Fundamentals of the development of connectivity in the human fetal brain in late gestation: from 24. *Weeks Gestation. Age Term J. Neuropathol. Exp. Neurol.* **80**, 393–414 (2021).
31. MacArthur-Bates Communicative Development Inventories. https://mb-cdi.stanford.edu/
32. Ashburner, J. & Friston, K. J. Unified segmentation. *NeuroImage* 26, 839–851 (2005).
33. Whitfield-Gabrieli, S. & Nieto-Castanon, A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* **2**, 125–141 (2012).
34. Behzadi, Y., Restom, K., Liau, J. & Liu, T. T. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage* **37**, 90–101 (2007).
35. Gholipour, A. et al. A normative spatiotemporal MRI atlas of the fetal brain for automatic segmentation and analysis of early brain growth. *Scientific Reports*, **7**(1). https://doi.org/10.1038/s41598-017-00525-w(2017).
36. Nieto-Castanon, A. Brain-wide connectome inferences using functional connectivity multivariate pattern analyses (fc-MVPA. *PLOS Comput. Biol.* **18**, e1010634 (2022).
37. Canini, M. et al. Functional connectivity markers of prematurity at birth predict neurodevelopmental outcomes at 6, 12, 24, and 36 months. *International J. Behav. Devel.* (2025).
38. Bornstein, M. H., Hahn, C. S., Putnick, D. L. & Pearson, R. M. Stability of core Language skill from infancy to adolescence in typical and atypical development. *Sci. Adv.* **4**, eaat7422 (2018).
39. Pace, A., Alper, R., Burchinal, M. R., Golinkoff, R. M. & Hirsh-Pasek, K. Measuring success: within and cross-domain predictors of academic and social trajectories in elementary school. *Early Child. Res. Q.* **46**, 112–125 (2019).
40. Hohm, E., Jennen-Steinmetz, C., Schmidt, M. H. & Laucht, M. Language development at ten months. *Eur. Child. Adolesc. Psychiatry*. **16**, 149–156 (2007).
41. Catts, H. W., Bridges, M. S., Little, T. D. & Tomblin, J. B. Reading achievement growth in children with Language impairments. *J. Speech Lang. Hear. Res.* **51**, 1569–1579 (2008).
42. Canini, M. et al. Subcortico-Cortical functional connectivity in the fetal brain: A cognitive development blueprint. *Cereb. Cortex. Commun.* **1**, (2020).
43. Schöpf, V., Kasprian, G., Brugger, P. C. & Prayer, D. Watching the fetal brain at 'rest'. *Int. J. Dev. Neurosci.* **30**, 11–17 (2012).
44. Thomason, M. E. et al. Intrinsic functional brain architecture derived from graph theoretical analysis in the human fetus. *PLOS ONE*. **9**, e94423 (2014).
45. Scheinost, D. et al. Functional connectivity for the Language network in the developing brain: 30 weeks of gestation to 30 months of age. *Cereb. Cortex.*. **32**, 3289–3301 (2022).
46. Cantiani, C. et al. Reduced left-lateralized pattern of event-related EEG oscillations in infants at Familial risk for Language and learning impairment. *Neurol. Clin.* **22**, 101778 (2019).
47. Langer, N. et al. White matter alterations in infants at risk for developmental dyslexia. *Cereb. Cortex. N Y N 1991*. **27**, 1027–1036 (2017).
48. Packman, A. et al. White matter connectivity in neonates at risk of stuttering: preliminary data. *Neurosci. Lett.* **781**, 136655 (2022).
49. Raschle, N. M., Zuk, J. & Gaab, N. Functional characteristics of developmental dyslexia in left-hemispheric posterior brain regions predate reading onset. *Proc. Natl. Acad. Sci.* **109**, 2156–2161 (2012).
50. Vandermosten, M., Hoeft, F. & Norton, E. Integrating MRI brain imaging studies of pre-reading children with current theories of developmental dyslexia: A review and quantitative meta-analysis. *Curr Opin. Behav. Sci.* **10**, (2016).
51. Yu, X. et al. Patterns of neural functional connectivity in infants at Familial risk of developmental dyslexia. *JAMA Netw. Open.* **5**, e2236102 (2022).
52. Skeide, M. A. et al. Genetic dyslexia risk variant is related to neural connectivity patterns underlying phonological awareness in children. *NeuroImage* **118**, 414–421 (2015).

53. Huber, E., Corrigan, N. M., Yarnykh, V. L., Ferjan Ramírez, N. & Kuhl, P. K. Language experience during infancy predicts white matter myelination at age 2 years. *J. Neurosci.* **43**, 1590–1599 (2023).
54. Tooley, U. A., Bassett, D. S. & Mackey, A. P. Environmental influences on the Pace of brain development. *Nat. Rev. Neurosci.* **22**, 372–384 (2021).
55. Lawson, G. M., Duda, J. T., Avants, B. B., Wu, J. & Farah, M. J. Associations between children's socioeconomic status and prefrontal cortical thickness. *Dev. Sci.* **16**, 641–652 (2013).
56. McDermott, C. L. et al. Longitudinally mapping childhood socioeconomic status associations with cortical and subcortical morphology. *J. Neurosci.* **39**, 1365–1373 (2019).
57. Noble, K. G. et al. Family income, parental education and brain structure in children and adolescents. *Nat. Neurosci.* **18**, 773–778 (2015).
58. Hanson, J. L. et al. Resting state coupling between the amygdala and ventromedial prefrontal cortex is related to household income in childhood and indexes future psychological vulnerability to stress. *Dev. Psychopathol.* **31**, 1053–1066 (2019).
59. Wang, Y., Wang, B., Zhu, D., Zheng, W. & Sheng, Y. Revealing morphological fingerprints in perinatal brains using quasi-conformal mapping: occurrence and neurodevelopmental implications. *Brain Imaging Behav.* https://doi.org/10.1007/s11682-025-00998-8 (2025).
60. Canini, M. et al. Maternal anxiety-driven modulation of fetal limbic connectivity designs a backbone linking neonatal brain functional topology to socio-emotional development in early childhood. *J. Neurosci. Res.* **101**, 1484–1503 (2023).
61. Topping, K., Dekhinet, R. & Zeedyk, S. Parent–infant interaction and children's Language development. *Educ. Psychol.* **33**, 391–426 (2013).
62. Wu, Y., De Asis-Cruz, J. & Limperopoulos, C. Brain structural and functional outcomes in the offspring of women experiencing psychological distress during pregnancy. *Mol. Psychiatry*. **29**, 2223–2240 (2024).
63. Thomason, M. E. et al. Prenatal lead exposure impacts cross-hemispheric and long-range connectivity in the human fetal brain. *NeuroImage* **191**, 186–192 (2019).
64. Thomason, M. E. et al. Miswiring the brain: human prenatal Δ9-tetrahydrocannabinol use associated with altered fetal hippocampal brain network connectivity. *Dev. Cogn. Neurosci.* **51**, 101000 (2021).
65. Smyser, C. D. et al. Resting-state network complexity and magnitude are reduced in prematurely born infants. *Cereb. Cortex.*. **26**, 322–333 (2016).
66. Afif, A., Bouvier, R., Buenerd, A., Trouillas, J. & Mertens, P. Development of the human fetal insular cortex: study of the gyration from 13 to 28 gestational weeks. *Brain Struct. Funct.* **212**, 335–346 (2007).
67. Ghaziri, J. et al. Subcortical structural connectivity of insular subregions. *Sci. Rep.* **8**, 8596 (2018).
68. Arichi, T. et al. Localization of spontaneous bursting neuronal activity in the preterm human brain with simultaneous EEG-fMRI. *eLife* **6**, e27814 (2017).
69. Oh, A., Duerden, E. G. & Pang, E. W. The role of the Insula in speech and Language processing. *Brain Lang.* **135**, 96–103 (2014).
70. Uddin, L. Q., Kinnison, J., Pessoa, L. & Anderson, M. L. Beyond the tripartite Cognition–Emotion–Interoception model of the human insular cortex. *J. Cogn. Neurosci.* **26**, 16–27 (2014).
71. Chen, T. L. et al. Human secondary somatosensory cortex is involved in the processing of somatosensory rare stimuli: an fMRI study. *NeuroImage* **40**, 1765–1771 (2008).
72. Grahn, J. A., Parkinson, J. A. & Owen, A. M. The cognitive functions of the caudate nucleus. *Prog. Neurobiol.* **86**, 141–155 (2008).
73. Chen, Y. et al. Maturation of auditory cortex neural responses during infancy and toddlerhood. *NeuroImage* **275**, 120163 (2023).
74. Williams, L. Z. J. et al. Structural and functional asymmetry of the neonatal cerebral cortex. *Nat. Hum. Behav.* **7**, 942–955 (2023).

Acknowledgements

We thank the mothers and infants who made this study possible, as well as their families, for completing the Family Background Questionnaire. We also thank all the doctors of the Department of Obstetrics and Gynaecology of the San Raffaele Hospital and their staff for their support and for allowing us to recruit women for the study. Finally we thank the MRI technicians of the Department of Neuroradiology of the San Raffaele Hospital for their help during the acquisition of fetal MRI data.

Author contributions

CC, MCanini, CO, MT and PADR conceptualized the study. MCandiani, AF and PADR acquired funding for the study. CC, NP, PIC, MCandiani, CB and AF provided software and resources. CC, MCanini, CO, PIC, CB and PADR collected the data. CC, MCanini, NP, PIC, CB, MT and PADR analyzed the data. CC, MCanini, CO, MT and PADR wrote the original manuscript draft. CC, MCanini, PIC, CB, MT and PADR reviewed and edited the manuscript.

Funding

This work was supported by the Italian Ministry of Health's "Ricerca Finalizzata 2016" (grant number RF-2016-02364081; principal Investigator: PADR).

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-17531-y.

Correspondence and requests for materials should be addressed to M.C., M.T. or P.A.D.R.