Title: Longitudinal associations between language network characteristics in the infant brain and school-age reading abilities are mediated by early-developing phonological skills

Abbreviated title: Infant language network scaffolds reading acquisition

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Abstract

Reading acquisition is a prolonged learning process relying on language development starting in utero. Behavioral longitudinal studies reveal prospective associations between infant language abilities and preschool/kindergarten phonological development, which in turn relates to subsequent reading performance. More recently, pediatric neuroimaging work has begun to characterize the neural network underlying language development in infants. However, it is still unknown how the infant language network scaffolds long-term language and reading acquisition. We addressed this question in a 7-year longitudinal study from infancy to school-age. Seventy-six infants (33 females) completed resting-state fMRI scanning during natural sleep, and were followed until kindergarten, where their language skills, including phonological processing abilities, were assessed behaviorally. Of this larger cohort, forty-one (21 females) were further assessed on their emergent word reading abilities after receiving at least one year of reading instructions. Hierarchical clustering analyses first identified a tripartite modular structure within the infant language neural network, consisting of the inferior frontal, middle frontal, and temporoparietal regions, respectively. Infant functional connectivity (FC) of the inferior frontal module prospectively correlated with kindergarten-age phonological skills and emergent word reading abilities, controlling for infant age and head movement during scanning, nonverbal IQ, and critical environmental factors. Further, kindergarten-age phonological skills mediated the relationship between infant FC and school-age reading abilities, implying a critical mid-way milestone for long-term reading development starting in infancy. Overall, our findings shed light on the neurobiological mechanisms underlying the infant's emergent language network serving as a scaffold for subsequent language and reading acquisition.

Significance Statement

A critical aspect of successful reading acquisition is language development starting in utero. While previous studies have started characterizing the neural network mechanisms underlying language development as early as infancy, their relationships to long-term language and reading acquisition remain unknown. Utilizing a seven-year longitudinal imaging dataset starting in infancy, the current study identified a modular infant language network in which functional connectivity (FC) of the inferior frontal module prospectively correlated with children's phonological skills in kindergarten. Infant FC of the inferior frontal module further contributed to individual differences in emergent word reading abilities and this relationship was mediated by kindergarten-age phonological skills. Our findings shed light on the neurobiological mechanisms by which infant language capacities could scaffold long-term reading acquisition.

Introduction

Learning to read relies on language development starting in utero. Infants show speech perception abilities (Gervain and Mehler, 2010), such as recognizing speech over non-speech sounds (Vouloumanos and Werker, 2007) and discriminating phonetic differences (Nazzi, 1998) since birth. Early linguistic experiences are theorized to serve as building blocks for various language skills, including phonological processing, in which children perceive and manipulate sound structures of words (Metsala and Walley, 1998; Vihman, 2014). Expressive and receptive oral language skills that typically develop before schooling, in turn, lay critical foundations for the acquisition of word reading abilities (e.g., Catts et al., 1999). Behavioral longitudinal studies repeatedly demonstrate that preschool/kindergarten language skills are prospectively associated with school-age reading performance (Puolakanaho et al., 2008; Hulme et al., 2015; Hjetland et al., 2020). By contrast, due to methodological difficulties in infant behavioral assessments and in acquiring data longitudinally, few studies have examined early trajectories of reading development. In these studies, infants' language abilities, i.e., vocabulary size, are shown to be associated with phonological skills in preschool; however, their specific contributions to school-age reading skills remain inconclusive (Silvén et al., 2004, 2007; Torppa et al., 2010). Empirical investigations are thus warranted to further unveil the mechanisms by which language development in infancy scaffolds long-term (pre-)reading acquisition.

Pediatric imaging techniques permit large-scale functional brain mappings at early developmental stages, providing insights into the neurobiological characteristics of the developmental trajectory of reading abilities. Learning to read in school-age children has been shown to associate with increasingly stronger neural connections among the frontotemporal language network (Fedorenko et al., 2010) and the occipitotemporal visual pathways (Yu et al., 2018). Moreover, while word-specific responses in the visual pathway (i.e., development of the visual word form area) are observed after reading onset (Dehaene-Lambertz et al., 2018), the emerging characteristics of the language neural network are already present in the infant brain (Dehaene-Lambertz, 2017). For example, speech-specific activations are observed in the inferior frontal and lateral temporal brain areas in preverbal infants (Dehaene-Lambertz et al., 2002; Shultz et al., 2014). These regions further display intrinsic functional connections in sleeping infants (Smyser et al., 2016), resembling the language neural network evident in adults at rest (Braga et al., 2020). Moreover, the language neural network in infancy seemed to contain an inferior frontal module and a temporal module, both of which showed greater functional connectivity (FC) for within-module connections than between-module connections, suggesting potentially differential developmental characteristics for each module (King et al., 2021). Longitudinally, whole-brain FC patterns of key components of the language network in infancy are associated with children's oral language performance in preschool (Emerson et al., 2016) and kindergarten (Yu et al., 2021), highlighting the cognitive significance relevance of the functional organization of the infant brain. However, it is still unknown whether and how early-emerging

language network characteristics in infancy *per se* relate to individual differences in children's reading achievements at school age.

Utilizing a seven-year longitudinal dataset spanning infancy to school-ages, the current study investigated long-term associations between FC in the infant language network and school-age language and reading outcomes. Seventy-six infants completed resting-state fMRI scanning during natural sleep, and their language skills, including phonological processing, were assessed behaviorally in kindergarten. Among them, 41 participants who received at least one year of reading instruction were further evaluated on their emergent word reading skills. Imaging data were analyzed to characterize the intrinsic functional organization of the infant language network using data-driven hierarchical clustering techniques. Partial correlations were then performed to evaluate whether infant language network characteristics were associated with kindergarten-age language skills and emergent reading abilities when controlling for infant age and head movement during scanning, critical environmental factors, and their general cognitive abilities measured at school-age. Finally, upon observed significant associations among infancy, kindergarten age and emergent reading stages, mediation analyses were applied to examine the hypothesized developmental pathway linking infant language development to word reading abilities through kindergarten-age language skills.

Materials and Methods

Participants

All participants were recruited as part of a longitudinal imaging project investigating the neural trajectory of long-term language and reading development since infancy (e.g., Yu et al., 2021, 2022; Zuk et al., 2021, 2022; Turesky, Sanfilippo et al., 2022). The current study included 76 participants (33 females) who had usable resting-state fMRI scans collected in infancy (mean age = 9.3 $\pm$ 3.5 months) and underwent language skill evaluation in kindergarten (mean age = 5.8 $\pm$ 0.9 years). By the time of data analyses, a subset of 41 children (21 females) who received at least one year of formal reading instruction (i.e., emergent readers, mean age = 8.1 $\pm$ 1.1 years) were further assessed on their word reading abilities (Figure 1, Table 1). All children were born full term (gestational age $\geq$ 36 weeks) and exposed to English since birth. No participant had birth complications, neurological trauma, or significant developmental delays, and their infancy structural images were examined by a pediatric neuroradiologist at Boston Children's Hospital (BCH) to ensure the absence of malignant brain features. Moreover, all subjects showed typical nonverbal IQ, demonstrated by above 80 standard scores (SS) on the Matrix Reasoning subset of the Kaufman Brief Intelligence Test-II (KBIT-II, Kaufman and Kaufman, 2004) administered at school-age. This study was approved by the Institutional Review Board at BCH and Harvard University. Informed written consent was obtained from a parent or legal guardian of each infant before participation.

Psychometric and environmental characterization at infancy and school-age time points

In infancy, participants' emergent receptive and expressive language skills were

evaluated using the Mullen Scales of Early Learning assessment (MSEL, Mullen, 1995; Table 1). Scale scores with a mean of 50 and a standard deviation (SD) of 10 were acquired for both language domains. Environmental characteristics relevant to long-term cognitive, language and literacy development were collected via parental questionnaires. These included socio-economic status (SES), measured as the average of the parents' highest degrees of education, and home literacy environment (HLE, adapted from Denney et al., 2001), which surveyed language- and literacy-related activities at home (see a full list of survey questions in Yu et al., 2021).

Children's language skills were assessed again in kindergarten (at the beginning and/or end of), this time using the Oral Language (OL) cluster and Phonological Processing subtest of the Woodcock-Johnson IV Tests (WJ-IV; Schrank and Wendling, 2015). The OL cluster is comprised of two subtests, which were picture vocabulary, measuring children's ability to identify pictured objects, and oral listening comprehension, requiring children to complete audio-recorded passages with appropriate words. The Phonological Processing subtest included 1) Word Access, which required participants to provide a word that has a specific phonemic element in a specific location; 2) Word Fluency, which measured the child's ability to name as many words as possible beginning with a specified sound in 1 minute; and 3) Substitution, which asked participants to substitute a word part to create a new word. SS for oral language and phonological processing tests were calculated automatically by the WJ-IV online scoring system.

Children who received at least one year of reading instruction (i.e., beginning at the end of kindergarten or later) were tested on emergent reading abilities using the Test of Word Reading Efficiency (TOWRE-2; Torgesen et al., 2012). As a timed measure of reading efficiency, TOWRE used both printed words (in the Sight Word Efficiency (SWE) subtest) and phonemically regular nonwords (in the Phonemic Decoding Efficiency (PDE) subtest) to measure the ability to pronounce words and nonwords accurately and fluently, respectively. Reading performance was obtained by averaging SS of the two subtests for each child. For children who completed the same assessments multiple times, only scores from their latest assessment were used in statistical analyses. To ensure that associations between kindergarten language skills and subsequent reading abilities could be evaluated prospectively, language skills were always assessed in the time point earlier than that for reading assessments (assessment interval = 22.6 ± 11.2 months, range: 10.6-62.7 months, Figure 1); however, results were similar when using the mean scores of each assessment across all the available time points (Extended Data Figure 3-5).

Image acquisition

Brain images of each infant were acquired during natural sleep on a Siemens 3T Trio MRI scanner with a 32-channel adult head coil (Raschle et al. 2012). Structural images were obtained using a T1 multi-echo MP-RAGE sequence with prospective motion correction (imaging parameters: TR = 2270 ms, TE1,2,3,4 = [1.66, 3.48, 5.3, 7.12] ms,

TI = 1450 ms, flip angle = 7°, field of view = 220 mm^2, voxel size = 1.1 × 1.1 × 1.0 mm^3, number of slices = 176). An 8-min EPI BOLD sequence was utilized to collect resting-state fMRI images. For images collected before 2017 (n = 43), the following acquisition parameters were used: TR = 3000 ms, TE = 30 ms, flip angle = 60°, voxel size = 3 × 3 × 3 mm^3. An additional simultaneous muti-slice (SMS) imaging technique with a shorter TR (950 ms) was utilized for resting-state fMRI acquisition in 2017 and after (n = 33) with the other parameters kept the same.

Imaging data preprocessing

An infant-appropriate preprocessing pipeline (Yu et al., 2021, 2022) was applied in the current study. Functional MRI images were first corrected for slice timing using FSL/SLICETIMER (separately on each SMS slice group for the SMS-acquired data, Viessmann et al., 2019). Rigid body alignment for motion correction and estimation of motion regressors were performed using FSL/MCFLIRT. Framewise displacement (FD) was estimated based on head movement estimates (Power et al., 2012) using an in-house script (https://github.com/xiyu-bnu/infant_restingstate_prediction). Volumes with FD > 0.3 mm were considered outliers. One preceding and two subsequent artifactual frames were also removed to minimize the potential spreading effect. An average of 2.6% (SD = 0.04, range: 0% ~ 17.6%) outlier scans were identified and removed from each participant dataset, leaving at least 5-min usable volumes for every infant included. All fMRI data were then spatially normalized to the UNC 1-year-old infant template (Shi et al., 2011) via the corresponding structural image using affine transformations (FSL/FLIRT). Linear regression was subsequently performed with six continuous motion regressors, mean CSF and WM signals, and motion outliers as nuisance regressors. Images were further temporally band-pass filtered (0.01-0.1 Hz) and spatially smoothed (Gaussian Filtered, FWHM = 6 mm). Finally, to keep temporal resolution consistent across the whole sample, we resampled images that were acquired with the multi-slice sequence to TR = 3000ms.

Functional connectivity analyses of the infant language network

Seed selection

Seed regions constituting the language network were defined based on the language parcels developed by Fedorenko and colleagues, which were derived from the group-level activation result of *Sentences* > *Nonwords* contrast in 220 participants (Mineroff et al., 2018; Fedorenko et al., 2020; available at https://evlab.mit.edu/funcloc/). Twelve bilateral regions of interest (ROIs) were included, which are the inferior frontal gyri (IFG), IFG *pars orbitalis* (IFGorb), middle frontal gyri (MFG), anterior (AntTemp) and posterior (PostTemp) part of middle temporal gyri, and angular gyri (AngG). This language network shows selective activation for high-level linguistic processes in adults (Fedorenko et al., 2011) across 45 languages and 12 language families (Malik-Moraleda et al., 2022), and initial evidence suggests the presence of intrinsic functional connections among component regions of the language network in infants (Smyser et al., 2016, King et al., 2021). All ROIs were further refined using a probabilistic atlas built on the convergence (i.e., percentage of participants) of language-specific

activation across 806 adults (LanA; Lipkin et al., 2022). Specifically, a region-level threshold of 25%, representing the top quarter of voxels with most consistent inter-participant responses to language processing within each region, was applied to enhance each ROI's functional specificity for language processing. Finally, all ROIs provided, which were defined in adult MNI space, were transformed to the UNC 1-year-old infant template space (Shi et al., 2011, Fig. 2A) using Advanced Normalization Tools (ANTs, Avants et al., 2009).

Modularity analyses

Given the modular structure of the infant language network reported in the previous study (King et al., 2021), the data-driven clustering techniques were applied in the current study to identify potential clusters (i.e., modules) of nodes based on the FC patterns of the language network (see similar approaches in Blank et al., 2014; Mineroff et al., 2018). Specifically, the FC patterns were first computed for each infant by performing Pearson correlations between the mean BOLD time series of each seed region. The Fisher-z scores derived from the correlation results were averaged across all infants and transformed back to *r* values, resulting in a group level FC matrix of the infant language network (Fig. 2B). A group level distance matrix was then created by subtracting the group level FC matrix from 1. This distance matrix was submitted into the hierarchical clustering analyses using the agnes function in the R package *cluster* (Maechler et al., 2012). These analyses produced a binary tree structure, which indicated how the whole network could be divided into different clusters and which regions constitute each cluster as the path length increases (Fig. 2C). Clustering was generated based on the average linkage, where the distance between two clusters was defined as the average distances between all node pairs in the two cluster. Then, to determine the optimal partition level in the resulting binary tree structure (i.e., the "ideal" modular structure), a modularity-optimization method was applied (Newman and Girvan, 2004) using the Modularity Calculation program available in Radatools (https://deim.urv.cat/~sergio.gomez/radatools.php). To do this, all 12 possible modularity structures were delineated by increasing the path length in the binary tree structure one step at a time, ranging from a twelve-module structure with each module consisting of one single ROI to a one-module structure with all 12 ROIs as one module. A modularity Q score was computed for each of these partition results by comparing the functional correlations of the cluster structure with the expected values under a null model (Bazzi et al., 2016). Here, a uniform null model was used, which is shown to be appropriate for analyses on correlation matrices of the imaging data (Kenett et al., 2020). The optimal modular structure of the infant language network was then selected based on the highest Q score that indicated the best clustering solution. Finally, FC of each module of the infant language network was calculated for every infant by averaging FC of all paths within one module and converted into Fisher-z values for subsequent analyses.

Longitudinal analyses between infancy and school-age time points

Association analyses of behavioral outcomes measured at all time points

Infants' language scores (i.e., MSEL receptive and expressive language) were first Pearson correlated with their kindergarten-age language performance (i.e., oral language and phonological skills) and emergent reading abilities to evaluate the long-term association effects of infants' language behaviors. Then, to estimate the concurrent associations among kindergarten-age language abilities, as well as their longitudinal relationships with emergent word reading skills, Pearson correlations were further conducted between psychometric results obtained at the school-age timepoints.

Association analyses between infant language network characteristics and kindergarten-age language skills

Partial correlations were performed between FC of each module within the infant language network and standard scores of each kindergarten-age language measurement, i.e., phonological skills and oral language. Infant age and head movement (mean FD) were incorporated as covariates. To minimize potential confounding effects of environmental factors and general cognitive abilities, infants' family SES and HLE characteristics, as well as their non-verbal IQ measured at school-age, were also included as control variables. In addition, multiple imputation procedures implemented in IBM SPSS 26.0 were applied to account for missing data in control variables (one nonverbal IQ, one SES, and three HLE estimates) using imputed values averaged across five imputation samples. No data imputation was performed for the language performance scores.

Furthermore, given the significant brain changes within the first two years of life (Knickmeyer et al., 2008; Gilmore et al., 2012, 2018), additional analyses were conducted to estimate whether the observed relationships between infant FC and kindergarten-age behavior were consistent across infancy (i.e., 2.5 to 18.6 months old). Specifically, we first replicated our analyses within a subset of infants whose images were collected within the first year of life (n = 51, mean age = 8.4 $\pm$ 2.2 months). We then generated 11 subsamples containing the same number of infants (n = 51) by sliding the age window along the dimension of infant age at scan until reaching the oldest age. The same partial correlations were run to evaluate whether the observed longitudinal associations based on all infants' data remained significant for these subsamples covering variable portions of the entire range of ages at scan.

Association analyses between infant language network characteristics and long-term reading development

To assess the prospective associations between the infant language network and long-term reading achievement, partial correlations were further performed between FC of each module and word reading abilities of participants who received at least one year of reading instruction. The same set of covariates as described above were applied.

Moreover, if any of the language skills measured in kindergarten showed significant associations with both infant FC and emergent reading abilities, the potential mediation role of the identified kindergarten-age skill was examined. To do this, a sub-group of

participants that had relevant data at all time-points were selected (Figure 1). Mediation analyses were conducted via structural equation modeling, with infant age and head movement during scanning, as well as family SES, HLE and school-age nonverbal IQ included as covariates. The statistical significance of the indirect effect (i.e., of the mediator) was computed using an estimate of the delta method standard error and compared against zero using a Z test, following Sobel's approach (Sobel, 1982). All statistical analyses were performed using JASP 0.17.1 (Love et al., 2019), and results were adjusted for multiple comparisons using FDR corrections.

Code and data availability

All ROIs and codes for the functional connectivity analyses are available at: https://github.com/XinyiTang16/LanNet_code. Because of the Institutional Review Board regulations at BCH, the data used in this study cannot be available on a permanent third-party archive currently. However, data sharing can be initiated through a Data Usage Agreement upon request.

Results

Intrinsic modular architecture of the infant language network

An overarching tripartite modular architecture (Fig. 2C) was identified in the tree structure obtained from hierarchical clustering, which had the highest modularity value (Q = 0.3) compared to all other partitions. Accordingly, the infant language network was optimally characterized by an internal tripartite modular structure, which included an inferior frontal module involving bilateral IFG and IFGorb gyri (i.e., IFG module), a middle frontal module comprised of bilateral MFG, and a temporoparietal module containing anterior and posterior temporal and angular gyri bilaterally. The same modular results were also obtained based on the thresholded group level FC matrix that only included positive functional connections (Extended Data Fig. 2), speaking to the robustness of the observed tripartite modular structure of the infant language network.

Association results of behavioral outcomes measured at infancy and school-age time points

The correlation results of behavioral performance were presented in Table 2. Infants' emergent language skills measured as MSEL receptive and expressive language scores correlated with each other (r = 0.44, $p_{\text{corrected}}$ = 0.002); however, neither were significantly correlated with any language or reading measure assessed at school-age (ps > 0.1). Therefore, infants' behavioral characteristics were not considered in subsequent analyses.

The language skills measured in kindergarten revealed significant positive correlations with each other (r = 0.41, $p_{\text{corrected}}$ = 0.004). Moreover, the kindergarten-age phonological skills were also prospectively associated with the emergent word reading abilities measured approximately two years later (r = 0.65, $p_{\text{corrected}}$ < 0.001).

Association results between infant language network characteristics and kindergarten-

age language skills

Among the three modules within the infant language network, positive partial correlations were observed between the FC of the IFG module in infancy and phonological skills assessed at kindergarten ($r = 0.38$, $p_{corrected} = 0.024$; Fig. 3A). These associations were observed when controlling for infants' ages and head movements during scanning, their HLE and SES characteristics, as well as nonverbal IQ assessed at school-age. No significant partial correlations were found for kindergarten-age oral language performance, nor the other two modules (i.e., MFG and TPG modules, *ps* > 0.1, Extended Data Fig. 3-1).

Replication analyses based on imaging data acquired within the first year of life also revealed significant longitudinal association between infant FC of the IFG module and kindergarten-age phonological skills ($r = 0.35$, $p_{corrected} = 0.023$). Moreover, significant partial correlations were obtained for all eleven subsamples with increasing infant ages ($p_{corrected}$s < 0.05, Extended Data Fig. 3-2), revealing the reliability of the observed longitudinal relationship across the age range of infant imaging data collection.

Association results between infant language network characteristics and long-term reading development

Utilizing partial correlation analyses with the same covariates described above, the FC of the IFG module was further demonstrated to be significantly and positively correlated with the emergent word reading abilities ($r = 0.42$, $p_{corrected} = 0.036$; Fig. 3A). The infant FC of the MFG and TPG modules did not show significant partial correlations with children's emergent reading abilities (*ps* > 0.5, Extended Data Fig. 3-1).

Moreover, given the significant associations of kindergarten-age phonological skills with FC of the IFG module within the infant language network and subsequent word reading achievement, the potential mediation role of phonological skill was further examined in participants whose kindergarten-age phonological and emergent reading performance were both available ($n = 37$; Fig. 3B). The total effect of infant FC of the IFG module on emergent reading abilities was significant (total effect = 0.42, *standard error (SE)* = 0.16, 95% CI = [0.12, 0.72]), replicating the main result. Notably, an indirect effect of infant FC on emergent reading abilities via kindergarten-age phonological skills was also found (indirect effect = 0.25, *SE* = 0.11, 95% CI = [0.04, 0.45], indirect/total effect = 60%) and further supported by a Sobel test ($z = 2.30$, $p = 0.021$), while the direct effect from infant FC to emergent reading skills after accounting for the indirect pathway was not significant (direct effect = 0.17, *SE* = 0.14, 95% CI = [-0.10, 0.44]). These results suggested that kindergarten-age phonological skills significantly mediated the relationship between FC characteristics of the infant language network and subsequent word reading abilities.

It is important to note that the result patterns obtained based on ROIs derived from the probabilistic atlas (LanA) using a region-level threshold of 25% (i.e., the threshold used

to refine the ROIs used in the preceding analyses) were also evident when other thresholds (50%, 75%, 100%; Extended Data Fig. 3-3) were applied, suggesting the consistency of results across different functional specificity levels of the language network. Moreover, similar results could be observed when using scores of the SWE and PDE subtests of the TOWRE assessment, respectively (Extended Data Fig. 3-4), further speaking to the general word reading abilities examined in the current study.

Discussion

The present study provides the first evidence for the prospective associations between the functional organization of the infant language network and school-age language and reading performance. Utilizing a data-driven clustering approach, we first identified a tripartite modular structure for the infant language network that included inferior frontal, middle frontal, and temporoparietal modules. We further observed that infant FC of the inferior frontal module (the IFG module), but not the middle frontal or temporoparietal modules, was prospectively associated with kindergarten-age phonological skills and emergent word reading abilities, with the latter longitudinal relationship significantly mediated by kindergarten-age phonological skills. Moreover, the effects were observed when controlling for participants' environmental characteristics and general cognitive abilities. Overall, these findings suggest that language network characteristics in infancy may scaffold long-term language and reading development.

Intrinsic functional connections of the IFG module within the infant language network are correlated with kindergarten-age phonological skills, highlighting the early emergence of functional circuits in the inferior frontal areas that might link to long-term phonological development. Infants show IFG activation in response to spoken language compared to non-linguistic signals, such as backward speech and biological non-speech (Dehaene-Lambertz et al., 2002; Shultz et al., 2014). Utilizing a slow event-related design in sleeping infants, Dehaene-Lambertz and colleagues (2006) observed that sentence processing elicited a cascade of activations beginning in temporal regions and proceeding to inferior frontal regions, suggesting a higher-level role of IFG in the hierarchical processing of speech. Indeed, the IFG of the infant brain has been shown to discriminate phonemic changes (Mahmoudzadeh et al., 2013), recognize specific pattern regularities (i.e., ABB) over tri-syllabic sequences consisting of different syllables (Gervain et al., 2008) and decode newly learned words from continuous speech steams (Minagawa et al., 2017). Collectively, these findings imply the early functional onset of IFG in facilitating infants' learning of the sound structural properties of one's native language. The current results support this putative role of IFG by relating its FC characteristics in infancy to individual differences in children's kindergarten-age phonological skills. Moreover, this relationship was observed when participants' environmental characteristics and general cognitive abilities were controlled, further speaking to the inherent network characteristics in infancy that may underlie learning of phonological skills in children.

Previous behavioral findings have led to a hypothesized role of early lexical

development (vocabulary size) on the phonological skill acquisition (Goswami, 2007). In English, the emerging lexicons in young children are characterized by high proportion of phonologically similar entries (>80% of words have at least one phonological neighbor, Dollaghan, 1994). Therefore, as children's vocabulary size increases, the phonological similarity neighborhoods of their lexicons also grow, which could facilitate more fine-grained analyses/representation of word sound patterns and support phonological development (Stoel-Gammon, 2011, Metsala and Walley, 1998). Consistent with this postulation, vocabulary size in late infancy is shown to be longitudinally associated with preschool- and kindergarten-age syllabic awareness skills (Silvén et al., 2002, 2007), and commensurate vocabulary and phonological development was documented both in late talkers (Rescorla and Ratner, 1996) and lexically precocious toddlers (Smith et al., 2006). Meanwhile, infant's IFG responses to speech are recently shown to significantly link to toddlerhood vocabulary growth, implying a potential role of IFG in supporting lexical development (Zhao et al., 2022). Within this context, the phonological-related FC of the IFG module could be interpreted as neural mechanisms underlying vocabulary acquisition in early childhood, which in turn foster subsequent phonological development. The potential involvement of IFG in early lexical development is not in contrast with its proposed role in abstract sound pattern recognition, as the latter could contribute to the sound-meaning mapping essential for vocabulary acquisition. This account could also be reconciled with the null results observed between infant FC of the IFG module and oral language skills measured in kindergarten using language tasks of picture vocabulary and oral comprehension. While the initial word learning might rely critically on word sound identification enabled by emerging phonological abilities, completion of more advanced lexical tasks would require access to the semantic knowledge represented by a rather distributed neural network (Lambon Ralph et al., 2017; Binder et al., 2009). Consistent with this speculation, we have shown that whole-brain FC patterns of the semantic hub -- left temporal pole in infancy (as opposed to the language network examined in the present study) is prospectively associated with school-age oral language performance (Yu et al., 2021). Given IFG's implications in multiple linguistic processes at early developmental stages, future studies are warranted to unravel functional properties of the inferior frontal regions in the infant brain and how these may contribute to the development of children's phonological skills and language abilities in general.

We further demonstrated that the FC of the IFG module within the infant language network was positively correlated with school-age word reading abilities, and kindergarten-age phonological skills significantly mediated this relationship. Previous fMRI and fNIRS studies showed that the neural activation of left IFG during oral comprehension among kindergarteners (Jasińska et al., 2021) and beginning readers (Preston et al., 2016) was predictive of subsequent reading gains, suggesting IFG's functional characteristics in kindergarteners as potential neural precursors of decoding abilities. Meanwhile, event-related potential studies (ERP) revealed longitudinal associations between newborns' neural responses to speech and their reading-related

skills at age 6.5 and 2nd grade (Guttorm et al., 2010; Leppänen et al., 2010). However, the limited spatial resolution of ERPs constrains the inferences on anatomical specificity. The current observation complements these findings by showing that IFG, specifically, exhibits infant functional characteristics in associations with school-age word reading abilities. Moreover, we identified the mediating role of kindergarten-age phonological skills in this long-term relationship. These results not only align with the well-established role of phonological skills as one of the key reading precursors (Wagner and Torgesen, 1987; Melby-Lervåg et al., 2012; Ozernov-Palchik and Gaab, 2016), but also highlight the continuous nature of reading development with phonological skills serving as an important mid-way rather than starting milestone. Overall, our results provide empirical findings of the neurobiological characteristics of the infant language network that may underlie the development of core language skills and lay the foundation for subsequent reading acquisition.

Finally, using a data-driving clustering approach, we identified a modular architecture of the language neural network early in life. Our results are in line with previous findings showing separate modules in the frontal and temporoparietal regions of the language network based on differently defined ROIs in five- to eight-month-old infants (King et al., 2021). Moreover, utilizing bilateral ROIs, we further observed that homologous regions in both hemispheres were grouped into the same module in the infant language network. This is different from the internal architecture of the adult language network, where clustering was dominated by hemisphere (Blank et al., 2014; Mineroff et al., 2018). These maturational changes are in line with the developmental shifts from bilateral activations during speech perception in infants (Perani et al., 2011) to left-hemispheric dominance in adults (Olulade et al., 2020), suggesting emergence of left-lateralization in the language network over the developmental timecourse. Considering clinical evidence of patients who exhibited typical language abilities despite early lesions in the left-hemispheric language areas (Bates et al., 2001; Newport et al., 2022), the early-emerging bilateral modular structure of the language network might equip infants with a flexible neural architecture that buffers changes or injury during the critical period of language learning (Sporns and Betzel, 2016).

The current findings should be interpreted in the context of several limitations. First, the current study recruited participants from English-speaking households, which limits result generalizability to other languages. Second, the home language and literacy questionnaire used in the current study may not capture all the critical environmental factors. For example, recent studies show that the adult-child conversational experiences recorded in naturalistic settings could facilitate infant language development (Ferjan Ramírez et al., 2020) and are associated with neural characteristics of IFG (Romeo et al., 2018a, 2018b). Future studies that more comprehensively characterize the infant environment are thus needed to investigate whether and how early linguistic exposure might contribute to the infant brain mechanisms underlying long-term verbal development. Third, the current analyses only considered the language network. Complex cognitive functions, such as reading, require coordination among

multiple neural systems, therefore, more work is needed to examine when and how other networks important for successful reading acquisition, such as attention or executive function networks (Meri et al., 2020), may interact with the language network to facilitate the learning of linguistic and literacy skills.

In conclusion, employing a seven-year longitudinal study starting in infancy, the current study revealed a modular structure of the infant language network that related to individual differences in school-age word reading and decoding achievements through a significant mediation effect of kindergarten-age phonological skills. These longitudinal effects were observed when controlling for participants' general cognitive abilities and environmental characteristics, highlighting the functional specificity of the early-emerging language network for subsequent verbal development. Overall, this work provides the first empirical evidence for the neurobiological characteristics of the early-emerging language network in infancy that may underlie children's language development and lay a critical foundation for long-term reading acquisition.

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Table 1. Participant characteristics at infancy, kindergarten-age and emergent reading stages

	Mean ± SD	Range
Infancy Imaging Time Point		
Characteristics at Scanning		
Scanning age (months)	9.3 ± 3.5	2.5 - 18.6
Framewise displacement (mm)	0.08 ± 0.02	0.04 - 0.14
Emergent Language Skills		
MSEL receptive language (*n* = 61)	45.3 ± 8.6	24 - 63
MSEL expressive language (*n* = 68)	49.1 ± 8.9	22 - 66
Environmental Characteristics		
Socioeconomic status† (*n* = 75)	3.7 ± 1.1	1 - 6
Home literacy environment& (*n* = 73)	-0.01 ± 0.54	-1.84 - 0.95
Kindergarten-age Language Skills		
Test age (years)	5.8 ± 0.9	4.6 - 7.7
Oral language (*n* = 76)	113.4 ± 13.9	73 - 145
Phonological skills (*n* = 61)	104.3 ± 16.1	69 - 138
Emergent Reading Abilities		
Test age (years)	8.1 ± 1.1	6.1 - 10.3
Test of Word Reading Efficiency (*n* = 41)	104.1 ± 15.8	70 - 135
General Cognitive Abilities		
Nonverbal IQ§ (*n* = 75)	107.3 ± 14.0	80 - 139

Note: Scale scores (mean = 50, standard deviation (SD) = 10) were reported for the infant language performance assessed by the Mullen scales of early learning assessment (MSEL), and standard scores (mean = 100, SD = 15) were reported for school-age assessment results for language, reading and general cognitive abilities. Sample sizes varied according to the data availability on the measures.

†Socioeconomic status was measured as the average of parents' highest education degrees reported on a six-point scale as follows: 1-High school diploma or equivalency (GED), 2-Associate degree (junior college), 3-Bachelor's degree, 4-Master's degree, 5-Doctorate, 6-Professional (MD, JD, DDS, etc.).

&Characteristics of home literacy environments were collected via ten questions completed by parents. Responses of each of the ten questions were first converted into z-scores and then averaged as one composite score of HLE per participant.

§Nonverbal IQ was assessed using the Matrix Reasoning subset of the Kaufman Brief Intelligence Test-II at school-age.

Table 2. Longitudinal correlation results of behavioral outcomes between infancy and school-age time points

	1	2	3	4	5
Infancy Language Abilities					
1. MSEL receptive language	-				
2. MSEL expressive language	0.44**	-			
Kindergarten-age Language Skills					
3. Oral language	0.01	-0.14	-		
4. Phonological skills	0.23	-0.002	0.41**	-	
Emergent Reading Abilities					
5. Word reading	0.17	-0.02	0.29	0.65***	-

Note. *R*-values were bivariate Pearson correlations between each pair of behavior assessments. Significances of correlation coefficients were computed based on corresponding sample sizes which varied slightly due to the availability of behavior scores in each assessment. Asterisks indicated the significance of the correlation coefficient after FDR correction. $^{*}p_{corrected} < 0.05$, $^{**}p_{corrected} < 0.01$, $^{***}p_{corrected} < 0.001$.

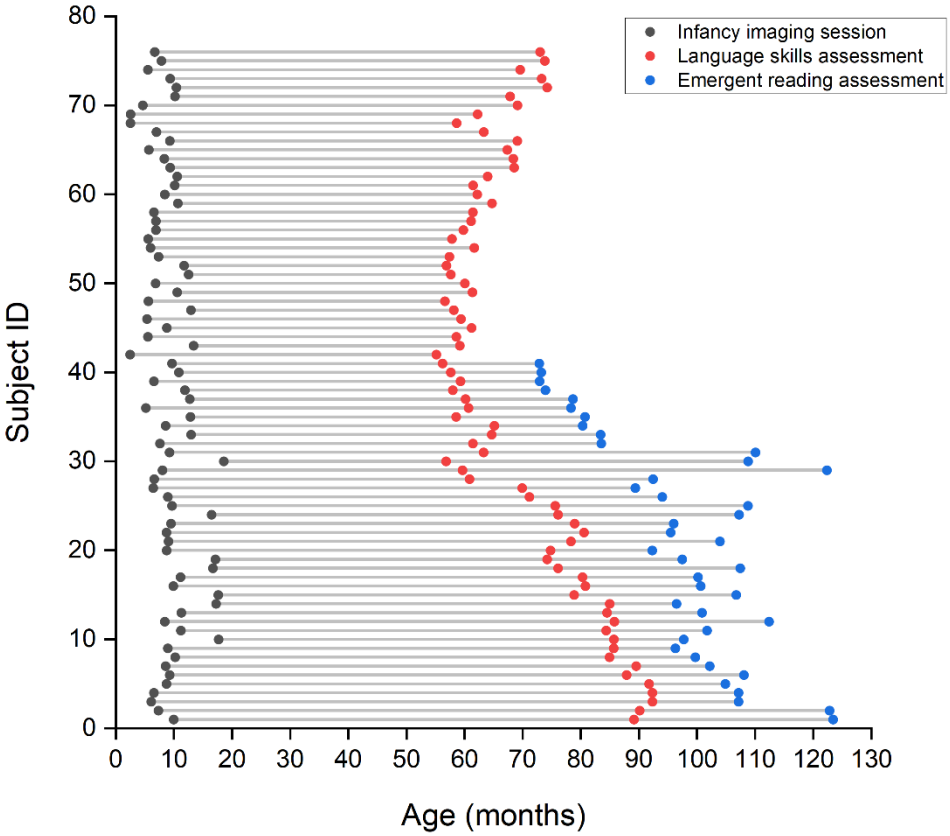

Figure 1. Age distribution (in months) of all included participants who completed resting-state fMRI scanning in infancy (gray dot) and were assessed in their language skills in kindergarten (red dot). A subset of children were further evaluated on their word reading abilities (blue dot) after receiving at least one year of reading instructions. Dots along each horizontal line represented all available longitudinal data of one participant.

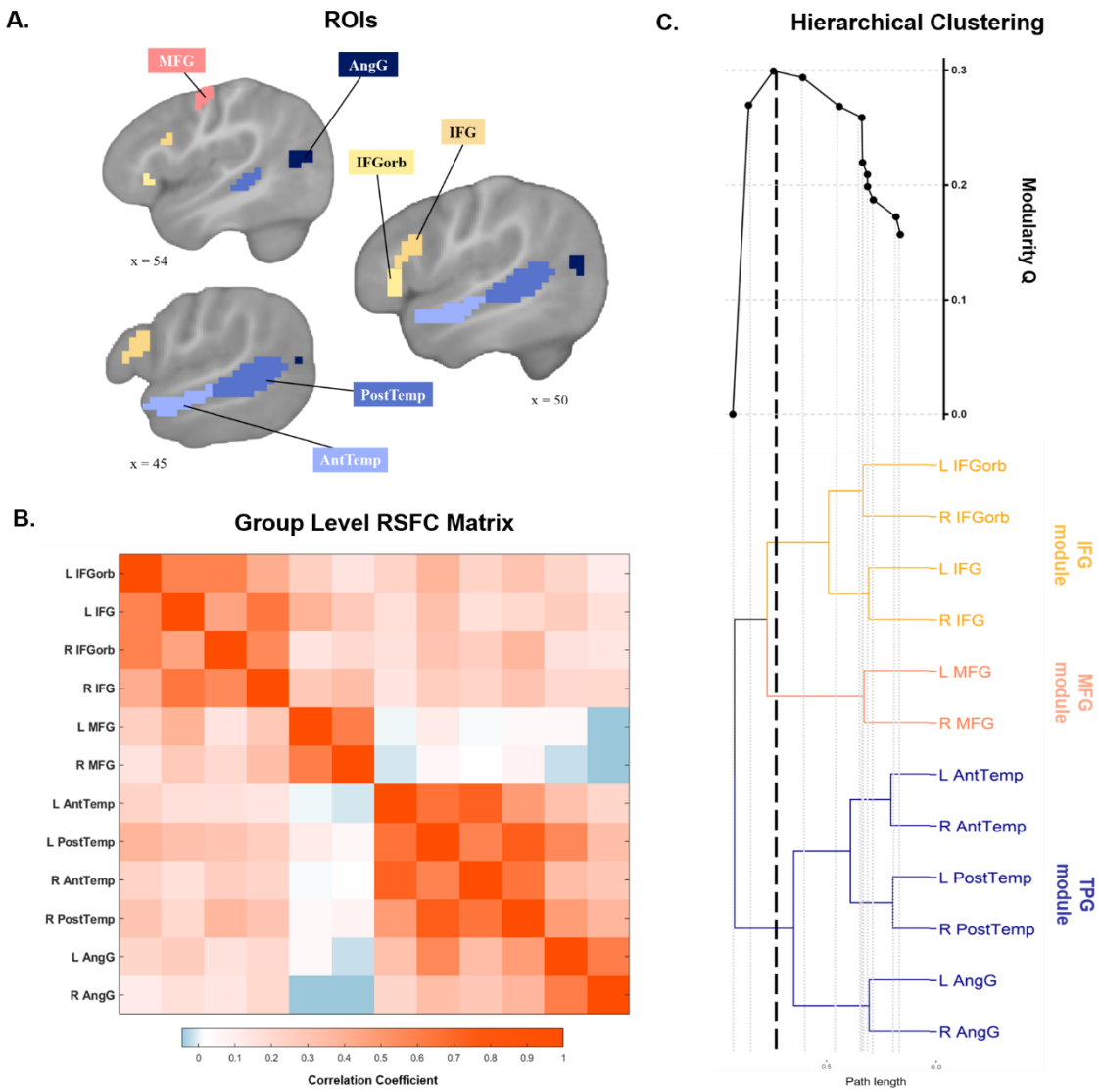

Figure 2. Functional connectivity and modular organization of the infant language network. (A) Bilateral ROIs of the language network were derived from the LanA probabilistic functional atlas (region-level threshold: 25%) and transformed to the UNC 1-year-old infant template (only ROIs in left hemisphere were illustrated here). IFG: inferior frontal gyrus; IFGorb: IFG *pars orbitalis*; MFG: middle frontal gyrus; AntTemp: anterior part of middle temporal gyrus; PostTemp: posterior part of middle temporal gyrus; AngG: angular gyrus. (B) Group level functional connectivity matrix of the infant language network. (C) Hierarchical clustering results revealed an optimal three-module structure for the infant language network. A binary tree created from hierarchical clustering is shown in the lower panel, which indicates the number and components of the divided clusters as the path length increases. In the upper panel, modularity values were plotted for all partition levels licensed by the binary tree. Each point on the modularity plot corresponded to a partition level indicated by the corresponding vertical line where the modular structure was defined based on branches on the right of the line. A tripartite modular architecture of the infant language network was indicated by a black dashed vertical line that had the highest modularity Q scores (Q = 0.30) among all possible partitions (indicated by gray dashed vertical lines) generated by the tree structure. IFG module: inferior frontal module; MFG module: middle frontal module; TPG: temporoparietal module.

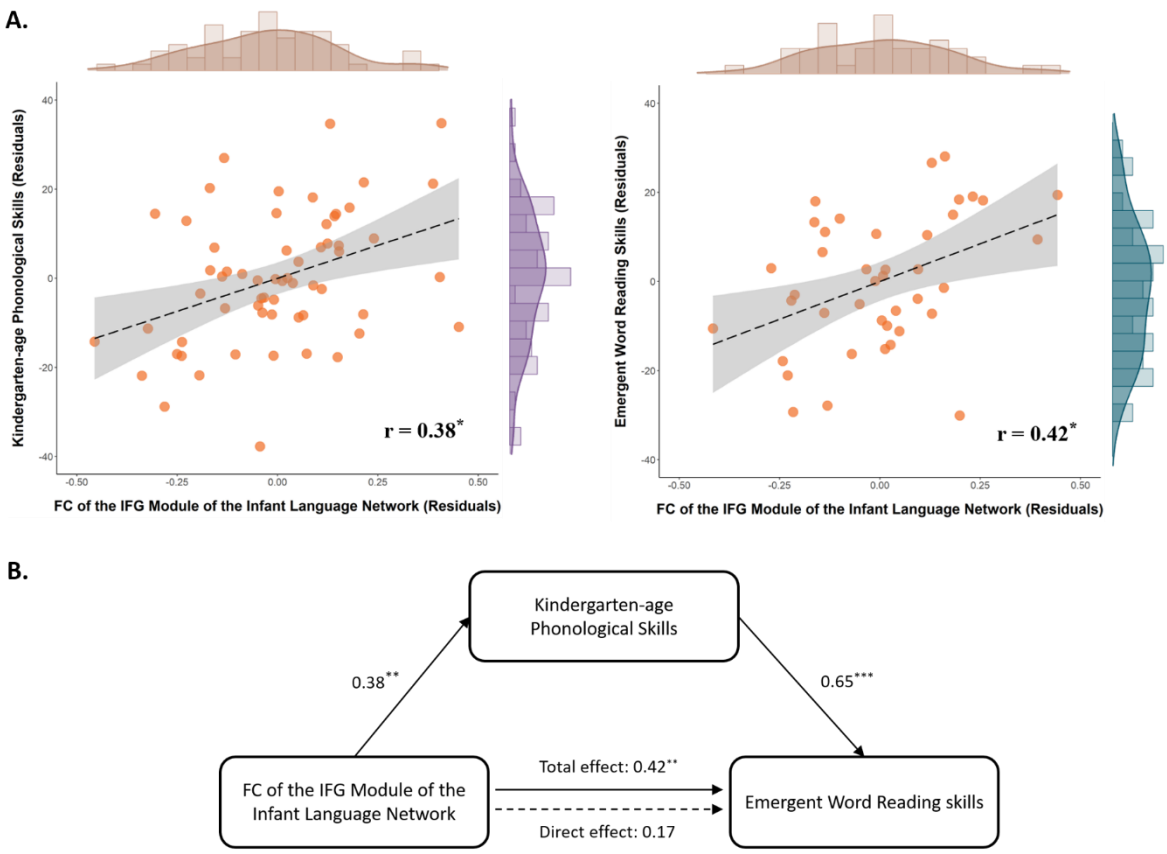

Figure 3. Prospective associations between infant language network characteristics and school-age language and reading outcomes. (A) Scatterplots showed significant associations between FC of the IFG module within the infant language network and kindergarten-age phonological skills (left), as well as between the infant FC of the IFG module and the emergent word reading skills (right). Residual values controlling for infant age and head movement during scanning, nonverbal IQ, HLE, and SES were shown. Histogram and density estimation plots along the perimeter showed distributions of the FC of the IFG module (x-axis) and behavioral outcomes (y-axis). $^{*}p_{corrected} < 0.05$ (B) The mediation model illustrated a significant mediation role of kindergarten-age phonological skills on the relationship between the infant FC of the IFG module and emergent word reading skills. Standardized effect estimates were shown, and the dotted arrow represented the direct effect after accounting for the mediation effect of the phonological skills. $^{**}p < 0.01$, $^{***}p < 0.001$.