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Functional connectivity in the developing language network in 4-year-old children predicts future reading ability

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Abstract

Understanding how pre-literate children's language abilities and neural function relate to future reading ability is important for identifying children who may be at-risk for reading problems. Pre-literate children are already proficient users of spoken language and their developing brain networks for language become highly overlapping with brain networks that emerge during literacy acquisition. In the present longitudinal study, we examined language abilities, and neural activation and connectivity within the language network in pre-literate children (mean age = 4.2 years). We tested how language abilities, brain activation, and connectivity predict children's reading abilities 1 year later (mean age = 5.2 years). At Time 1, children (n = 37) participated in a functional near infrared spectroscopy (fNIRS) experiment of speech processing (listening to words and pseudowords) and completed a standardized battery of language and cognitive assessments. At Time 2, children (n = 28) completed standardized reading assessments. Using psychophysiological interaction (PPI) analyses, we observed significant connectivity between the left IFG and right STG in pre-literate children, which was modulated by task (i.e., listening to words). Neural activation in left IFG and STG and increased task-modulated connectivity between the left IFG and right STG was predictive of multiple reading outcomes. Increased connectivity was associated later with increased reading ability.

KEYWORDS
fNIRS, language, neuroimaging, psychophysiological interaction, reading development

1 | INTRODUCTION

Learning to read is an acquired skill that depends on many linguistic and cognitive abilities and begins to develop with instruction around the time that children first enter school (age five to six in the US). Understanding how pre-literate children's language abilities and underlying brain networks relate to future reading ability is important because it allows us to better understand the foundation of literacy in the brain, but also, it is important for identifying pre-literate children who may be at-risk for reading problems. Previous research has shown that brain activation during reading and language processing

tasks in young readers in related to reading ability as children develop and become more skilled readers (Preston et al., 2016; Pugh, Mencl, Jenner, et al., 2000; Pugh, Mencl, Jenner, Katz, et al., 2001; Pugh, Mencl, Jenner, Lee, et al., 2001; Saygin et al., 2013; Schlaggar & McCandliss, 2007; Turkeltaub et al., 2003; Yu et al., 2018). Young children who have yet to begin reading instruction are already proficient users of spoken language, however, it is not yet clear exactly how the existing language processing capacity of the brain becomes integrated into a functional reading network. During reading development, children's brain networks for language will overlap with those that are critical for literacy acquisition. In the present study,

we examined language abilities, neural activation, and functional connectivity within the language network of pre-literate children who were between the ages of 3.5 and 5.5 years. We tested how language ability, neural activation, and connectivity in pre-readers predict reading ability 1 year later once children begin learning to read. To the best of our knowledge, this study represents one of the first investigations of how children's language abilities, brain activation, and brain connectivity, relates to reading ability a year later, during the earliest stages of literacy development.

Developmental changes in neural language and reading circuits occur as children transition from being early/emergent readers to more skilled and fluent readers. Young children's language abilities across the domains of phonological awareness and vocabulary knowledge are strongly predictive of later reading success (Goswami & Bryant, 1990; Wagner & Torgesen, 1987). Children with better phonological awareness (the awareness of and ability to manipulate the phonemes of their native language), who perform better on tasks such as identifying syllables or phonemes in a word, are more likely to become better readers (Foy & Mann, 2006; Goswami & Bryant, 1990; Hulme, 2002; Hulme et al., 2005; Wagner & Torgesen, 1987). The ability to store phonological information in short-term memory (phonological memory), is also predictive of reading (Alloway et al., 2004; Baddeley, 1987; Chein & Schneider, 2005; McCallum et al., 2006). Although phonological processing has received much research focus for reading, fast, automatic item retrieval and naming are also key components of skilled and fluent reading (Wolf & Bowers, 1999). Rapid Automatized Naming (RAN), which measures a child's speed and accuracy in naming familiar stimuli such as digits, letters, or colors (Denckla & Rudel, 1974), contributes to fluent word reading, alongside phonological processing (Wolf & Bowers, 1999).

Tight connections among text (orthography), sound (i.e., phonology), and meaning (e.g., vocabulary) are essential to skilled reading (Boukrina & Graves, 2013; Graves et al., 2010; Harm & Seidenberg, 2004; Hoffman et al., 2015; Perfetti & Hart, 2002; Perfetti et al., 2006; Rueckl, 2016). Processing visual (orthographic) information and accessing corresponding phonological and semantic representations is supported by dedicated brain regions in the left hemisphere that overlap with brain regions for language processing. The reading network consists of occipitotemporal, temporoparietal, and anterior frontal areas. Orthographic processing is relayed to the occipitotemporal region, including a portion of the left fusiform gyrus, and often referred to as the "visual word form area"; VWFA, Brodmann's area (BA) 37 (McCandliss et al., 2003; Pugh, Mencl, Jenner, et al., 2000; Schlaggar & McCandliss, 2007). Visual input to the VWFA extends to the temporoparietal system (inferior parietal lobule); to the angular gyrus which is involved in lexical-semantic processing (Seghier et al., 2010), and to the supramarginal gyrus in converting orthography into phonology (Bookheimer et al., 1995; Moore & Price, 1999). Language architecture such as the superior temporal gyrus (STG, BA 21/22/42) is associated with phonological processing (e.g., Petitto et al., 2000; Zatorre & Belin, 2001). The left inferior frontal gyrus (LIFG), which includes pars opercularis and pars triangularis (Broca's area, BA 44 and 45), and pars orbitalis (BA 47), is involved in syntax,

Research Highlights

- Neural activation for language in 4-year-olds is important for reading 1 year later
- Connectivity in the left IFG and right STG is modulated by speech in 4-year-olds
- Functional connectivity in pre-literate children predicts future reading ability

morphology, semantics (anterior LIFG), and articulatory phonology (posterior LIFG), including the search and retrieval of information about the meanings of words (Bookheimer, 2002; Caplan, 2001; Price, 2000, 2010, 2012; Sabb et al., 2007).

As children learn to read, a relatively greater reliance on direct orthographic-to-semantic coding, rather than orthographic-to-phonological-to-semantic coding, becomes increasingly important (Berends & Reitsma, 2006; Hoover & Gough, 1990; Snowling, 2004) though there is also good evidence that sublexical phonology continues to play a key role even as lexical semantic processing increases (see Harm & Seidenberg, 2004; Lukatela & Turvey, 1994; van Orden, 1987). This relative shift in the weighting from phonologically mediated processing to direct orthographic-semantic processing over reading development is associated with a shift in the recruitment of the left STG (classically associated with phonological processing) to recruitment of the left IFG (classically associated with lexical access) (Jasińska & Petitto, 2014; Turkeltaub et al., 2003), and may reflect children's intensive experience with literacy instruction over their years in primary school, in addition to the developmental changes these structures undergo as part of brain maturation. In addition, young readers rely on a left temporoparietal–inferior frontal phonological decoding circuit for reading; early reading is characterized by activation in this left temporo-parietal cortex, also referred to as the dorsal reading circuit (Pugh, Mencl, Jenner, Lee, et al., 2001). Over time, this left temporo-parietal network connects to the left IFG to support processing of phonological and lexico-semantic information. Learning to read is accompanied by increased left-lateralized activation in the left inferotemporal "word form area" (Pugh, Mencl, Jenner, Katz, et al., 2001), left inferior frontal (associated with lexical access) and middle temporal cortices (Turkeltaub et al., 2003), and disengagement of the right inferotemporal cortex (Pugh, Mencl, Jenner, et al., 2000; Pugh, Mencl, Jenner, Katz, et al., 2001; Pugh, Mencl, Jenner, Lee, et al., 2001; Turkeltaub et al., 2003); these developmental processes occur as a function of literacy instruction and overall maturational changes in the brain.

Recent research suggests that as children become more skilled readers, and printed language processing is increasingly integrated with the left-hemisphere language network (Dehaene et al., 2015; Dehaene et al., 2010; Preston et al., 2016). For example, Preston et al. (2016) followed a sample of 68 children for 2 years from the ages of 8.5-10.5 who completed behavioral assessments of language and reading, and participated in an fMRI task designed to

elicit activation for spoken and written language. Children who showed greater left-hemisphere print-speech co-activation, that is, greater neural activation in the same regions for processing both printed and spoken language, showed greater reading skill 2 years later. Importantly, this co-activation for print and speech was predictive of future reading above and beyond brain activation for print alone, and key behavioral predictors such as phonological awareness (Preston et al., 2016).

Children who are poor readers or dyslexics show reduced activation in the left hemisphere language and reading network, and corresponding increased activation in the right hemisphere and frontal regions (Pugh, Mencl, Jenner, et al., 2000; Pugh, Mencl, Jenner, Katz, et al., 2001; Pugh, Mencl, Jenner, Lee, et al., 2001; Pugh, Mencl, Shaywitz, et al., 2000; Sandak et al., 2004; Shaywitz et al., 1996, 1998, 2002, 2003, 2004, 2007). Patterns of neural activation predict reading outcomes in dyslexic children. For example, Hoeft et al. (2011) followed a sample of 25 individuals with dyslexia (mean age 14 years) and 25 control individuals (mean age 11 years) and observed that activation in the right inferior frontal region at the onset of the study predicted reading skill 2.5 years later. However, the predictive relationship between right inferior frontal activation and subsequent reading skill was limited to the dyslexic cohort. McNorgan et al. (2011) followed 26 typically developing children between the ages of 9 and 15 years and observed that brain activation during a word rhyming task was related to future pseudoword reading ability. Critically, this predictive relationship was age dependent: activation associated with phonological decoding (left IFG) was predictive of reading in younger children (9-11 years), whereas activation associated in orthographic processing (e.g., visual word form area; left fusiform gyrus) was predictive of reading in older children (13-15 years). Such a pattern is consistent with the early role that phonological processing has in reading, followed by a later shift to great direct processing between orthography and semantic access.

Beyond activation in the brain's language and reading circuitry, functional connectivity in the emerging reading circuitry informs how connections within this distributed network are related to developmental changes in reading ability. Previous research finds that increased connectivity between regions in the reading circuit is associated with better reading performance (Finn et al., 2014; Pugh, Mencl, Shaywitz, et al., 2000; Wang et al., 2013). For example, 9-year old children with dyslexia show reduced connectivity in the visual word form area compared with typically developing children (Finn et al., 2014), and adolescents and adults with dyslexia showed poorer connectivity between the angular gyrus and reading-related regions in the temporal and occipital cortices (Pugh, Mencl, Shaywitz, et al., 2000). These functional connectivity findings also correspond to observations about anatomical connectivity in younger children, suggesting that reduced functional connectivity may have a structural basis (Saygin et al., 2013). White matter volume and integrity in the left arcuate fasciculus, which connects anterior and posterior language regions in the brain, is smaller and weaker in kindergarteners who are at risk of dyslexia due to poor phonological awareness skills (Saygin et al., 2013). However, these

results were based on populations with or at-risk for reading disorders, rather than healthy typical development. In a study of healthy 10-year-old children, increased functional connectivity between regions associated with semantic processing was predictive of improvement in behavioral performance on a semantic judgment task 2 years later (Lee et al., 2016). Importantly, functional connectivity in the semantic network predicted behavioral performance above and beyond the variance explained by the amount of activation alone (Lee et al., 2016). Recently, graph theoretical approaches have also been applied to examining task-related (i.e., reading) connectivity (Wang et al., 2013). Wang et al. (2013) studied the relation between individual differences in children's reading skill and large-scale patterns of connectivity across hubs corresponding to regions that comprise the reading circuit and areas associated with aspects of higher cognition. Children between the ages of 9 and 15 (mean age 11.92 years) who demonstrated better reading performance showed greater short-range functional synchrony in hub regions known to be critically important to reading, and greater long-range connectivity between networks (Wang et al., 2013). Increased long-range frontal to temporal reading task-related connectivity is thought to support higher cognitive engagement, and indeed, the pattern of increased long-range connectivity is generally observed over development (Fair et al., 2007, 2009).

More recent work by Yu et al. (2018) showed that functional connectivity patterns of 5-year-olds was predictive of reading outcomes. Yu et al. (2018) compared patterns of brain activation and functional connectivity during a fMRI phonological processing task with reading scores when children first entered kindergarten (pre-readers), 1 year later at the end of kindergarten (beginning readers), and 3 years later (emergent readers). Pre-readers showed greater activation in the left inferior parietal cortex and precuneus compared with emergent readers. Neural pathways between left inferior parietal cortex and other key reading regions, left inferior frontal gyrus, left occipitotemporal cortex, and the right angular gyrus, showed increased connectivity over time. Specifically, increased connectivity was observed in children whose phonological abilities increased most over the course of reading development. The strength of the connection between the left inferior parietal cortex and the left occipitotemporal cortex at pre-reading stages significantly predicted reading skills at emergent reading stages (Yu et al., 2018).

There are well-described changes in activation across regions that form the reading network: increased engagement of the left hemisphere with corresponding disengagement of the right hemisphere, increased activation in the left inferior frontal cortex and the visual word form area, as well as the co-activation for both spoken and written language. Furthermore, studies of functional connectivity of the reading circuit (and regions implicated in higher cognition) indicate that increased connectivity within this increasingly specialized reading network and long-range connectivity with other cognitive hubs is associated with better reading performance. Imaging studies of reading, in both typically developing children and children with dyslexia, mainly focus on older children who are already readers. Comparatively less is known about how the pre-literate brain's emerging language and

reading network relates to a child's future reading ability (but see Yu et al., 2018). The developmental relation between activation and connectivity in the classic reading network, and later reading skill during *early stages of reading development* remains understudied. The functional organization of the brain *before* a child learns to read (or begins formal literacy instruction) can inform how that child will learn to read and whether she will encounter difficulties.

In the present study, we directly addressed the extent with which task-related activation and connectivity were predictive of future reading ability in a sample of preliterate children who were just beginning to learn to read. Previous work, chiefly Yu et al. (2018), has shown that 5-year-old pre-readers' connectivity between left inferior parietal cortex and other hubs in the reading network predicted later reading skill. Our study extends this line of research to a younger group of pre-readers. Our young sample (3.5-5.5 years of age) allowed us to examine whether the neurodevelopmental patterns observed for older children would be present even before children acquired formal experience with literacy, and critically, during a time in development when the brain's language network is still developing. Children participated in a functional near infrared spectroscopy (fNIRS) neuroimaging paradigm that involved listening to speech.

While undergoing fNIRS neuroimaging, children completed a passive spoken language task where blocks of real words and pseudowords were aurally presented, as well as standardized assessments of language abilities. Words and pseudowords differentially activate neural regions; this difference is hypothesized to reflect greater effort associated with the search and retrieval of meaning in word-like forms (nonwords) compared with real words (Heim et al., 2005; Mechelli et al., 2003; Philipose et al., 2007). For instance, the inferior frontal gyrus and inferior parietal lobule has shown greater activation for nonwords compared to words (Bookheimer et al., 1995; Graves et al., 2010; Heim et al., 2005; Herbster et al., 1997; Mechelli et al., 2003; Shaywitz et al., 2002).

One year later, at the end of the first grade, children were re-assessed on the same behavioral language measures as well as additional reading measures. This design allowed us to examine how behavioral indices of language skill, and neural activation and connectivity underlying spoken language processing, related to future reading outcomes. Specifically, we examined both neural activation patterns using general linear model (GLM)-based analyses and task-related connectivity using psychophysiological interaction (PPI) analyses. Standard GLM analysis can reveal functionally segregated brain areas that change their activity in response to task conditions (e.g., listening to words or pseudowords, or baseline condition consisting of fixation). On the other hand, PPI is a measure of functional connectivity that provides complementary information about how these brain areas are functionally integrated (Friston, 2011; O'Reilly et al., 2012), and has been applied to study language processing (Kireev et al., 2015; La et al., 2016), and recently with fNIRS data (Hirsch et al., 2017). PPI does not permit inferences about casual relations between activation in separate brain regions, but rather PPI can test the interactions between different brain regions during language processing in different psychological conditions (i.e.,

task—words, pseudowords; rest). Using both approaches, we examined, first, the extent with which activation in left hemisphere language areas (and their right hemisphere homologues) during language processing in preliterate children, and secondly, whether task-modulated connectivity between regions in the classic language and reading circuitry, was predictive of future reading ability. Understanding how functional neural segregation (specific brain regions that support reading functions) and integration (emergence of reading networks across those brain regions) of pre-literacy language processing relates to future learning outcomes can shed new light on the mechanisms by which a neural circuitry for reading forms and integrates with the existing speech network. Critically, this reading network forms in response to intensive reading practice (e.g., daily formal literacy instruction in the classroom). Although activation in regions that support literacy is well-documented, complex cognition (i.e., learning to read) is an emergent property of the integration of specific brain regions, rather than regional activation. The regions that make up the reading network undergo specialization for reading through their increasing integration with other brain structures. Here we examine the pre-reading network prior to experience-driven (i.e., reading instruction) neural specialization. This allows us an even earlier insight into the role of inter-regional connectivity in shaping a specialized cognitive system.

2 | METHOD

2.1 | Participants

Thirty-seven participants participated in near-infrared spectroscopy (NIRS) neuroimaging and behavioral assessments in the laboratory across multi-day visits. Of these 37 participants, 28 returned a year later to complete additional behavioral assessments. Time 1 participants (n = 37) were between the ages of 3.4 and 5.4 (M = 4.2, SD = 0.5), and had not yet started formal literacy instruction at school, termed *pre-literacy*. Time 2 participants (n = 28) were between the ages of 4.4 and 6.4 (M = 5.3, SD = 0.6) and were in the earliest stages of learning to read, termed *emergent literacy*. See Table 1 for participant details. Participants were recruited in preschool or during the first quarter of kindergarten to ensure that they have not yet been exposed to formal literacy education. Only native English speakers who were learning to read in English in school were included in the study. Parents of children reported home literacy exposure (on a likert scale from 1 to 10; 10 being highest), the number of times per week parents read to their child, and the total number of book in the house (on a likert scale from 1 to 5; 5 being highest). Overall, most parents rated high home literacy exposure (M = 8.82; SD = 0.46; range 7-9); reading to their children (M = 2.88/week, SD = 0.48, range 1-3), and having books at home (M = 4.61; SD = 0.92; range 1-5). Children who had a formal diagnosis of cognitive delay or developmental disorders, such as autism spectrum disorder or Down's syndrome, did not meet the eligibility criteria for the needs of this study.

TABLE 1 Participant characteristics at time 1 and time 2. Mean standard score values and standard deviations are noted.

Measure	Time 1	Time 2
N	37	28
Age	4.2 (0.5)	5.2 (0.6)
Gender (Male:Female)	22:13	16:13
IQ	114 (10)	–
Letter Knowledge (TOEPL)	115 (16)	–
Phono. Awareness (CTOPP)	31 (7)	36 (7)
Phono. Memory (CTOPP)	9 (3)	12 (3)
Rapid Naming (CTOPP)	15 (8)	20 (6)
Picture Vocabulary (PPVT)	122 (14)	120 (11)
Letter-Word Decoding (WJ)	–	117 (16)
"Word Attack" Pseudoword Reading (WJ)	–	121 (15)
Passage Comprehension (WJ)	–	108 (13)

2.1.1 | Socioeconomic status

Children came from a range of socioeconomic (SES) backgrounds. We collected parental reports of total family income, parental education, and parental occupation status as an index of socioeconomic status. SES was coded as a composite score based on total family income level (1—lowest, 5—highest), mother's highest educational attainment (1—lowest, 7—highest), and father's highest educational attainment (1—lowest, 7—highest) for a total possible score out of 19 (M = 16.4, SD = 2.3).

2.2 | Behavioral assessment

Behavioral testing sessions assessed children's speech, language, reading, and cognitive abilities. Standardized assessments included the Comprehensive Test of Phonological Processing Second Edition (CTOPP-2; Wagner et al., 2009, 2013), the Peabody Picture Vocabulary Test Fourth Edition (Dunn et al., 2007), and the Woodcock-Johnson III Tests of Achievement (WJ-III; Woodcock et al., 2001). Children's verbal and performance intelligence quotient (IQ) was measured using the Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler, 2011) or the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition, for children under the age of six (WPPSI-IV; Wechsler, 2012). The CTOPP-2 was used to assess reading-related phonological processing skills in English (Wagner et al., 2013). The PPVT-4 was used to assess receptive vocabulary skills in the English language (Dunn et al., 2007). The Woodcock-Johnson Tests of Achievement—Edition III was used to assess children's reading abilities, including decoding in letter-word identification, "word attack" pseudoword reading, and passage comprehension; this assessment was administered at Time 2 only. All assessments were widely used norm-referenced tests that meet stringent standards of reliability and are valid measures of phonological processing, receptive vocabulary, and reading respectively.

2.3 | Neuroimaging task and procedure

Before starting the task, participants were given instructions to listen to the words played through headphones on their head and look at a fixation cross that appeared in the middle of the monitor. We used a block design to present 22 auditory blocks (11 real words and 11 pseudo-words). Blocks were presented in random order. Blocks consisted of one word or nonword trials that repeated six times with an inter-stimulus interval of 100 ms. Each block was 7 seconds in length. Rest periods between blocks were 13 seconds (see Figure 1).

Short video clip showing animals (Animal Planet) was presented between blocks for 5 seconds to help keep young children engaged. These short clips were shown immediately after rest periods and just prior to a new block start. The entire experiment, including set-up, lasted approximately 45 minutes. PsychoPy software (Peirce, 2007, 2008) was used to present stimuli. Stimuli in each of the word and nonword conditions consisted of only consonant-vowel-consonant (CVC) words with equal representation of short vowels, long vowels, and diphthongs. Nonwords were matched to real words for length, orthographic neighborhood densities, phonological neighborhood densities, and summed bigram frequencies, see Table 2.

2.4 | fNIRS data acquisition

Children's hemodynamic response was measured with a Shimadzu Lab NIRS Near Infrared Spectroscopy system with 39 optodes (58 channels), acquiring data at 15.385 Hz. fNIRS is exceptionally well-suited to studying young children and infants because of its participant-friendly set-up (Jasińska et al., 2017; Jasińska & Petitto, 2014; Petitto et al., 2012; Quaresima et al., 2012; Quaresima & Ferrari, 2016; Shalinsky et al., 2009). Like fMRI, fNIRS measures the brain's hemodynamic response, but the fNIRS measurements are completed while a child is comfortably seated in a chair. fNIRS is less susceptible to movement artifacts, and the experiment does not require mock scanning trials. Overall, these advantages permit neuroimaging studies with younger cohort of participants that may not tolerate fMRI well.

The lasers were factory set to 780, 805, and 830 nm. The 20 lasers and 19 detectors were segregated into alternating grid placement (see Figure 2).

Once the participant was comfortably seated, a cap was placed on the participant's head. Positioning of the array was accomplished using the 10-20 system (Jasper, 1958) to maximally overlay the key regions of interest (for additional details, including neuroanatomical fMRI-fNIRS co-registration procedures to establish neuroanatomical precision of probe placements (Jasińska & Petitto, 2013, 2014; Kovelman, Baker, et al., 2008; Kovelman, Shalinsky, et al., 2008;
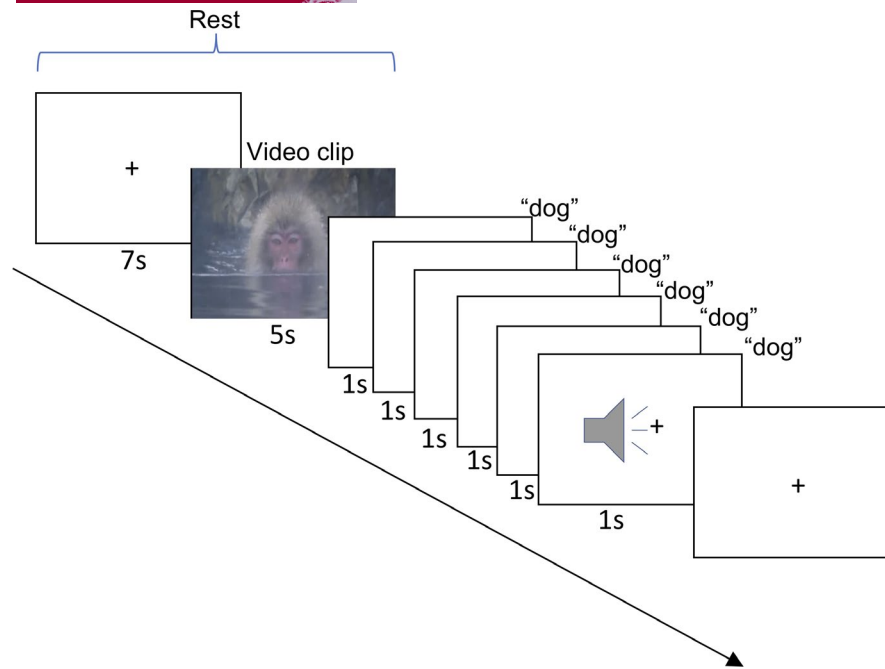
FIGURE 1 Task design

Kovelman et al., 2009; Petitto et al., 2012; Shalinsky et al., 2009). The depth of recording in the cortex is approximately 3 cm. Prior to recording, every channel was tested for optimal signal to noise ratio using Lab NIRS fNIRS inbuilt software.

2.5 | Data analysis

2.5.1 | fNIRS data preprocessing

Data were analyzed using a Matlab-based NIRS-SPM Version 4 (Jang et al., 2009; Ye et al., 2009), which uses the neuroimaging suite SPM12. Using the modified Beer–Lambert equation, NIRS-SPM converts optical density values into concentration changes in oxygenated and deoxygenated hemoglobin response (HbO and HbR, respectively). Changes in HbO and HbR concentrations were filtered with a HRF filter and decomposed using a Wavelet-Minimum Description Length (MDL) detrending algorithm in order to remove global trends resulting from breathing, blood pressure variation, vasomotion, or participant movement artifacts and improve the signal-to-noise ratio (Jang et al., 2009). We filtered out step functions that were identified in each time series. This allowed us to correct for motion artifacts as well as drift in signal related to respiration.

2.5.2 | Spatial registration

NIRS channels were registered to MNI space with the Haskins Pediatric Brain Atlas (Molfese et al., 2015) in NIRS-SPM's stand-alone registration function (Singh et al., 2005) by using a three-dimensional digitizer (Polhemus Corp.). Registration was done individually for each child. The spatial registration function yielded MNI coordinates represented by each channel with corresponding labels for anatomical regions, including Brodmann labels, maximally located at each channel position. Specifically, the function provides a coverage percentage for a given anatomical region at each channel. This information was used in the selection of specific channels for region of interest (ROI) definition where coverage percentage was above 70%; specifically, channel 34 for Wernicke's area (STG, Supramarginal gyrus, and Angular gyrus), and channels 27 and 38 for Broca's area (see Figure 2).

2.5.3 | Time 1 statistical parametric mapping (SPM)

We used a general linear model-based analysis approach that allows for the creation of activation maps with super-resolution localization. Models for HbO and HbR contain experimental regressors convolved with the corresponding hemodynamic response function

TABLE 2 Stimuli characteristics.

Condition	Log frequency, M (SD)	Number of phonemes, M (SD)	Orthographic neighborhood, M (SD)	Phonological neighborhood, M (SD)	Summed bigram frequencies, M (SD)
Word	2.33 (0.61)	3.19 (0.40)	21.18 (9.23)	35.64 (11.66)	4,503.36 (2,314.34)
Nonword	N.A.	3.09 (0.30)	13.64 (5.37)	14.27 (5.44)	4,600.09 (2,569.51)
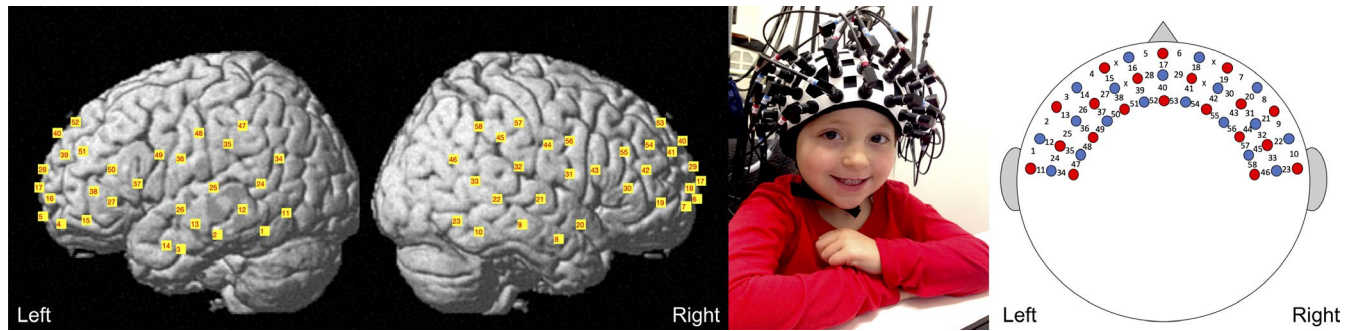
FIGURE 2 Placement of fNIRS optodes and channel mapping to cortex. 39 probes with 58 channels

with time derivatives. NIRS-SPM creates the models for HbO and HbR with opposing polarity so that a significant model fit for HbO indicates increased concentration and for HbR decreased concentration. Group activation maps include Sun's tube formula correction (Sun, 1993; Sun & Loader, 1994). Sun's tube formula and Lipschitz–Killing curvature-based expected Euler characteristics are applied for *p*-value corrections (Li et al., 2012). Group activation maps were generated comparing word and nonword conditions relative to baseline, where baseline is defined as the 13-second interblock interval consisting of 7 seconds of fixation followed by 5 seconds of video. Individual subject GLM beta weights in channels corresponding to left STG, right STG, and left IFG were extracted for use in additional analyses detailed below. HbR results are less susceptible to noise and more reliable in test–retest as compared to HbO and therefore these more conservative results are reported below (Dravida et al., 2018).

2.5.4 | Time 1 psychophysiological interactions

Psychophysiological interactions (PPI) analysis assesses task-dependent increases in functional connectivity between two regions; specifically PPI analysis can address how activation within a seed ROI is correlated with task-dependent activation in another region. PPIs allow us to examine the contribution of one ROI to another with regard to the experimental condition. PPI analysis is based on the general linear model (GLM) in which the main effects for task is removed from the neural signal in the ROI, and subsequent residual signals, and the interaction between activation in the seed ROI and voxels in other regions are entered into the model. PPI analysis has been implemented largely with fMRI, PET, and EEG (Friston, 1994, 2011; Friston et al., 1997), and recently for fNIRS (Hirsch et al., 2017). Here similar to Hirsch et al. (2017), PPI analysis is applied to functional near-infrared spectroscopy data.

Standard GLM analysis was conducted to model the contribution of predictors (i.e., onset and offset of experimental stimuli) to the time-course of each channel, as described above in *SPM*. To estimate the neural signal from the hemodynamic response, the first eigenvariate time-course data of the voxels within the seed ROI were deconvolved. We performed PPI analyses independently on two seeds:

a seed ROI of left IFG and left STG. These are key regions in the left hemisphere language and reading circuit. The PPI analyses consisted of (1) a vector corresponding to the experimental factor, (2) the deconvolved neural signal in the ROI, and (3) the interaction term generated from the element-by-element product of the mean-centered time-course neural signal data in each region. A contrast vector where the interaction term is weighted 1 and all other regressors are weighted 0 assigns the main effects of the experimental task and physiological correlations as covariates of no interest. This contrast accounts for voxels which may exhibit non-task-specific correlations with the seed ROI due to shared anatomical connectivity or subcortical inputs. Group maps were generated comparing the activation to the word versus nonword task relative to baseline as modulated by activation in the seed ROI.

2.5.5 | Time 2 reading ability

We examined whether behavioral and neural variables at Time 1 were predictors of children's reading abilities at Time 2. Time 1 behavioral variables were age, socioeconomic status, IQ, letter knowledge, phonological awareness, phonological memory, rapid naming, and picture vocabulary. We selected the Time 1 neural variables based on the results of SPM and PPI analyses described above. Time 1 variables were HbR beta weights from our SPM GLM analysis, as well as mean PPI values corresponding to left IFG-to-right STG, left IFG-to-left STG, and left STG-to-right STG. PPI values for this analysis were selected based on the a priori ROI selection of "classic" left hemisphere language regions: left IFG, left STG, as well as regions which showed significant patterns of activation during language processing as revealed by GLM analyses. The dependent Time 2 variables indicating reading ability were letter-word decoding, "word attack" pseudoword reading, and passage comprehension from the Woodcock Johnson Test of Achievement.

We conducted forward and backward stepwise regression, an optimal approach compared with forward- or backward-only regression (Halinski & Feldt, 1970), to identify optimal models that predict Time 2 reading outcomes from Time 1 behavioral and neural variables. We used the stepAIC function of the MASS package (Venables et al., 2002) in R software (The R Core Team, 2016). This

function selects optimal models based on comparisons of the Akaike information criterion (AIC) per model (Akaike, 1973). ANOVA analyses are performed on each model's AIK value to identify the optimal multiple regression model. Three models were analyzed, each for letter-word decoding, "word attack" pseudoword reading, and passage comprehension. The three tasks constitute a comprehensive measure of early reading ability. Given that three separate models, for each outcome variable, were evaluated, we adopted Bonferroni correction and results that met $p < 0.017$ were interpreted.

3 | RESULTS

3.1 | Neural activation patterns at time 1

Greater HbR activation was observed for both words and nonwords compared with baseline in the left and right STG. We also observed a main effect of word type (word, nonword). Greater HbR signals

were observed for words compared with nonwords in the left IFG and the right inferior parietal lobule (IPL). We also observed greater HbR activation for nonwords compared with words in the right middle temporal gyrus (MTG). Figure 3 shows activation for speech compared with baseline in the left and right hemispheres, of HbO and HbR time series. Figure 4 shows group contrasts maps between words and nonwords and average activation for each word type and baseline conditions by region. Please see Table 3 for details.

3.2 | Psychophysiological interaction between word type and neural activation patterns at time 1

The left IFG seed showed significant task-modulated connectivity with the right STG (peak $t(35) = 2.592$, $p = 0.05$; see Figure 5). That is, functional connectivity between the left IFG and right STG was differed while participants listened to words versus nonword stimuli. We did not observe significant PPI connectivity
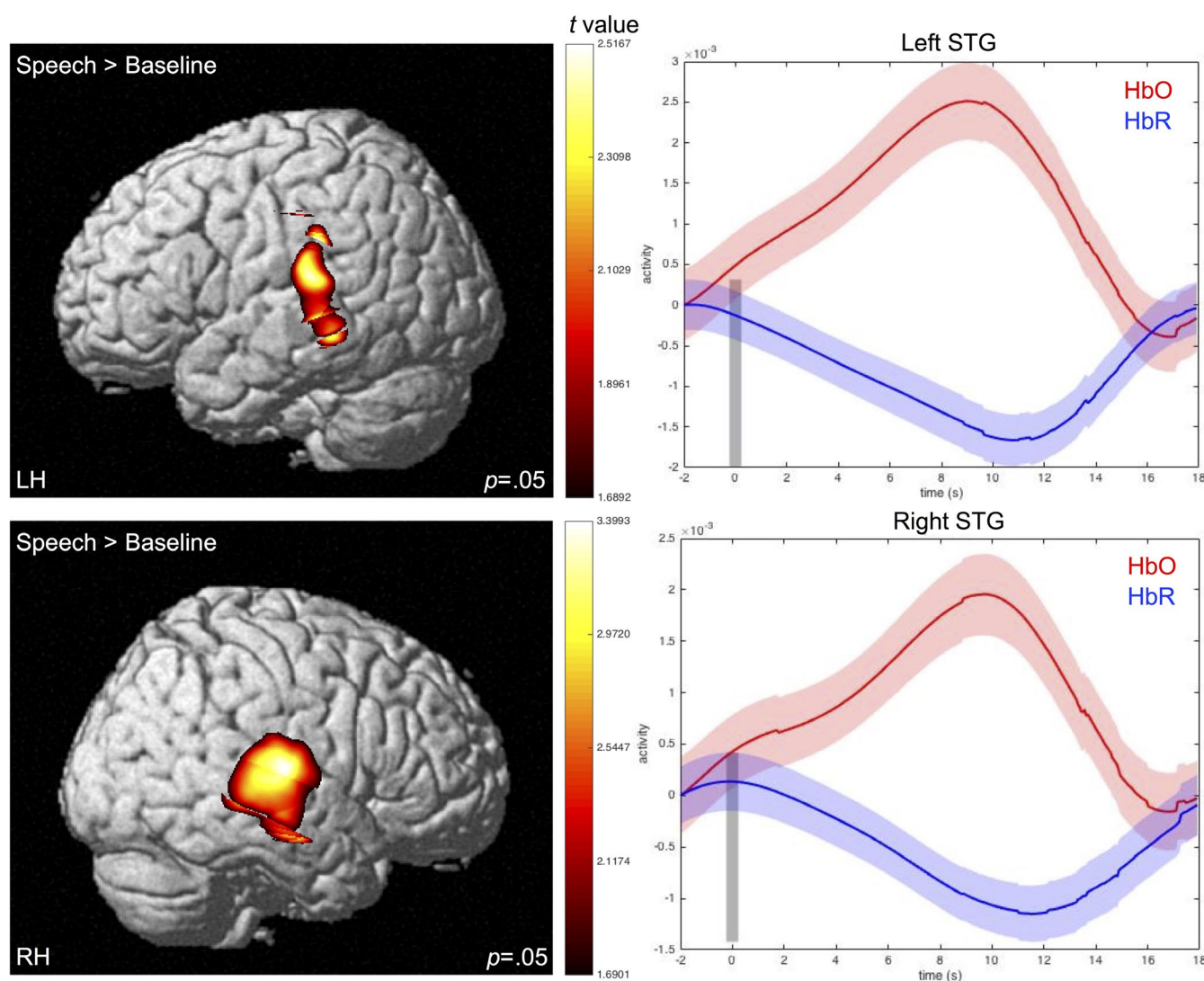
FIGURE 3 Greater HbR activation for speech compared with baseline condition in left STG and right STG. Averaged timeseries of HbO and HbR during speech conditions are shown. Onset of block is at time 0 and indicated by grey bar
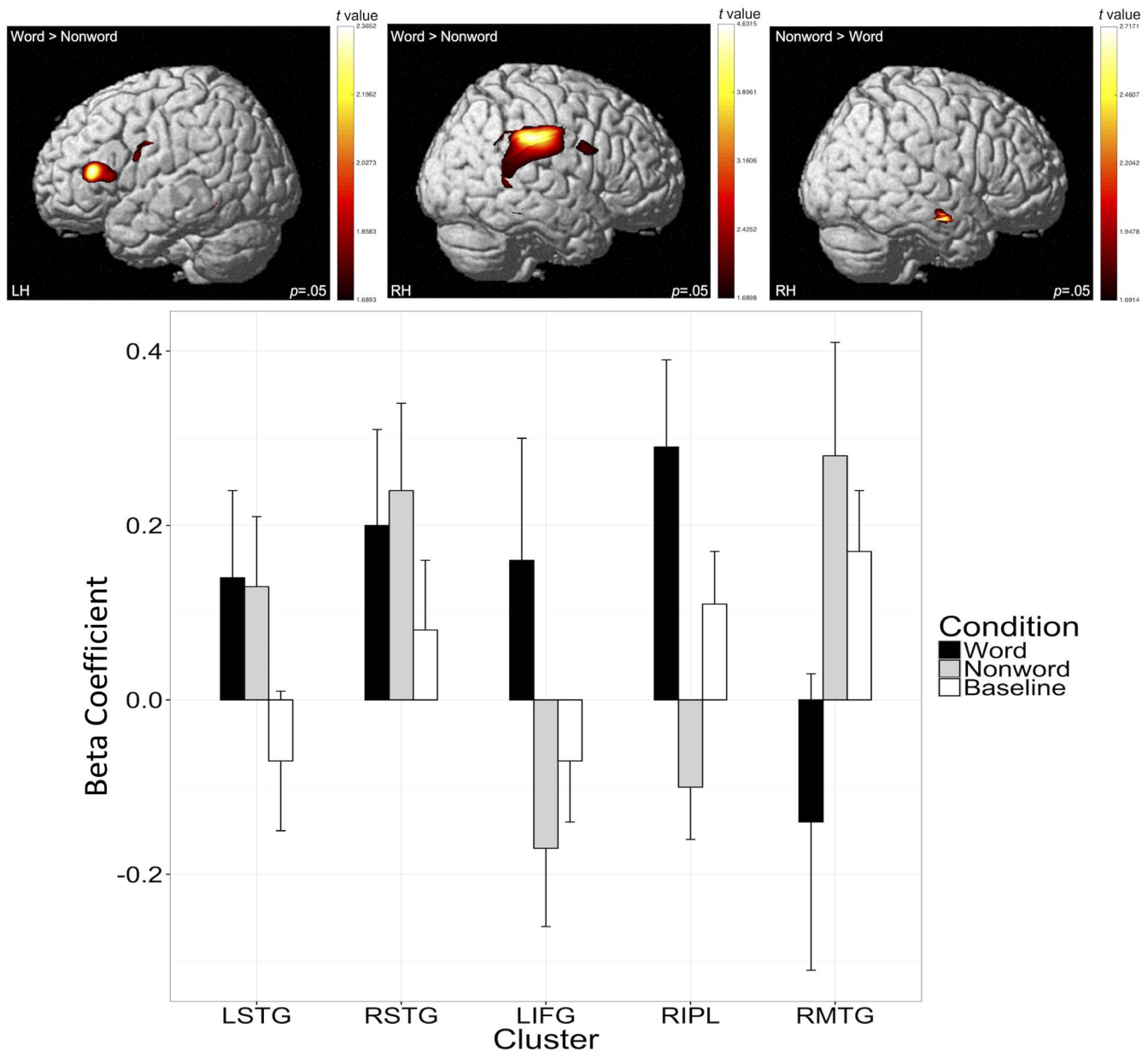
FIGURE 4 Greater HbR activation for words compared with nonwords in left IFG and right inferior parietal lobule (IPL). Greater HbR activation for nonwords versus words in right middle temporal gyrus (MTG). Plots of average activation values and standard errors in each region are shown by condition (word, nonword, baseline)

TABLE 3 Significant differences in neural activation for each word type. Neural region and corresponding Brodmann Area and MNI coordinates are listed. t statistics and p values for each contrast.

Contrast	Region	Brodmann Area	X	Y	Z	t value	p value
Speech >Baseline	L. STG	22/42	−69.3	−34.6	10.4	2.01	0.05
Speech >Baseline	R. STG	22/42	71.7	−27.2	7.4	2.46	0.05
Words >Nonwords	L. IFG	46	−54.1	33.4	13.0	1.90	0.05
Words >Nonwords	R. IPL	40	69.0	−35.3	35.7	2.57	0.05
Nonwords >Words	R. MTG, R. ITG	21	69.7	−8.0	−19.0	2.04	0.05

STG, superior temporal gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MTG, middle temporal gyrus; ITG, inferior temporal gyrus.
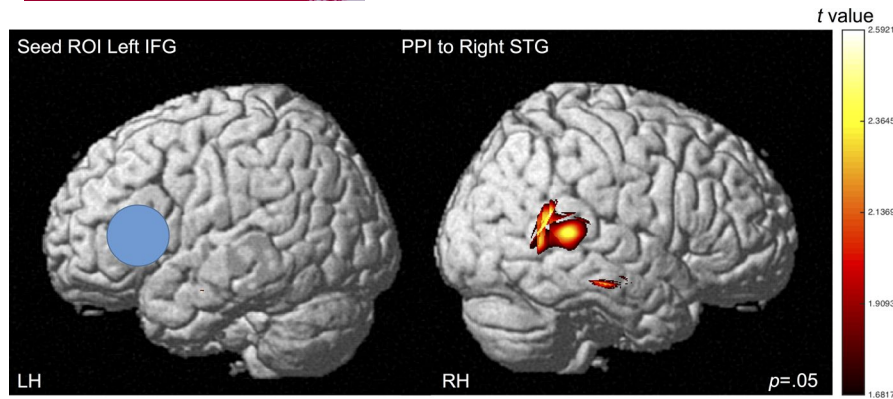
FIGURE 5 Significant psychophysiological interaction between seed ROI of left IFG (shown in blue) to right STG modulated by task

between our left STG ROI seed and any other left or right hemisphere region.

3.3 | Brain-behavior results

Histograms of children's Time 1 and Time 2 language and reading scores are shown in Figure 6.

3.3.1 | Letter-word decoding

Children's letter-word decoding ability at Time 2 was significantly predicted by phonological awareness at Time 1. Letter-word decoding at Time 2 was also marginally predicted by phonological memory, connectivity (LIFG-RSTG PPI), and bilateral STG connectivity (LSTG-RSTG PPI) at Time 1.

3.3.2 | Pseudoword reading

Children's pseudoword reading ability at Time 2 was significantly predicted by IQ, phonological awareness, LIFG activation, and connectivity (LSTG-RSTG PPI) at Time 1. Pseudoword reading at Time 2 was also marginally predicted by right STG activation and connectivity (LIFG-LSTG, LIFG-RSTG PPI) at Time 1.

3.3.3 | Passage comprehension

Children's passage comprehension ability at Time 2 was significantly predicted by phonological awareness and connectivity (LSTG-RSTG, LIFG-RSTG PPI) at Time 1, and marginally predicted by phonological memory at Time 1.

In summary, phonological awareness at Time 1 was a significant predictor of all Time 2 reading abilities. Increased phonological awareness scores were associated with increased reading scores. Beyond the proportion of variance in reading ability accounted for by language ability at Time 1, neural activation in left IFG also

accounted for additional variance. Most notably, Time 1 connectivity during our word and nonword speech task (as compared to baseline) between left IFG and right STG and between left STG and right STG significantly accounted for children's reading abilities at Time 2 beyond behavior (namely, phonological awareness, phonological memory) and neural activation. Increased connectivity was associated with increased reading ability. See Table 4 for detailed statistical values.

4 | DISCUSSION

We examined pre-literacy language abilities, neural activation, and connectivity in language networks in young children between the ages of 3.5 and 5.5 who had not yet begun formal literacy instruction. Specifically, we measured the extent with which activation in left hemisphere network for language processing and task-modulated connectivity between regions in this network was predictive of future reading ability. In combination with behavioral assessments of language and literacy, neural activation and task-related connectivity analyses were used to understand how functional neural segregation (specific brain regions that support reading functions) and integration (emergence of reading networks across those brain regions) of pre-literacy language processing relate to future reading outcomes.

The children in our study showed canonical neural responses for processing spoken language: greater activation was observed for both words and nonwords compared to baseline in bilateral STG. With respect to connectivity, activation in the right STG was related to activation in the left IFG depending on whether children are listening to speech versus baseline conditions. Bilateral STG supports speech processing at all ages, but there are divisions between the left and right hemispheres' contributions to speech processing (Zatorre & Belin, 2001). For example, the right hemisphere has a preference for processing spectral change information over long integration time windows, whereas the left hemisphere has a preferences for integrating rapid spectral changes, which may be modulated by task demands (Boemio et al., 2005). The connectivity between the left IFG and right STG in particular may reflect the
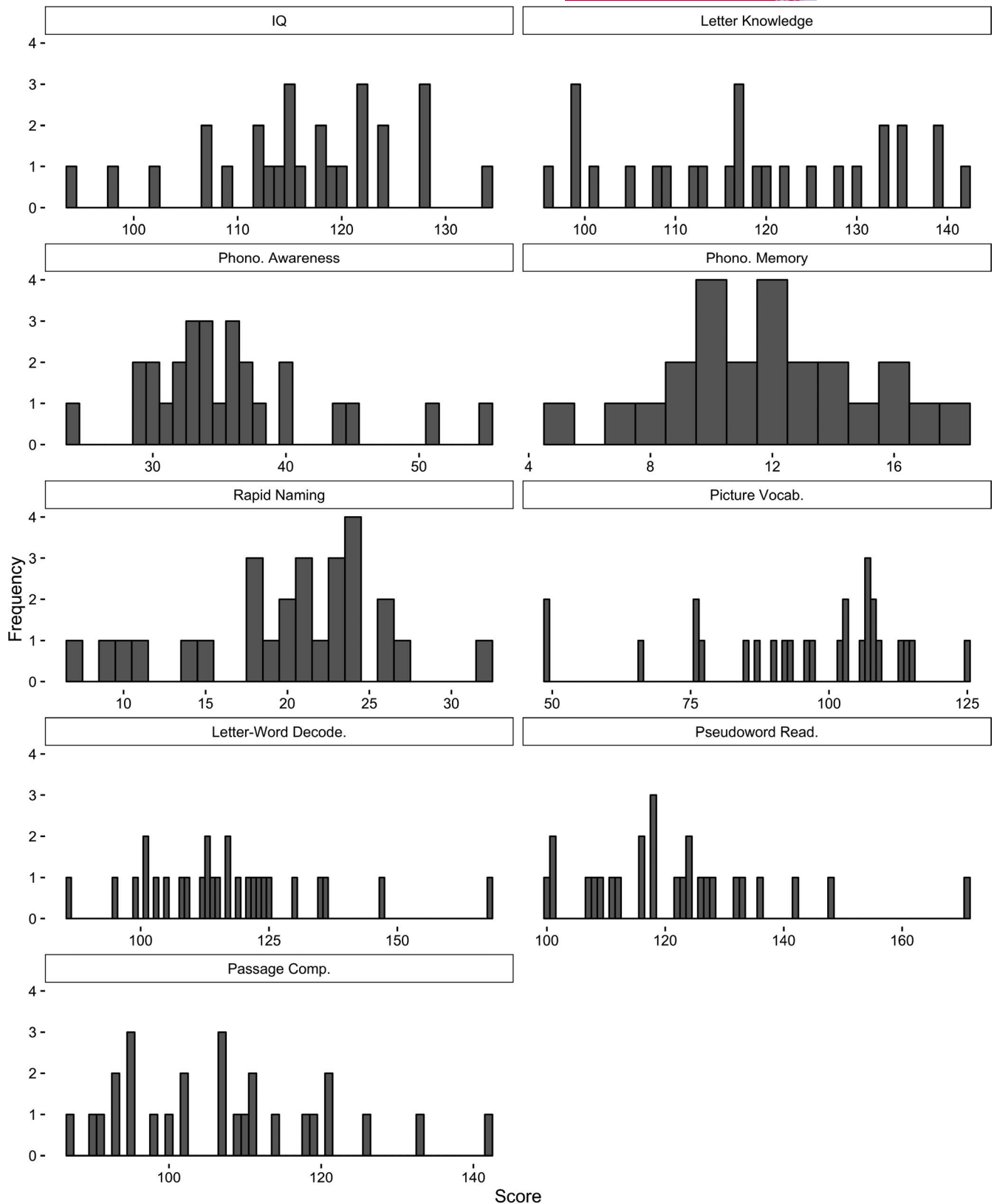
FIGURE 6 Histogram of behavioral scores on language and reading assessments. Standard assessment scores are shown

different computations of the right hemisphere during speech processing (Brechmann & Scheich, 2005). Moreover, as language skills improve, the right hemispheres' role in language processing may be downregulated as left hemisphere engagement increases, that is, increased left lateralization over development (Holland et al., 2007; Spironelli & Angrilli, 2009), and also becomes increasingly more

TABLE 4 Models of Letter Word Decoding, Pseudoword Reading, and Passage Comprehension at Time 2. Final models are the result of forward and backward stepwise regression. Adjusted R^2 are shown for each model. Beta coefficients are standardized. Two tailed results are reported, significant results ($p < 0.017$; Bonferroni corrected) are noted in bold.

Predictor	Letter word decoding						"Word Attack" pseudoword reading						Passage comprehension					
	Initial model: $R^2 = 0.700$			Final model: $R^2 = 0.748$			Initial model: $R^2 = 0.688$			Final model: $R^2 = 0.757$			Initial model: $R^2 = 0.566$			Final model: $R^2 = 0.683$		
	$F_{(14,12)} = 5.28, p = 0.003$			$F_{(10,16)} = 8.70, p < 0.0001$			$F_{(14,12)} = 5.10, p = 0.006$			$F_{(7,19)} = 12.55, p < 0.0001$			$F_{(14,12)} = 3.43, p = 0.002$			$F_{(7,19)} = 9.02, p < 0.0001$		
	β	t	p	β	t	p	β	t	p	β	t	p	β	t	p	β	t	p
Demographic																		
Age at Time 2	-0.056	1.665	0.122	0.212	1.847	0.083	0.123	0.847	0.414	–	–	–	0.154	0.901	0.385	0.161	1.254	0.225
IQ	0.112	0.586	0.569	–	–	–	-0.176	-0.906	0.383	**-0.284**	**-2.795**	**0.012**	-0.285	-1.243	0.238	-0.198	-1.527	0.143
SES	-0.121	-0.709	0.492	–	–	–	-0.138	-0.793	0.443	–	–	–	0.077	0.373	0.715	–	–	–
Language ability																		
Letter knowledge	0.265	1.130	0.280	0.258	1.633	0.122	-0.091	-0.381	0.710	–	–	–	-0.029	-0.104	0.919	–	–	–
Phono. awareness	**0.710**	**3.210**	**0.007**	**0.659**	**4.295**	**0.001**	**0.889**	**3.964**	**0.002**	**0.722**	**6.349**	**<.001**	0.570	2.155	0.052	**0.642**	**5.072**	**<.001**
Phono. memory	-0.254	-1.647	0.125	-0.236	-2.050	0.057	-0.171	-1.097	0.294	–	–	–	-0.250	-1.356	0.200	-0.280	-2.129	0.047
Rapid Naming	-0.094	-0.760	0.462	–	–	–	-0.035	-0.281	0.783	–	–	–	-0.036	-0.247	0.809	–	–	–
Picture vocabulary	-0.266	-1.087	0.298	-0.231	-1.607	0.128	0.089	0.358	0.726	–	–	–	0.056	0.190	0.852	–	–	–
Brain activation																		
LSTG activation	-0.056	-0.321	0.754	–	–	–	-0.123	-0.691	0.503	–	–	–	-0.045	-0.216	0.833	–	–	–
RSTG activation	-0.204	-1.226	0.244	-0.184	-1.321	0.205	-0.278	-1.645	0.126	-0.235	-1.796	0.088	-0.209	-1.050	0.315	–	–	–
LIFG activation	-0.173	-1.031	0.323	-0.191	-1.492	0.155	**-0.420**	**-2.472**	**0.029**	**-0.333**	**-3.236**	**0.004**	-0.207	-1.031	0.323	-0.155	-1.301	0.209
Connectivity																		
LIFG-LSTG PPI	0.200	1.109	0.289	0.217	1.576	0.135	0.312	2.215	0.047	0.252	2.026	0.057	**0.095**	**0.442**	**0.666**	–	–	–
LSTG-RSTG PPI	0.237	1.539	0.150	0.232	1.816	0.088	0.165	0.905	0.383	**0.322**	**2.604**	**0.017**	**0.484**	**2.624**	**0.022**	**0.384**	**3.265**	**0.004**
LIFG-RSTG PPI	0.276	1.987	0.070	0.239	2.125	0.050	0.361	2.310	0.040	0.253	2.481	0.023	**0.469**	**2.821**	**0.015**	**0.478**	**4.004**	**0.001**

specialized for processing written language. Over reading development, greater temporoparietal cortex activation is observed early on, when reading is more dependent on phonologically mediated print to meaning pathways. We observed speech-related modulation between activation in right hemisphere temporoparietal cortex, which is associated with early stages of reading development, and activation in left hemisphere inferior frontal cortex, which is associated;with the later processing of print and speech.

Moreover, we observed neural sensitivity to lexicality (words versus nonwords) in the left IFG, right IPL, and right MTG. The left IFG is classically associated with language, including phonological and morphological processing, syntax, and lexical access. Over the course of reading development, left IFG engagement increases which may correspond to a relatively greater reliance on direct orthographic-to-semantic coding that is a hallmark of skilled reading, rather than orthographic-to-phonological-to-semantic coding which characterizes emergent reading stages (Berends & Reitsma, 2006; Hoover & Gough, 1990; Jasińska & Petitto, 2014; Snowling, 2004; Turkeltaub et al., 2003). Moreover, word and nonwords exploit differences in reading processing related to the conversion of graphemes (i.e., letters) to phonemes (i.e., sounds) and reading processing related to the lexical access of semantic content. The activation of the right IPL for nonwords versus words for pre-readers in our study differs from Yu et al.'s (2018) findings where decreased left IPL activation was observed over development from the pre-reading to emergent reading stages, and increased connectivity between the left IPL and left IFG, posterior occipitotemporal cortex, and right angular was associated with phonological processing. Yu et al., hypothesized that decreased activation in this region known to have a role in letter-sound mapping might reflect a more fine-tuned specialized mechanism, specifically in response to extensive literacy instruction in the classroom that targets letter-sound mapping. In the present study, we examined younger children *before* they experience formal literacy instruction; children who have not yet had the critical exposure to prompt this neural specialization. Indeed, observed activation in the right hemisphere in this study, rather than the left, may reflect more immature lateralization processes which occur concurrently with experience-based neural specialization. Furthermore, the differences between Yu et al.'s (2018) finding and the present study may reflect the different developmental stages that were investigated in each study. Yu et al., (2018) examined pre-readers who were 5 years old (4.6-6.2 years), whereas the current study examined pre-readers who were 4 years old (between 3.4 and 5.4 years). Between 4 and 5 years of age, children's brains continue to undergo maturation. Over childhood, cortical thickness gradually declines, cortical white matter volume, and fractional anisotropy (FA) increase—changes that reflect the increasing organization of white matter tracts myelination, and functional networks continue to specialize, particularly in response to experience (Gilmore et al., 2018). Pre-readers who are not yet receiving formal literacy instruction at school are nonetheless gaining exposure with language and informal literacy, given the strong reciprocal associations between language and literacy, this experience would support children's phonological

processing skills and may be reflected in the downregulation of the IPL among older pre-readers (Yu et al., 2018). Although the findings of this study are not directly comparable to Yu et al. (2018), given that Yu et al. (2018) examined longitudinal changes in brain activation among an older cohort of children, and the present study examined brain activation and connectivity in younger children in relation to later behavioral outcomes, both studies converged on the relevance of connectivity for future reading outcomes, as discussed further below.

Language abilities at Time 1 (phonological awareness, phonological memory) significantly predicted reading skills at Time 2, including letter-word decoding, pseudoword reading, and passage comprehension. Neural activation patterns in the left IFG at Time 1 also predicted reading outcomes, specifically passage comprehension. Decoding and pseudoword reading is thought to be predominantly supported by phonological processing and grapheme-to-phoneme mapping, whereas passage comprehension requires the recruitment of multiple level of linguistic knowledge, including syntax and semantics. The observation that activation of the left IFG, which is associated with these linguistic faculties, is related to higher level reading ability (i.e., passage comprehension) is in line with previous reports (Ryherd et al., 2018).

Most importantly, task-modulated connectivity between the left IFG and right STG, and between left and right STG was predictive of reading outcomes. Increased connectivity was associated with increased reading ability. This finding suggests that specialized cognitive abilities such as reading may develop as a product of earlier connectivity between regions that are key to language processing. Crucially, given that we were able to examine this "precursor to reading" network before formal literacy exposure, our findings may suggest that experience (i.e., literacy instruction) may drive the specialization of this *existing* network.

Moreover, beyond the proportion of variance in reading ability accounted for by language ability at Time 1, neural activation in left IFG also accounted for additional variance. Notably, the predictive value of connectivity was beyond that of Time 1 behavior and neural activation alone. To be sure, significant predictive value was added by collecting both behavioral and neural measures in this sample of young, preliterate children. fNIRS' ease of use with young children, as compared to fMRI, permitted insights into earlier stages of development at an age where fMRI can often be a challenge.

4.1 | Limitations and future directions

There are also limitations of this study to consider. The study sample consisted of only monolingual English-speaking children and the extent with which our findings extend to other orthographies, languages, and bilingual/biliterate children requires further investigation. Another limitation of the current study is the small sample size, and the reduced Time 2 sample (n = 28) from Time 1 (n = 39); interpreting the results should remain cautious. Moreover, while we define pre-readers (Time 1 sample) as children who have not yet begun

formal literacy instruction (i.e., at school), children may have more informal experience with reading prior to starting school (e.g., parents read to children). Indeed, the parents do report informal literacy exposure. There is a need to acquire more detailed information concerning pre-reading activities, particularly as these are likely to vary across families, and sample from a more diverse range of families with more varied literacy exposure at home.

Future work will expand on the current findings by following neurodevelopmental changes for reading in children for a longer period spanning critical years for literacy development, including neuroimaging at multiple time points. More specifically, the current study examined brain activation and connectivity of 3.5- to 5-year-old pre-readers at one time point, and related work (i.e., Yu et al., 2018) examined longitudinal changes in brain activation and connectivity of 5-year-old pre-readers. However, the results of this study suggest that neurodevelopmental changes and children's language experience between 4 and 5 years of age are relevant to understanding a child's future reading outcomes. Future work should examine the development of pre-readers at multiple time points (i.e., age four, age five) in relation to later outcomes.

5 | CONCLUSION

Functional connectivity in the emerging reading circuitry is related to developmental changes in reading ability. Previous research with older children who are already reading has shown that increased connectivity between regions in the reading circuit corresponds to increased reading performance (Finn et al., 2014; Pugh, Mencl, Shaywitz, et al., 2000; Wang et al., 2013). However, the mechanisms by which connectivity relates to reading ability remain unclear from studies of children have already begun reading and have accumulated years of practice. Increased connectivity may be driven by the vast number of hours a typical school-aged child will spend practicing reading. Our findings provide a novel perspective given that the children studied here were as young as three and a half at the time of participation, and therefore their neural activation and connectivity patterns to spoken input could not have yet been shaped by years of exposure to literacy.

Our findings also have important practical considerations: while language skills are highly predictive of future reading ability, patterns of neural connectivity can additionally explain individual differences in reading abilities of school-aged children. Such insights into the brain basis of emergent healthy/typical reading can be used to understand children who are struggling to learn to read, and inform policies that can target child reading outcomes even earlier in development, before a child has begun to learn to read.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (Kaja Jasińska, kaja.jasinska@utoronto.ca) upon reasonable request.

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