THE NEURAL SIGNATURES OF PLASTICITY IN DEVELOPMENTAL AND EARLY ACQUIRED SPEECH, LANGUAGE AND READING DISORDERS

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EDITORIAL
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Editorial: The Neural Signatures of Plasticity in Developmental and Early Acquired Speech, Language and Reading Disorders

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Keywords: plasticity, childhood, neurodevelopment, brain damage, language disorders, reading disorders

Editorial on the Research Topic

The Neural Signatures of Plasticity in Developmental and Early Acquired Speech, Language and Reading Disorders

The brain has an astonishing capacity to change, allowing both learning throughout life and recovery from brain damage. However, different brain injuries during the development and maturation of speech, language, and reading functions may impact the neurodevelopmental outcomes by interfering with adaptive neural plasticity. Therefore, studying children and adolescents born preterm, suffering from congenital deafness, developmental dyslexia (DD), brain malformations or acquired damage is paramount to gain further insights into the neuroplastic mechanisms operating in the developing brain. In this Research Topic, we assemble a collection of nine studies that apply the most advanced neuroimaging technology in different populations to bring new vitality and insight to this complex topic.

The article by Demir-Lira et al. shows that early language experience may play a relevant role in developing brain structure. These researchers describe a longitudinal study spanning 15 years and reveal, for the first time, that features of parental language input before school predict the level of change in cortical thickness between 5 and 12 years later. An essential role of deprivation on white matter tract maturation is shown by Cheng et al.'s study, which evaluated children with different early language experiences, including deaf native signers of American Sign Language (ASL), hearing L2 signers of ASL, and children with limited early language experience. This research provides evidence that the sensory modality of early language experience does not affect the structure of the dorsal and ventral white matter language pathways as revealed using DTI-Tractography. Conversely, early deprivation of linguistic experience of any kind does affect the structure of the left arcuate fasciculus.

Neuroplasticity is also the prevailing model for explaining the neuroimaging correlates of recovery in children with prenatal or perinatal brain injuries that show normal development after an initial delay. In one study, Bruckert et al. demonstrate that at the age of 8 years, there is no difference in reading performance between children born full-term and pre-term, nor there are differences in the microstructural properties of dorsal and ventral white matter pathways related to reading between the two groups. However, the microstructure of these pathways forecasts later

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reading outcomes only in children born full-term. By contrast, reading in children born pre-term may rely on alternative brain routes or on a broader set of cognitive skills related to more extensive brain networks (e.g., executive functions) to achieve proficiency in reading performance. In another study, Northam et al. evaluate oromotor and speech production abilities while structural and functional magnetic resonance imaging (MRI) was acquired in adolescents born prematurely. They detected persistent subclinical oromotor control difficulties in 31% of the sample, yet no speech disorders were found in any participants. However, the authors found altered microstructure in the impaired group within the part of the corticospinal tract associated with the control of the lips, tongue and larynx, as well as greater recruitment of the perisylvian areas in the right hemisphere, suggesting that the right hemisphere may compensate for early damage in left-hemispheric areas that may be important for normal speech production.

Neuroplasticity may be inefficient in cases of language deficits associated with bilateral developmental brain malformations. The multimodal study of Berthier et al. describes, for the first time, a case of developmental dynamic dysphasia in an adolescent showing bilateral perisylvian cortical anomalies (left greater than right) together with atypical configuration of white matter tracts, including the corpus callosum. Dynamic dysphasia, characterized by deficits in verbal fluency and sentence generation, probably arose from a limited capacity of the malformed right hemisphere to take over left hemisphere language deficits and from altered interhemispheric interaction. A second case of developmental dynamic dysphasia has recently been described by Barker et al. (2021) in an adult patient related to a congenital malformation of the rhombencephalon and corpus callosum.

While language deficits associated with developmental brain malformations persist throughout life, focal brain lesions acquired during childhood can improve when treatments based on neuroscience principles are used. Indeed, language recovery can even be boosted by using combined interventions. Dávila et al. report the case of a 9-year-old girl with chronic anomic aphasia after traumatic brain injury in the left temporoparietal cortex. The patient received a novel combined therapy to promote brain plasticity, involving a cholinergic agent (donepezil) alone and in combination with intensive anomia therapy. Treatment with donepezil alone was enough to improve executive and language deficits, while adding the language therapy boosted the gains that remained after the washout period. For the first time, this study demonstrated that donepezil, a drug effective for treating adult aphasia (Berthier et al., 2006) administered alone and in combination with intensive naming therapy is well-tolerated, safe and effective in treating childhood aphasia.

DD, one of the most prevalent developmental disorders, is a selective deficit of reading abilities not explained by a deficit of general intelligence or educational opportunities (Peterson and Pennington, 2012). Causative factors, both biological or cognitive, have been proposed, but the precise characterization of the etiology and different profiles of dyslexia must be conclusively demonstrated. On studying DD, Horowitz-Kraus et al. highlight the role of executive functions associated with the activity of medial prefrontal brain areas such as the anterior cingulate cortex (ACC) using proton magnetic resonance spectroscopy. Specifically, they show that processing speed exerts a protective action against dyslexia. Furthermore, this cognitive function in female dyslexics correlates with low levels of metabolites associated with myelination and connectivity in the ACC. Cao et al. examine brain mechanisms underlying visuo-orthographic processing through lexical and perceptual tasks in children with DD. Brain activation analysis revealed decreased activation in the left precuneus associated to both visual and orthographic deficits, likely reflecting a deficit in visual attention; while Psycho-Physiological Interaction (PPI) analysis revealed task-specific alterations in functional connectivity. An alternative view is provided by Zakopoulou et al., who address DD from a multifactorial causal model to explore the link between brain asymmetries, personality traits, cognitive skills, specific gene expression profiles, neuroplasticity, and stress in an adult diagnosed with DD. This single case study suggests a stress-related dyslexia endophenotype characterized by asymmetries in the amygdala and cerebellum, altered stress response and personality traits such as difficulties coping with intense emotional situations.

In conclusion, these papers demonstrate that early brain injuries contribute to but are not the sole predictors of language outcomes. Taken together, we see the importance of brain structure to language function, not only classic brain areas but also other areas. We learned that children born preterm learn to speak despite subclinical oromotor abnormalities and read despite different patterns of white matter association. We documented the importance of experience for brain development, including the positive impact of parental input and the negative effects of deprivation. We documented that a medication affecting neural transmitters can boost recovery after traumatic injury. Thus, we hope that this Research Topic will help resolve long-standing questions on plasticity during the early stages of development and propel new ideas for future studies.

AUTHOR CONTRIBUTIONS

GD and DL-B contributed to the design of the work and drafted the Editorial. HF revised the draft for important intellectual content and contributed with the interpretation of the work. GD, DL-B, and HF approved the final version to be published. All authors contributed to the article and approved the submitted version.

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Children With Dyslexia and Typical Readers: Sex-Based Choline Differences Revealed Using Proton Magnetic Resonance Spectroscopy Acquired Within Anterior Cingulate Cortex

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Children with dyslexia exhibit slow and inaccurate reading, as well as problems in executive functions. Decreased signal activation in brain regions related to visual processing and executive functions has been observed with functional magnetic resonance imaging with reports of sex differences in brain patterns for visual processing regions. However, the underlying neurochemistry associated with deficits in executive functions for children with dyslexia has not been thoroughly evaluated. Reading ability and executive functions were assessed in fifty-three children [ages 8–12 years old, dyslexia (n = 24), and typical readers (n = 30)]. We employed short echo, single voxel, proton magnetic resonance spectroscopy to evaluate the perigenual anterior cingulate cortex (ACC). Pearson correlations were calculated between metabolite concentrations and measures of reading, processing speed, and executive function. Logistic regression models were used to determine the effects of brain metabolite concentrations, processing speed, and reading scores on dyslexia status. Differences by child's sex were also examined. Compared to typical readers, higher global executive composite t-score is associated with greater odds for dyslexia (OR 1.14; 95% CI 1.05, 1.23); increased processing speed appears to be protective for dyslexia (OR 0.95; 95% 0.89–1.00). After adjustment for multiple comparisons, females with dyslexia showed strong and significant negative correlations between processing speed and myo-inositol (r = −0.55, p = 0.005) and choline (r = −0.54, p = 0.005) concentrations; effect modification by sex was confirmed in linear regression models ($p_{sex*Cho}$ = 0.0006) and (p_{sex*ml} = 0.01). These associations were not observed for males or the group as a

whole. These findings suggest that children with dyslexia share difficulty in one or more areas of executive function, specifically those related to response time. Also, metabolite changes in the ACC may be present in children with dyslexia, especially for females, and may hold value as possible markers for dyslexia.

Keywords: dyslexia, MRI, spectroscopy, reading, executive functions

HIGHLIGHTS

- Compared to typical readers, higher global executive composite t-score is associated with greater odds for dyslexia.
- Increased processing speed appears to be protective for dyslexia.
- Processing speed in females was negatively correlated with perigenual anterior cingulate concentrations of choline and myo-inositol.

INTRODUCTION

Reading Difficulties and Executive Functions

Reading difficulties (or dyslexia) are characterized by slow and inaccurate reading which continues into adulthood despite remedial intervention and exposure to the written language (International Dyslexia Association IDA, 2011). Specific challenges related to phonological and orthographical processing deficits, and more broadly the reading process, have been observed in individuals with dyslexia (Seidenberg and McClelland, 1989; Pugh et al., 2000). However, our accumulated data suggests that children with reading difficulties also demonstrate challenges in several higher order abilities, i.e., in executive functions (Horowitz-Kraus, 2014). More specifically, we found that children and adults with dyslexia demonstrate decreased error monitoring ability, as manifested using electroencephalographic (EEG)-event related potentials (ERP) amplitudes following a commission of an error (i.e., decreased error related negativity potential) compared to age matched typical readers (Horowitz-Kraus and Breznitz, 2008, 2013; Horowitz-Kraus, 2011, 2012). This alteration was not specific to reading materials but was also extended to tasks which do not contain verbal stimulation (i.e., the Wisconsin task) (Horowitz-Kraus, 2014). This ERP pattern, which is related to a mismatch between an actual and a desired response, is an evoked post-response and is related to a change in dopaminergic serge (Falkenstein et al., 1991, 2000). The error related negativity evoked from the anterior cingulate cortex (ACC) (Falkenstein et al., 2000) is part of the error detection system in the brain. The ACC is a critical part of the cingulo-opercular network which is related to a top-down monitoring process (Dosenbach et al., 2008). Support for the altered brain activation related to the ACC was found in our study showing a decreased functional connection within the cingulo-opercular network during reading in children with dyslexia and an increased functional connectivity following intervention that accompanied reading achievement (Horowitz-Kraus et al., 2015b). Since decreased ERPs are related to decreased neuronal firing, which in turn points at decreased signal activation on functional magnetic resonance imaging (fMRI), it is therefore not surprising that this network showed decreased functional connections with visual processing during a reading task in children with dyslexia, and altered functional connection during a Stroop task in this population (Levinson et al., 2018) emphasizing its critical role in monitoring during reading (Horowitz-Kraus et al., 2015a) as well as in the absence of a task (i.e., during rest) (Horowitz-Kraus et al., 2015b). Other ERP and fMRI studies revealed differences between individuals with dyslexia and typical readers, including manipulations aimed at improving reading through a specific triggering of executive functions, increased ERPs related to error monitoring (Horowitz-Kraus and Breznitz, 2014), and increased activation of the ACC (Horowitz-Kraus et al., 2014) and of functional connectivity of the cingulo-opercular network (Horowitz-Kraus et al., 2015b). These EEG and fMRI findings led us to examine the specific differences in metabolite concentrations within the ACC mediating reading ability.

Are There Neurochemical Characteristics for Reading Difficulties?

Lebel et al. (2016) observed using proton magnetic resonance spectroscopy (MRS) in typical preschool children that phonological processing ability was positively associated with glutamate (Glu), creatine (Cr), and myo-inositol (mI) concentrations in the pregenual anterior cingulate. As mI concentrations are thought to have a role as a marker of glial cells, the increased levels supported increased Glu neurotransmission and this metabolism provided a coupled relationship with phonological processing. However, most studies in the field of dyslexia focus on the role of phonological and orthographical routes (Shaywitz and Shaywitz, 2003a,b; Shaywitz et al., 2003). Pugh et al. (2014) characterized metabolite levels in children with dyslexia within the occipital cortex. This study employed English speaking, 6–10 year old typical readers and individuals with dyslexia and suggested a negative correlation between Cho and Glu concentrations with reading and phonological processing abilities (Pugh et al., 2014). The authors speculated that elevated Glu, a marker for hyperexcitability, may influence the coherence of neuronal networks involved in learning, which may also be the case for other pathologies. These researchers suggested that an unstable performance of children with reading difficulties is characterized with a moment to moment variance in performance and a lack of consistency (Pugh et al., 2014). This may provide a link to the monitoring challenges found in this population, which are not restricted to the reading domain. In a subsequent study, Del Tufo et al. (2018) found in children

that cross-modal word matching mediates the relationship with increased Glu and increased Cho with poorer reading ability. Given that Cho levels represent membrane turnover as well as cellular and white matter density (Miller et al., 1996), elevated levels are in-turn related to increased connectivity or atypical myelination of the occipital cortex with additional regions in children with dyslexia (Pugh et al., 2014). Similarly, higher Cho levels in the angular gyrus are also associated with low reading scores in adults (Bruno et al., 2013). There it was suggested that Cho may be related to less efficient neuronal activity in this regions related to phonological processing and lower reading scores (Bruno et al., 2013). Bruno et al. (2013) also indicated that N-acetylaspartate (NAA) levels in the angular gyrus, a marker for intact neuronal ability, was related to a higher cognitive ability in adults (Jung et al., 2005). Del Tufo et al. (2018) also found that higher NAA predicted faster cross-modal matching reaction times in children. Increased NAA in the prefrontal cortex was also related to enhanced metabolic rates in these regions, probably due to differences in prefrontal maturation, as was observed in Asperger patients (Murphy et al., 2002). Higher NAA was previously related as a marker of viable neurons (Erickson et al., 2012) and there is conflicting evidence of positive and negative correlations (Mohamed et al., 2010) of NAA levels and cognitive control abilities. However, there is still a gap in knowledge as to the significance of metabolite concentrations in regions specifically related to executive functions in children with dyslexia.

Therefore, the goals of the current study were to: (1) determine whether metabolite concentrations in the ACC predict silent reading and sight word efficiency, processing speed or executive functions, (2) evaluate whether metabolite concentrations, reading ability, processing speed or executive functions vary in children with dyslexia compared to typical readers, and (3) determine if the associations vary by sex.

MATERIALS AND METHODS

Participants

Participants were recruited from posted ads and through commercial advertisements. All participants gave their informed written assent and their parents provided informed written consents prior to inclusion in the study. This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

Behavioral Measures

Baseline Reading Measures Used to Confirm Dyslexia Status

We confirmed the existence of reading difficulties using a battery of normative reading tests in English. Children with dyslexia were all diagnosed as having difficulty reading. Inclusion criteria for the dyslexia group were standard score of −1 and below or meeting the 25% or below cutoff in words reading, decoding and comprehension abilities. This battery included (a) words reading accuracy/orthography: the "Letter-Word" subset from the Woodcock and Johnson-III (WJ-III) battery (Woodcock and Johnson, 1989); (b) decoding: the "Word Attack" subset from the WJ-III (Woodcock and Johnson, 1989); and (c) reading comprehension subset from the WJ-III (Horowitz-Kraus et al., 2016). Participants in the typical readers group were age-matched students who volunteered for the study with fluent and accurate reading according to established normative levels for the WJ-III.

Reading Abilities

We further evaluated children's reading abilities using the Tests of Word Reading Efficiency (TOWRE) to assess the participant's ability to pronounce printed words (sight word efficiency) and the Tests of Silent Reading Efficiency and Comprehension (TORSEC) to assess the participant's fluency ability.

Executive Functions and Cognitive Abilities

To assess executive functions and cognitive abilities, we used the Behavioral Rating Inventory of Executive Functions (BRIEF) (Gioia et al., 2002) parents questionnaire as well as the speed of processing tests from the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V) (Wechsler, 2014). The BRIEF questionnaire includes questions covering the child's cognitive abilities (i.e., inhibition, organization, attention, monitoring, and emotional regulation). In the speed of processing subtests of the WISC-V, participants performed the symbol search and the coding sub-tests, both result in the Processing Speed Index (PSI) employed for the analyses.

Magnetic Resonance Measures

Acquisition Methods

Brain magnetic resonance imaging (MRI) and spectroscopy (MRS) were acquired using a Philips Achieva MR scanner operating at 3 Tesla (3T) and equipped with a 32-channel head coil. A three-dimensional (3D), high-resolution, isotropic, T1-weighted fast Fourier echo (FFE) anatomical imaging sequence was performed using 8.2 ms repetition time (TR), 3.7 ms echo time (TE), 1057 ms inversion time (TI), 8 degree flip angle, sensitivity encoding factor (SENSE) of 2, contiguous slices with a 1 mm thickness, and 1 × 1 mm voxel size. A single voxel, point resolved spectroscopy (PRESS) sequence was conducted using a 2000 ms TR, 30 ms TE, and 96 averages with water suppression along with an embedded unsuppressed water reference series of 16 averages. The 8 cubic centimeter single voxel was prescribed about the perigenual ACC within the medial frontal lobe localized from the 3D T1-FFE anatomical imaging sequence similar to the position described by Lebel et al. (2016) See **Figure 1**.

Participants were acclimated and desensitized to condition them for comfort inside the scanner (see Byars et al., 2002 for details). Head motions were controlled using elastic straps that were attached to either side of the head-coil apparatus. An MRI-compatible audio/visual system (Avotec, SS3150/SS7100) was used for the presentation of a movie during the session.

MRS Data Analysis

The raw spectroscopy data were imported into LCModel (Provencher, 1993) commercial software for quantitative

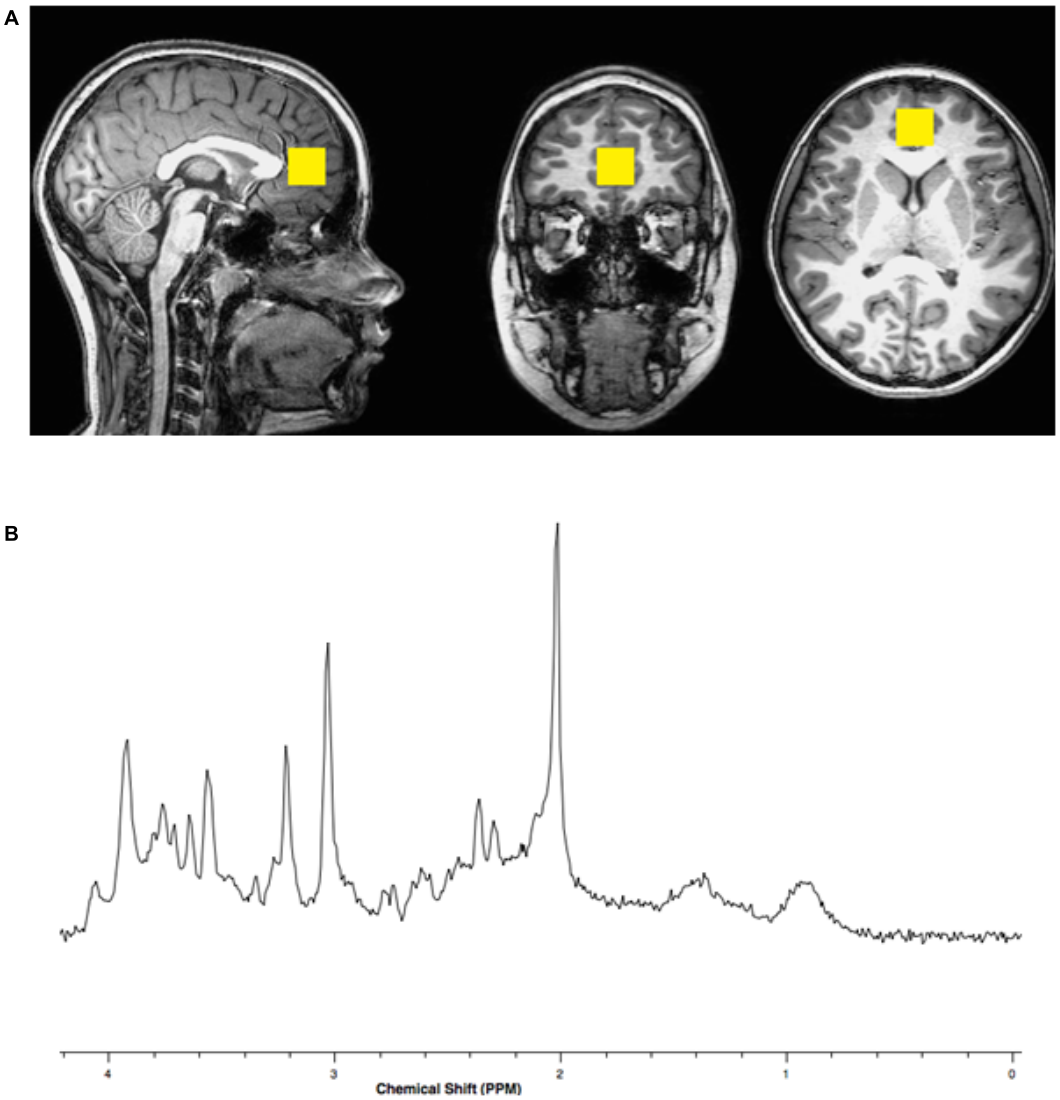

FIGURE 1 | (A) Representative location within the anterior cingulate cortex for the 8 cubic centimeter (2 cm per side) spectroscopic voxel positioned on T1 weighted imaging slices centered in the sagittal, coronal and axial plane orientations. **(B)** Representative single voxel, short echo, magnetic resonance spectrum with N-acetylasparate appearing on the *x*-axis with a peak at a chemical shift value of 2 parts per million (PPM), glutamate at 2.3–2.4 PPM, creatine at 3.0 PPM, choline at 3.2 PPM and myo-inositol at 3.5 PPM.

processing. Metabolite and water reference levels were determined in institutional units. The raw metabolite levels were adjusted for the tissue contributions from gray matter, white matter and cerebrospinal fluid (CSF) using FSL (Woolrich et al., 2009) adjusted to the T1 and T2 relaxation decay rate of the corrected water concentration and corrected for literature reported T1 and T2 relaxation decay rates of the primary metabolites including NAA, Cho, Cr, and mI (Wansapura et al., 1999; Traber et al., 2004; Tal et al., 2012). However, pure Glu as well as the combined glutamate and glutamine (GLX) concentrations were unadjusted for metabolite T1 and T2 relaxation decay (Gussew et al., 2012). Reported values were concentrations in units of millimolar (mM).

Statistical Analyses

First, two sample *t*-tests were used to examine differences in age and IQ measures, reading and executive function measures as well as metabolite concentrations among children with dyslexia and typical readers.

Second, Pearson (*r*) correlations were calculated between individual metabolite concentrations and reading scales, processing speed, and global executive function. Correlation differences by dyslexia status and sex were examined. Correction for multiple comparisons was conducted by False Discovery Rate (FDR) estimation.

Third, significant correlations (FDR cutoff of 0.05) were then evaluated by linear regression adjusting for child's sex and age at visit/test. Effect modification by sex was investigated by

(1) including a two-way interaction term between metabolite concentration and child's sex in the model, and (2) performing sex-stratified linear regression if the two-way interaction term was significant ($p < 0.05$). Effect sizes (β) represent the change in outcome for an interquartile range (IQR) increase in metabolite concentration.

Fourth, to determine if metabolite concentrations, processing speed, and global executive function predict dyslexia status, logistic regression models were implemented. For logistic models of metabolites, all metabolites were included in the same model after the investigation of multi-collinearity (based on correlations among metabolites).

Lastly, to confirm reading difficulty among children with dyslexia, we evaluated the association between silent reading and sight word efficiency and dyslexia status using the TOWRE and TOSREC. While it is likely these measures would be associated with dyslexia, it should be noted that these specific measures were not used to define the individuals in our study (see section 2.2.1). Logistic models were adjusted for child's sex and age at visit/testing. Effect modification was evaluated by including a two-way interaction term between reading/behavior measure and child's sex in the model and by stratification if interaction term was significant. Analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, NC, United States) and SPSS13 (IBM, Armonk, NY, United States).

RESULTS

Participants

Twenty four children with dyslexia (mean age = 9.79 years, *SD* = 1.11, 8 females) and 30 typical readers (mean age = 10.73 years, *SD* = 1.07 year; 17 females) participated in the current study, all matched for age [$t(51) = -1.77$, non-significant (ns)]. All participants were within the normal range of non-verbal IQ (mean 101.45, *SD* = 10.26; children with dyslexia, mean 98.69, *SD* = 11.81 and typical readers mean 103.57, *SD* = 8.49) with [$t(51) = -1.75$, ns].

All participants were native English speakers, Caucasian, and with United States average socioeconomic status by income and education, as reported by the families using a socio-economic status questionnaire (Barratt, 2006) Participants were right-handed, displayed normal or corrected-to-normal vision in both eyes, and had normal hearing. None had a history of neurological or mood disorders, and individuals with reported history of attention difficulties were excluded.

Behavioral Measures

Overall, children with dyslexia demonstrated significant lower scores in all reading measures taken in the study: these readers showed lower phonological and orthographical abilities. Executive functions and speed of processing in children with dyslexia were significantly lower than typical readers. See **Table 1**.

Neurochemical-Behavior Correlations

Pearson correlation coefficient (*r*) values between mI, NAA, Cr, Cho, Glu, GLX, reading scales, processing speed, and global executive function were evaluated. There were no significant correlations observed among the group as a whole; however, there were differences observed by dyslexia status and sex (**Table 2**). Among children with dyslexia, there was a strong negative correlation between Cho and silent reading score ($r = 0.51$, $p = 0.01$); typical readers showed a strong negative correlation between mI and processing speed ($r = -0.42$, $p = 0.02$). After correction for multiple comparisons, no significant differences were found between group metabolite concentrations in children with dyslexia and typical readers.

Females showed strong and significant negative correlations between processing speed and mI ($r = -0.55$, $p = 0.005$), Cr ($r = -0.49$, $p = 0.01$), Cho ($r = -0.54$, $p = 0.005$) levels. See **Table 2**. After correction for multiple comparisons, the correlations between PSI, mI, and Cho remained significant (FDRs = 0.05). Among males, there was a positive correlation between global executive function and mI ($r = 0.35$, $p = 0.05$); this did not hold up after correction for multiple comparisons (FDR = 0.49).

Effect of Neurochemical Levels on Processing Speed

The overall effect of Cho and mI on processing speed was not significant; however there was indication of effect modification by child's sex. **Figure 2** shows the effect of (a) Cho ($p_{interaction} = 0.0006$) and (b) mI ($p_{interaction} = 0.01$) on predicted mean scores for processing speed by child's sex. Higher levels of Cho (β −8.10; 95% CI −12.73, −3.45) and mI (β −5.22; 95%CI −8.22, −2.22) are associated with decreased processing speed among females but not males (**Table 3**).

Effect of Global Executive Function, Processing Speed, Reading Measures, and Metabolites on Dyslexia Status

Children with a higher global executive composite t-score are more likely to have dyslexia (OR 1.14; 95% CI 1.05, 1.23) suggesting some difficulty in one or more areas of executive function is present among children with dyslexia compared to typical readers (**Table 4**). We also observed a marginally significant ($p = 0.049$) association between increased processing speed and protective odds for dyslexia (OR 0.95; 95% 0.89–1.00) compared to typical readers. Metabolite concentrations did not predict dyslexia status. Metabolite concentrations were moderately to significantly correlated (*r* ranging from 0.22 to 0.59, $r = 0.80$ for GLX/Glu correlations) and given the strong correlation between GLX and Glu, a sensitivity analysis was conducted to determine if removal of one of these metabolites impacted the results; the findings remained insignificant. As expected, higher scores on silent reading and sight word efficiency are observed among typical readers as evident by the ORs less than 1 (**Table 4**). There was no evidence of effect modification by child's sex (all interaction *p*-values > 0.20).

TABLE 1 | Group assessment results for children with dyslexia and typical readers.

Assessment	Group	Mean	Standard deviation	T (*p*)
Baseline measures				
Test of non-verbal intelligence (percentile)	Dyslexia	49.61	23.542	−1.1417 (ns)
	Typical readers	57.50	17.021	
Letter word, Woodcock Johnson (standard score)	Dyslexia	89.04	12.448	−9.308 ($p < 0.001$)
	Typical readers	114.87	7.660	
Passage comprehension, Woodcock Johnson (standard score)	Dyslexia	83.70	12.893	−7.606 ($p < 0.001$)
	Typical readers	105.70	5.855	
Word attack, Woodcock Johnson (standard score)	Dyslexia	93.43	8.649	−7.007 ($p < 0.001$)
	Typical readers	109.77	8.224	
Executive functions and reading measures				
Speed of processing PSI, WISC (standard score)	Dyslexia	99.17	13.134	−2.431 ($p < 0.05$)
	Typical readers	107.47	11.643	
General executive functions, BRIEF (T score)	Dyslexia	54.68	9.317	4.038 ($p < 0.001$)
	Typical readers	44.97	7.989	
Fluency, TOSREC (standard score)	Dyslexia	84.27	9.171	−5.626 ($p < 0.001$)
	Typical readers	108.07	18.181	
Word reading, TOWRE, SWE (scaled score)	Dyslexia	81.91	12.210	−7.981 ($p < 0.001$)
	Typical readers	108.33	11.740	
Pseudoword reading, TOWRE, SWE (scaled score)	Dyslexia	81.13	10.476	−10.325 ($p < 0.001$)
	Typical readers	109.60	9.529	
Metabolite concentrations				
Myo-inositol (mM)	Dyslexia	5.76	0.43	0.686 (ns)
	Typical readers	5.66	0.58	
N-acetyl aspartate (mM)	Dyslexia	9.43	0.68	1.294 (ns)
	Typical readers	9.12	0.97	
Creatine (mM)	Dyslexia	8.08	0.39	0.630 (ns)
	Typical readers	7.99	0.55	
Choline (mM)	Dyslexia	1.63	0.11	−0.929 (ns)
	Typical readers	1.66	0.15	
Glutamate (mM)	Dyslexia	8.19	0.51	−0.355 (ns)
	Typical readers	8.24	0.59	
Glutamate and glutamine (mM)	Dyslexia	11.12	0.68	−1.32 (ns)
	Typical readers	11.41	0.84	

Non-significant (ns), millimolar (mM), Behavioral Rating Inventory of Executive Functions (BRIEF), Global executive composite (BRIEF), Processing speed index (PSI), Tests of Word Reading Efficiency (TOWRE), Tests of Silent Reading Efficiency and Comprehension (TORSEC), sight word efficiency (TOWRE-SWE).

TABLE 2 | Pearson correlation among metabolites and reading scales, processing speed, and global executive function by sex.

Metabolite(s)	Silent reading		Sight word efficiency		Processing speed index		Global executive composite	
	Female	Male	Female	Male	Female	Male	Female	Male
mI	0.26	−0.20	−0.36	−0.004	**−0.55**	0.18	0.04	**0.37**
NAA	−0.10	−0.05	−0.15	0.12	−0.30	0.08	0.01	0.32
Cr	−0.29	−0.09	−0.35	0.03	**−0.49**	0.24	−0.14	0.35
Cho	−0.24	0.24	−0.31	0.17	**−0.54**	0.35	−0.01	−0.18
Glu	−0.05	−0.20	−0.23	0.003	−0.34	0.06	−0.21	−0.10
Glx	0.21	−0.09	−0.08	0.11	−0.16	0.26	−0.28	−0.06

mI (myo-inositol), NAA (N-acetyl aspartate), Cr (creatine), Cho (Choline), Glu (glutamate), GLX (glutamate and glutamine), Silent reading (TOSREC), sight word efficiency (TOWRE-SWE), processing speed index (WISC), global executive composite (BRIEF). ***Bold text*** *denotes significant correlation at $p < 0.05$. Correlations significant after correction for multiple comparisons are Cho/PSI (FDR = 0.05) and mI/PSI (FDR = 0.05). Cho and silent reading were correlated among children with dyslexia ($r = -0.51$, $p = 0.01$) and mI and processing speed were negatively correlated among typical readers ($r = -0.42$, $p = 0.02$); these were not significant after multiple comparisons.*

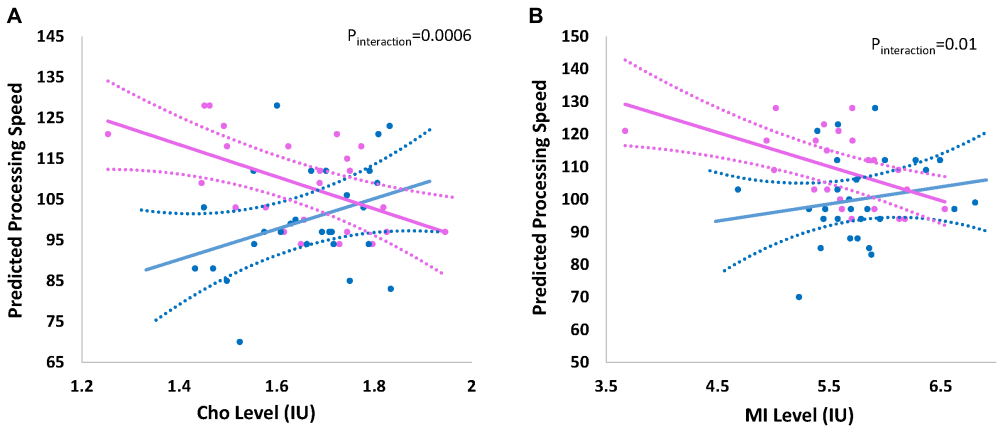

FIGURE 2 | Effect of **(A)** choline and **(B)** myo-inositol on processing speed by sex. Graph represents the effect of **(A)** choline (Cho) and **(B)** myo-inositol (mI) on the predicted processing speed of participants by child's sex Sex-stratified regression models are adjusted for age at visit/testing. Blue and pink indicates the effect for males and females, respectively. Dashed lines represent 95% confidence intervals. Actual individual level data are overlaid for males (blue circles) and females (pink circles). Interaction *p*-value represents the *p*-value for the formal two-way interaction between metabolite level and child's sex in the linear regression model.

TABLE 3 | Overall and sex-stratified results for associations between choline, myo-inositol and PSI.

Model	β	95%CI	*P*-value
Overall			
Cho	−1.56	−6.15, 3.03	0.51
mI	−2.03	−5.02, 0.96	0.18
Females			
Cho	−8.10	−12.73, −3.45	**0.0006**
mI	−5.22	−8.22, −2.22	**0.0006**
Males			
Cho	7.11	−0.03, 14.25	0.06
mI	2.51	−2.49, 7.51	0.33

Choline (Cho), myo-Inositol (mI). Overall models are adjusted for sex and child's age at visit; sex-stratified models are adjusted for child's age at visit/testing. β represent the change in PSI for an interquartile range (IQR) increase in metabolite (Cho IQR = 0.19 IU, MI IQR = 0.47 IU).

TABLE 4 | Relationship between reading scales, processing speed, global executive function, and metabolite levels on dyslexia status.

Predictor(s)	OR	95%CI	*P*-value
Silent reading	0.88	0.82, 0.95	0.001
Sight word efficiency	0.85	0.77, 0.92	0.0002
Processing speed	0.95	0.89, 1.00	0.049
Global executive composite	1.14	1.05, 1.23	0.002
Metabolite predictors[a]			
mI	1.439	0.193, 10.72	0.72
NAA	1.563	0.530, 4.62	0.41
Cr	4.078	0.459, 36.20	0.21
Cho	0.006	0.001, 4.48	0.13
GLX	0.353	0.069, 1.80	0.21
Glu	1.368	0.137, 13.65	0.79

[a]*Metabolites are included in the same model; All models are adjusted for sex and child's age at visit and represent the odds of having dyslexia. Behavioral Rating Inventory of Executive Functions (BRIEF), Tests of Word Reading Efficiency (TOWRE), Tests of Silent Reading Efficiency and Comprehension (TORSEC). Silent reading (TOSREC-index), sight word efficiency (TOWRE–SWE), processing speed index (WISC–PSI), global executive composite (BRIEF–GEC T score). mI (myo-inositol), NAA (N-acetyl aspartate), Cr (creatine), Cho (Choline), Glu (glutamate), GLX (glutamate and glutamine).*

DISCUSSION

Over the past decade, multiple studies have implicated difficulties in executive functions for individuals with dyslexia. However, there is still a gap in knowledge as to the neurochemical characteristics related to reading difficulties in neural circuits associated with challenges in executive functions for this population. The current study aimed to characterize the metabolite concentrations related to reading ability in typical readers and in children with dyslexia, specifically focusing on the ACC. As hypothesized, lower reading ability was associated with high Cho levels, however, it was negatively associated with processing speed in females with dyslexia. The current study also demonstrated a negative relationship between processing speed and mI concentration. To our knowledge, this is among the first pediatric studies to look at MRS measures in the ACC and to report higher levels of Cho in the brain of females with dyslexia. Also, the study confirmed children, both boys and girls, with dyslexia demonstrated lower reading ability and executive functions scores compared to typical readers.

The study did not observe relationships of the cognitive and reading measures with other metabolites, such as NAA, Glu, or GLX, nor did it observe metabolite changes in males. In this study, metabolite concentrations were determined with corrections for metabolite and water relaxation along with contributions from different tissue types contributing to the voxel. Other studies report relative metabolite levels to one another, usually to creatine, and fail to account for differences in tissue contributions, which may explain observed differences. The voxel placement within the pregenual ACC in the current study matches the location described by Lebel et al. (2016)

however, it differs from that of other studies of individuals with dyslexia focused on the occipital lobe including lingual gyrus, calcarine sulcus, and cuneus.

High Cho and Reading Difficulty

Previous studies have pointed at high Cho levels related to reading levels in the occipital lobe (Pugh et al., 2014; Del Tufo et al., 2018) in the cerebellum (Laycock et al., 2008) and the left temporoparietal region (Bruno et al., 2013). The authors suggested that these high Cho levels in individuals with reading difficulties for reading-related regions reflect high membrane turnover, cellular density, and white matter density. These results are in line with evidence of impaired myelination in this population in white matter tracts passing the temporoparietal regions and the occipital lobe (Yeatman et al., 2012; Wandell and Yeatman, 2013). Our study is believed to be among the first to reveal metabolite changes in regions that were not traditionally included as part of the classical reading circuitry. However, in recent years there are additional models pointing at the critical role of executive functions-related neural circuits in reading, including the ACC (Horowitz-Kraus et al., 2013, 2018; Horowitz-Kraus and Hutton, 2015). Our results provide additional evidence for the involvement of neural circuits related to executive functions in children with dyslexia extending the high Cho findings also to the ACC. The relationship to alterations in myelination (especially in the genu which passes though the ACC) should also be examined. As the ACC in a major hub in the cingulo-opercular network, (Dosenbach et al., 2008) it would be interesting to measure Cho levels in other sub-regions of the ACC (as outlined in) (de la Vega et al., 2016) and other brain regions that are related to the fronto-parietal network and the fast monitoring of cognitive processes also impaired in children with dyslexia.

Differences in mI Between Children With Dyslexia and Typical Readers

myo-inositol is a carbocyclic sugar molecule localized to glial cells. There are several known roles for mI in the brain. It is primarily considered a glial cell marker as it's concentration increases with glial cell based neoplasms and gliosis. However, it also functions as an osmolyte such that during periods of osmotic stress, as balance is maintained via mI transport across plasma membranes. However, in the context of the current study with Cho findings, there is support for the role of mI as a key precursor of phosphoinositides and phospholipids, cell membranes and myelin structures. The composition of these structures within the brain networks could directly influence reading abilities.

Sex-Specific Findings

We were able to explore sex-based differences as eight of twenty-four children with dyslexia and seventeen of thirty typical readers in our study were females. Sex differences are known in many disorders, including ADHD, and dyslexia, with greater male frequency with the diagnosis (Shaywitz and Shaywitz, 2003a,b, 2008). Multiple genetic, and non-inherited factors have been posited to explain this observation. The sex hormones, estrogen and progesterone, demonstrate cognitive and neuroprotective effects (Brann et al., 2007; Dumitriu et al., 2010).

Arnett et al. (2017) concluded that the higher prevalence in males with reading difficulties can be explained by slower and more variable processing speed along with worse inhibitory control. Geschwind and Levitsky (1968) first reported structural differences and asymmetry in persons with dyslexia upon post-mortem brain examinations. Non-invasive neuroimaging investigations of brain structure have provided further insight into the neurobiological basis for sex-specific differences. Evans et al., found gray matter volume differences in adults and children, male and female with developmental dyslexia, specifically in the occipital lobe for girls (Evans et al., 2014).

Study's Limitations

The results of this study should be considered in light of the following limitations. First, the sample size of this study is relatively small. Second, the perigenual placement of the MRS voxel within the ACC limited the ability to relate to executive functions of the ACC assigned to more posterior aspects, such as cognitive control and conflict monitoring. Third, technical differences in the MRS acquisition and quantitation of metabolite levels, as previously discussed, can influence the results. Also, the relationship between BOLD and functional connectivity and our findings should be validated in a future study using a joint MRS-fMRI model combining the results of these two methodologies.

CONCLUSION

The current study's findings pinpoint metabolic differences related to the medial frontal lobe in females with dyslexia and typical readers. Further investigations are necessary to explore the metabolism and function of the ACC and how they influence reading abilities.

AUTHOR CONTRIBUTIONS

All authors contributed to data analysis and manuscript writing.

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Brain Mechanisms Underlying Visuo-Orthographic Deficits in Children With Developmental Dyslexia

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Multiple hypotheses have been proposed to explain the reading difficulty caused by developmental dyslexia (DD). The current study examined visuo-orthographic processing in children with dyslexia to determine whether orthographic deficits are explainable based solely on visual deficits. To identify orthographic-specific, visual perception-specific, and overlapping deficits, we included two tasks (lexical and perceptual) in three Chinese subject groups: children with DD, age-matched controls (AC), and reading matched controls (RC) using functional magnetic resonance imaging (fMRI). We found that the left precuneus showed decreased activation across both tasks for the DD group compared to the two control groups, thus reflecting visual processing deficits in children with DD, which also affects orthographic processing. Furthermore, we found that the functional connectivity between left middle occipital gyrus (LMOG) and left inferior frontal gyrus (IFG) was decreased in the DD group compared to AC and RC for only the lexical task. This suggests a weaker association between orthography and phonology for children with DD. In addition, the children with DD showed decreased functional connectivity between the LMOG and right parahippocampal gyrus for only the visual perceptual task, thereby indicating a weaker association between visual regions for DD during visual symbol processing. Taken together, our findings suggest that the observed orthographic processing deficit in DD might be driven by both a basic visual deficit, and a linguistic deficit.

Keywords: dyslexia, fMRI, orthographic deficit, visual deficit, PPI

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INTRODUCTION

Developmental dyslexia (DD) is characterized as a specific and significant impairment in reading ability, which cannot be explained by deficits in general intelligence, motivation, or educational opportunity (Critchley, 1970). The phonological deficit hypothesis is one of the most commonly used theories to explain the etiology of dyslexia, and speculates that underspecified phoneme representations or the unsuccessful retrieval of phoneme representations are the core causes of

reading difficulties in readers with dyslexia (Snowling, 1980; Muter et al., 1998; Boets et al., 2013). In addition to behavioral studies, evidence from neuroimaging studies have also documented support for the phonological deficit hypothesis. For example, reduced brain activation has been reported among left temporo-parietal areas during phonological processing in both the visual (Paulesu et al., 2001; Schulz et al., 2009; Van der Mark et al., 2009; Tanaka et al., 2011) and auditory modalities (Eden et al., 2004; Dufor et al., 2007; Kast et al., 2011). The left temporo-parietal region has been associated with phonological representation and the conversion between orthography and phonology (McCrory et al., 2000; Blau et al., 2010; Kast et al., 2011; Pecini et al., 2011; Paulesu et al., 2014). Reduced brain activation has also been found in the left inferior frontal gyrus (IFG) (Hoeft et al., 2006; Richlan et al., 2011; Cao et al., 2017), which has been associated with phonological segmentation and manipulation during phonological awareness tasks (Pugh et al., 1996; Fiez, 1997; Tan et al., 2001).

Although an abundance of evidence supports the phonological deficit hypothesis, the orthographic deficits observed in readers with dyslexia cannot be overlooked. Indeed, reading is a complex process that involves extensive orthographic analysis of letters, letter strings, and word recognition. People with dyslexia have shown to exhibit difficulties identifying letters within letter strings (Bouma and Legein, 1977; Geiger and Lettvin, 1987), selecting the correct spelling of a target word presented with homophones (Coltheart et al., 1983), and identifying words with similar orthography (Hawelka et al., 2006; Ziegler et al., 2010). Researchers have argued that orthographic deficits may be due to limited exposure and experience with the writing system or inadequate instruction, rather than dyslexia (Mol and Bus, 2011; Huettig et al., 2018). However, compared to reading-matched children, children with DD have been reported to show deficient orthographic processing (Suarez-Coalla et al., 2014), thereby suggesting that orthographic deficits are not purely due to developmental delay.

In opaque and coarse-grained orthographies, such as Hebrew and Chinese, orthographic skills seem to play an even more prominent role in reading acquisition. This is because there are no obvious rules to map orthography to phonology in these languages, and there are many homophones. Therefore, reading these orthographies relies on direct mapping from orthography to semantics to a greater degree, and accurate recognition of orthography is critical for successful reading acquisition. Moreover, Chinese characters consist of strokes in a two-dimensional square; therefore, the complex visual–spatial configurations increase the demand of visual–spatial analysis in reading (Cao et al., 2013). A number of previous studies have reported that orthographic processing skills play a more important role than phonological skills in Chinese reading development (McBride-Chang et al., 2005; Chung et al., 2012; Li et al., 2012; Zhang et al., 2012).

Researchers have found that DD is associated with an impairment in visual attention and visual–spatial analysis (Vidyasagar and Pammer, 2010; Collis et al., 2013), which might help explain an orthographic deficit. These impaired visual processes may be due, in part, to an abnormality within the magnocellular system, which is sensitive to moving stimuli and is involved in visual motion detection. Therefore, the magnocellular system plays an important role in identifying blurred and/or moving letters during reading (Stein and Walsh, 1997). A number of studies have reported anomalous function of the magnocellular system amongst individuals with DD (Meng et al., 2011; Franceschini et al., 2013; Qian and Bi, 2014). For example, Meng et al. (2011) reported that children with DD had a higher threshold for detecting coherent motion than controls, which also predicted overall performance on a Chinese orthographic judgment task. Based on the aforementioned studies, it appears that visual deficits might underlie orthographic deficits observed in DD.

Neurologically speaking, readers with dyslexia exhibit abnormal brain activation during visual and orthographic processing tasks. For example, it has been reported that, compared to controls, people with dyslexia exhibit decreased activation in the middle occipital gyrus (MOG) during visual-perception tasks such as number identification (Boros et al., 2016), symbol detection (Boros et al., 2016), and arrow shape judgment (Zhang et al., 2013). Interestingly, decreased activation in the MOG has also been reported for orthographic tasks that involve pseudoword reading (Shaywitz et al., 2002; Van der Mark et al., 2009; Dehaene et al., 2010; Boros et al., 2016), lexical decision making (Siok et al., 2004), font judgment (Siok et al., 2008), letter matching (Temple et al., 2001), and letter identification (Boros et al., 2016). In summary, the reduced activation in the MOG during visual and orthographic processing tasks in people with DD suggests deficits in visual processing.

Visual–spatial processing has been associated with the posterior parietal cortex (PPC), including the inferior parietal lobule (IPL), superior parietal lobule (SPL), and precuneus (Fiez et al., 1995; Mangun et al., 1998; Shen et al., 1999). Interestingly, people with dyslexia have been reported to exhibit reduced activation among these brain regions, which support visual–spatial processing. Previous studies have found that stimuli placing a greater tax on visual attention elicit greater activation within the left precuneus/superior parietal lobule in control children; however, children with DD do not exhibit this same increase in activation at this region (Peyrin et al., 2011), which suggests a deficit in the visual–spatial processing of visually complex stimuli. This same region has also been reported to play an important role in visuo-orthographic processing during Chinese visual word recognition, and show a developmental increase with age (Cao et al., 2009). Furthermore, studies have shown that children with dyslexia exhibit decreased brain activation in the SPL during tasks involving character size judgment compared to control children (Siok et al., 2009). More recently, it was reported that adults with dyslexia exhibit decreased activation in the left SPL, left precuneus, and the bilateral IPL compared to control subjects while performing a letter string identification task, relative to perceptual analysis, (Reilhac et al., 2013). Taken together, reduced activation in the PPC has been observed during both visual-perceptual and visual-orthographic tasks in people with DD.

Currently, the relationship between the visual deficit and orthographic deficit experienced by readers with DD has yet to be explored completely. Namely, is the orthographic deficit caused solely by visual deficits, or is there a language specific deficit that is not explained by the visual deficit? One way to answer this question is to directly compare the two deficits in a single study. Very few studies have addressed this issue, and existing studies have reported different findings. Temple et al. (2001) found that children with DD exhibited decreased activation in the bilateral occipital-parietal region (including the bilateral MOG, right precuneus, and left cingulate) compared to controls during a letter-matching task in comparison to a line-matching task. The authors suggested that the reduced activation in the occipital-parietal region was language specific; however, poorer performance on the letter-matching task may have been due to greater complexity among the stimuli. More recently, Boros et al. (2016) reported that the processing of digits, letters, and symbol strings was associated with reduced activation in the left MOG and the left visual word form area. These findings suggest that a task-universal neural deficit in visual processing exists among children with DD; however, the same brain region may be connected with different regions to conduct different neural calculations (e.g., Menon and Uddin, 2010). Therefore, it is necessary to examine functional connectivity to determine whether visual and orthographic deficits have the same brain mechanisms in DD.

In the current study, we investigated the brain mechanisms underlying visual processing and orthographic processing in children with DD compared to age-matched controls (AC) and reading-matched controls (RC). We examined both brain activation and functional connectivity to determine similarities and differences between visual deficits and orthographic deficits in children with DD. The current study is unique in that it utilizes two control groups to thoroughly examine whether visuo-orthographic deficits observed in DD are due to a delay in maturation or dyslexia.

MATERIALS AND METHODS

Participants

A total of fifty-eight Chinese children were recruited from 8 public elementary schools in Beijing. Twenty-three fifth-grade children were defined as individuals with DD (mean age = 11.11, range: 10.11–12; 17 males); 19 fifth-grade children served as AC (mean age = 11.03, range: 10.11–12.03; 10 males); 16 third-grade children served as reading-matched controls (RC; mean age = 8.80, range: 8.06–10.02; 9 males).

Children within the DD group were first referred by teachers, who were asked to recommend children who performed at the bottom 10% of the class in reading. After parental consent was obtained, children completed assessments of character naming, reading fluency, and non-verbal-IQ using Raven (Raven et al., 2000). The character naming and reading fluency assessments were norm-referenced tests (Xue et al., 2013; Song et al., 2015). The character naming test consists of 150 characters with increasing difficulty. Each child was asked to name characters without the presence of a time constraint. The character naming test has been widely used as an indicator of Chinese literacy skills in children (McBride-Chang et al., 2003; Lei et al., 2011). The reading fluency test required children to silently read up to 100 sentences within 3 min. After reading each sentence, the child was asked to evaluate whether each sentence was literally correct or not. The reliability of the character-naming test is 0.96 and the reliability of the reading fluency test is 0.97 (Xue et al., 2013). The inclusion criteria for the DD group was: (1) a standard score greater than 80 on Raven, and (2) the standard score on either the character naming test or the reading fluency test had to be one standard deviation below the mean.

Children within the AC and RC groups were recommended by teachers based on normal reading achievement. After parental consent was obtained, each child was tested on the Chinese character-naming test. **Table 1** lists the raw score on the character-naming test for each of the three groups, along with the *Z*-score for AC and DD based on the age-matched norm (reported in Song et al., 2015). No age-matched norms are available, therefore, we were unable to calculate a *Z*-score for the RC group. An ANOVA was conducted on the raw score for character naming and found a significant group (AC, RC, DD) effect [$F(2,54) = 39.795$, $p < 0.001$]. *Post hoc* *t*-tests revealed that AC had significantly higher scores than DD [$t(39) = 8.963$, $p < 0.001$] and RC [$t(24) = 4.888$, $p < 0.001$], while DD had a significantly greater raw score than RC on the character naming test [$t(37) = 2.613$, $p = 0.013$]. Finally, an ANOVA of group (AC, DD) was conducted on the *z*-score of the character naming test, which revealed a significantly higher score for AC than DD [$F(1,40) = 85.515$, $p < 0.001$].

An informal interview was conducted with parents to confirm the following inclusionary criteria: (1) native Chinese speaker, (2) right-handed, (3) free of neurological or psychiatric disorders, (4) free of ADHD, Autism, or stuttering, and (5) no metal in the body such as pacemakers, braces, and/or piercings. The Institutional Review Boards at Michigan State University and Beijing Normal University approved the informed consent procedures.

Lexical and Perceptual Tasks

In the lexical task, two words were presented sequentially in the visual modality, and participants were asked to determine whether the second character of the two words had a similar orthography by sharing a phonetic radical. Each word consisted of two characters. If the word pair shared similar orthography, the participant was asked to press a button on a response pad with the right index finger; if the word pair did not share similar orthography, they were asked to press another button with the right middle finger. Four types of lexical trials were included: similar orthography and phonology (O+P+, e.g., 弥补/bu3/, 纯朴/pu3/), similar orthography and different phonology (O+P−, e.g., 翻译/yi4/, 选择/ze2/), different orthography and similar phonology (O−P+, e.g., 环保/bao3/, 大炮/pao4/), and different orthography and phonology (O−P− e.g., 压缩/suo1/, 傍晚/wan3/). The written-word frequency was matched across four

TABLE 1 | Demographic information and Means (standard deviation, range) of the standardized tests and performance on the fMRI task for all three groups of participants.

	RC	AC	DD
N	16	19	23
Gender	9 males, 7 females	10 males, 9 females	17 males, 6 females
Age	8.80 (0.66, 8.06–10.02)***	11.03 (0.46, 10.11–12.03)	11.11 (0.38, 10.11–12)
Non-verbal IQ	–	–	106 (10.94, 81–127)
Reading fluency (raw score)	–	–	49.26 (13.35, 24–78)
Reading fluency (*Z* score)	–	–	−1.10 (0.69, −2.14–0.31)
Character naming (raw score)	98.13 (13.97, 84–134)*	125.39 (6.99, 114–137)***	107.30 (5.93, 92–119)
Character naming (*Z* score)	–	0.21 (0.58, −0.78–1.16)***	−1.34 (0.50, −2.63–−0.36)
Accuracy (lexical)	0.92 (0.06, 0.81–1)	0.94 (0.06, 0.70–0.99)	0.91 (0.06, 0.73–0.98)
Accuracy (perceptual)	0.93 (0.13, 0.49–1)	0.95 (0.07, 0.78–1)	0.94 (0.09, 0.67–1)
Reaction time (lexical)	1194 (320, 619–1707)	1294 (333, 620–1906)**	1019 (301, 586–1581)
Reaction time (perceptual)	1103 (304, 579–1710)	1242 (322, 544–1861)**	948 (351, 499–1595)

*Significant difference with DD (independent-sample t-tests) *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

conditions (O+P+, 40.5; O+P−, 28.1; O−P+, 27.5; O−P−, 20.2), and was calculated based on the occurrence out of 1 million written words, (Beijing Language and Culture University, 1990). There were 24 word pairs for each trial type. For the perceptual task, two Tibetan symbols were visually presented side-by-side following another two Tibetan symbols. The participant was asked to determine whether the second stimulus matched the first. For example, ꡁꡁ and ꡁꡁ were the same, while ꡁꡁ and ꡃꡃ were different. Half of the symbol pairs were same, while the other half were different. There were 24 symbol pairs for the perceptual condition. For the lexical and perceptual tasks, each word/symbol was presented for 800 ms, followed by a 200 ms blank interval. The second word was presented for 800 ms followed by a 2200 to 3400-ms jittered inter-stimulus interval (ISI), during which a red fixation cross (+) would appear on the screen indicating the need to make a response. There were also 48 null trials, which served as resting baseline, in which a black cross changed to red, and participants were asked to press the button with their index finger. Null trials were presented using the same procedure as the lexical and perceptual trials. An event-related design with two 6-min 44 s runs was employed. The presentation order of stimuli in each run was optimized using Optseq[1].

MRI Data Acquisition

All MRI images were acquired at Beijing Normal University, Beijing, China, on a 3T Siemens scanner with a standard head coil. MRI scans took place within 2 weeks of standardized testing and practicing of the functional magnetic resonance imaging (fMRI) task. Echo planar imaging (EPI) was used to acquire the BOLD functional images. The following parameters were used: TR = 2000 ms, TE = 20 ms, flip angle = 80°, matrix size = 128 × 128, field of view = 220 mm, slice thickness = 3 mm, number of slices = 33. These scanning parameters resulted in a 1.7 mm × 1.7 mm × 3 mm voxel size. At the beginning of the functional imaging session, T1-weighted structural 3D images were acquired (TR = 2300 ms, TE = 3.29 ms, TI = 900 ms, flip angle = 20°, matrix size = 256 × 256, field of view = 256 mm, slice thickness = 1 mm, number of slices = 160).

Image Analysis

Data analysis was performed using SPM 12 (Statistical Parametric Mapping)[2]. The images were spatially realigned to the first volume to correct for head movement. Two individuals in the DD group had volumes with more than 3 mm or 3° of movement, however, these volumes counted for less than 10% of the total amount of data for each individual. Artifact Detection Tools (ART) for SPM[3] was used for head movement correction for trials containing head movement greater than 3 mm. For the AC group and RC group, no participants moved more than 3 mm or 3° during scanning. Functional images were co-registered with the anatomical image and normalized (12 linear affine parameters for brain size and position, 8 non-linear iterations and 2 × 2 × 2 non-linear basis functions) to the standard T1 template volume (MNI). The images were then smoothed with an 8 mm isotropic Gaussian kernel. Statistical analyses at the first level were calculated using an event-related design. A high pass filter with a cutoff period of 128 s was applied. Word pairs were treated as individual events for analysis and modeled using a canonical hemodynamic response function.

A flexible factorial ANOVA of three groups (AC, RC, and DD) by 2 tasks (perceptual and lexical task) was conducted separately on the contrasts lexical minus null and perceptual minus null. All reported results were uncorrected $p < 0.001$ at the voxel level, with voxels > 20, and FDR corrected $p < 0.05$ at the cluster level.

In order to identify the common dyslexia effect shared between the two tasks, two sets of conjunction analyses were conducted. Namely, the conjunction of lexical RC > DD, lexical AC > DD, perceptual RC > DD, and perceptual AC > DD; and the conjunction of lexical DD > RC, lexical DD > AC, perceptual DD > RC, and perceptual DD > AC.

[1]http://surfer.nmr.mgh.harvard.edu/optseq

[2]http://www.fil.ion.ucl.ac.uk/spm

[3]https://www.nitrc.org/projects/artifact_detect/

Psychophysiology Interaction (PPI) Analysis

Psychophysiology interaction was used to calculate functional connectivity in the current study, because it determines which voxels in the brain increase their responses as the influence of a seed region of interest in a given context, such as during a particular behavioral task (O'Reilly et al., 2012). Therefore, it serves our purpose to study different functional connectivity during different tasks.

In the current study, the left MOG and right MOG were selected as seed regions for PPI analysis, as they are two important regions involved in visuo-orthographic processing (Cao et al., 2011). The left precuneus and right pre/post central gyrus were selected as two additional seed regions because of the presence of a dyslexia effect observed during brain activation analysis.

The group peaks for all participants at the four seed regions were identified using an anatomical mask in WFU PickAtlas[4], which were the same for the contrast of lexical versus null and perceptual versus null [left middle occipital gyrus (LMOG): $x = -26$, $y = -92$, $z = 2$; RMOG: $x = 22$, $y = -98$, $z = 2$; left precuneus: $x = -22$, $y = -58$, $z = 34$; right pre/postcentral gyrus: $x = 38$, $y = -22$, $z = 56$]. The same group peaks were applied in all three groups because of the similarity of brain activation in these groups at these seed regions. Individualized seed regions were defined as an 8 mm sphere centered at the most significant voxel within 25 mm of the group peak for each individual, with the constraint that the individual's peak was also within the anatomical mask defined by the WFU PickAtlas. The deconvolved time series of the seed region was extracted for each individual in each task. For the first-level GLM regression analysis, we were interested in finding brain regions where responses were significantly influenced by the interaction of the seed region and the experimental design. In the GLM model, the following regressors were used: the time series of each single seed region, the experimental design, the interaction between the time series of the seed region and the experimental design (lexical versus baseline; perceptual versus baseline), and the six head movement parameters with the interaction between seed region and experimental design as the variable of interest.

An ANOVA of group (RC, AC, and DD) by task (lexical, perceptual) was conducted for each of the four seed regions: left precuneus, right pre/post central gyrus, left MOG, and right MOG in order to investigate how the functional connectivity from each of these seed regions to the whole brain varies in different groups during different tasks. All reported results were uncorrected $p < 0.001$ at the voxel level, with voxels > 20, and FDR corrected $p < 0.05$ at the cluster level.

The ROI analysis was conducted for all connectivity where there was a significant interaction between group and task to examine what was driving the interaction. We created ROIs as spheres, centered at the peak of the interaction effect with a 6 mm radius. For each ROI, group comparisons were conducted using independent sample t-tests in SPSS separately for each task.

[4]fmri.wfubmc.edu/software/pickatlas

RESULTS

Behavioral Results

We calculated a group (AC, RC, and DD) by task (lexical, perceptual) ANOVA separately for accuracy and RT. It revealed a significant main effect of task [$F(2,57) = 32.68$, $p < 0.001$] for RT, with a faster reaction time for the perceptual task than the lexical task. We also found a significant main effect of group for RT [$F(2,55) = 4.20$, $p = 0.020$]. As indicated in **Figure 1**, *post hoc* tests revealed that children with DD were faster at responding than the AC group, [$t(40) = 2.84$, $p = 0.007$]. There was no significant difference between DD and RC [$t(37) = 1.597$, $p = 0.119$], or AC and RC [$t(33) = -1.11$, $p = 0.275$]. For accuracy, the main effect of group by task was not significant. There was no group by task interaction for accuracy [$F(2,55) = 0.21$, $p = 0.811$] or RT [$F(2,55) = 0.71$, $p = 0.499$]. For the RT, we ran an ANCOVA

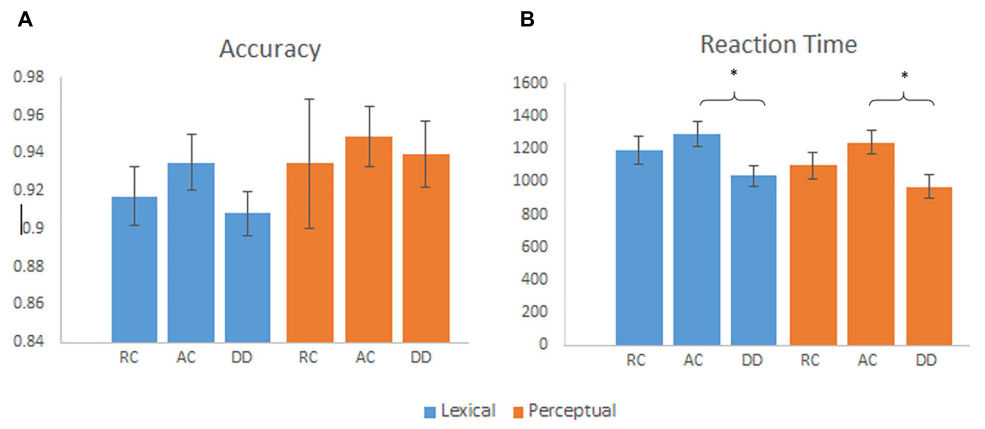

FIGURE 1 | (A) Mean accuracy by group for the lexical and perceptual tasks, error bars are standard error. There were no significant group differences on accuracy. **(B)** Mean reaction time by group for the lexical and perceptual tasks, error bars are standard error. DD had a faster reaction time than AC for the lexical and perceptual tasks. $^*p < 0.01$.

of group (AC, RC, and DD) by task (lexical, perceptual) with RT on the null trials as a covariate, we found that the main effect of group was not significant any more [$F(2,46) = 2.034$, $p = 0.142$]. This indicates that the faster RT in the DD group during the lexical and perceptual tasks was not due to a higher performance, but a strategy that they might use by responding fast to everything.

We found a significant effect of lexical condition (O+P+, O+P−, O−P+, O−P−) on accuracy [$F(3,120) = 5.498$, $p = 0.001$], and on reaction time [$F(3,120) = 9.511$, $p = 0.000$], driven by greater accuracy and faster reaction time on the two consistent conditions: O+P+ and O−P− (accuracy: 0.95; RT: 1271) than the two inconsistent conditions: O+P−, O−P+ (Accuracy: 0.91, RT: 1284). It suggests that even though the task can be done perceptually, orthographic and phonological processes are involved.

Brain Activation Results

The ANOVA of group by task did not show any significant interaction; therefore, we report group differences in each task. In the lexical task, AC had greater activation than DD in the left precuneus and left MOG. RC had greater activation than DD in the left precuneus and bilateral MOG (**Table 2**). DD showed greater activation than AC in the left STG, right inferior temporal gyrus (ITG), and the right pre/postcentral gyrus (**Table 2**). DD showed greater activation than RC in the left IFG, and the right pre/postcentral gyrus. RC showed greater activation than AC in the left cingulate gyrus, while AC showed greater activation than RC in the left MTG and right ITG.

In the perceptual task, AC showed greater activation than DD in the left precuneus, precentral gyrus, lentiform nucleus, right SPL, fusiform gyrus, STG, SPL, MOG, and precuneus. RC showed greater activation than DD in the left MOG, inferior occipital cortex (IOC), precuneus, SPL and right cuneus. DD showed greater activation than AC in the right pre/postcentral gyrus. DD showed greater activation than RC in the right pre/postcentral gyrus. No brain activation differences existed between AC and RC.

No brain regions showed a group by task interaction effect between DD and readers without dyslexia, which included the summation of the AC and RC groups. Detailed brain activation results for each group are reported in the **Appendix Table 1**.

The conjunction analysis of lexical AC > DD, lexical RC > DD, perceptual AC > DD, and perceptual RC > DD revealed an overlap at the left precuneus for the four contrasts. The conjunction analysis of lexical DD > AC, lexical DD > RC, perceptual DD > AC, and perceptual DD > RC showed an overlap at the right pre/postcentral gyrus for the four contrasts, with a conjunction peak at precentral gyrus, which extended to the postcentral gyrus (**Table 2** and **Figure 2**).

PPI Results

The following reports group by task interaction effect because task specific group differences in the PPI analysis was the focus of the investigation.

A task by group interaction effect was not observed at the left precuneus seed region. However, an interaction effect for functional connectivity was observed between the right pre/postcentral gyrus seed region and the right anterior cingulate cortex (ACC). Further analysis revealed that the DD group had reduced connectivity between the right pre/postcentral and the ACC compared to AC [$t(34) = 2.837$, $p = 0.008$] and RC [$t(38) = 3.125$, $p = 0.003$] in the perpetual task, but not in the lexical task {DD and AC: [$t(34) = -0.527$, $p = 0.602$]; DD and RC: [$t(38) = -0.482$, $p = 0.633$]} (**Figure 3**).

For the connectivity with the left MOG seed region, a significant task by group interaction effect was found in two brain regions: the left IFG and the right parahippocampal gyrus (RPHIP). There was reduced functional connectivity between the left MOG and the left IFG in DD compared to AC [$t(38) = 2.220$, $p = 0.035$] and RC [$t(34) = 2.733$, $p = 0.010$)] in the lexical task. However, in the perceptual task, DD showed increased functional connectivity with the left IFG compared to AC [$t(38) = -2.167$, $p = 0.037$], but not RC [$t(34) = -1.689$, $p = 0.100$]. For the functional connectivity between the LMOG and RPHIP, DD was lower than AC [$t(38) = 2.931$, $p = 0.006$], but not RC [$t(34) = 1.385$, $p = 0.175$] for the perceptual task. However, for the lexical task, DD did not show difference from AC [$t(38) = -1.699$, $p = 0.098$] or RC [$t(34) = -1.184$, $p = 0.244$] (**Figure 4**).

At the right MOG, we found a significant interaction effect between task and group in the RPHIP, which overlapped with the RPHIP cluster found for the seed region of the LMOG. In the lexical task, we did not find any difference between DD and AC [$t(38) = -0.919$, $p = 0.364$], or between DD and RC [$t(34) = -0.740$, $p = 0.464$]. In the perceptual task, the right MOG showed reduced functional connectivity with the RPHIP for the DD group compared to the AC [$t(38) = 2.751$, $p = 0.009$] and RC groups [$t(34) = 2.483$, $p = 0.018$] (**Figure 4**).

DISCUSSION

The present study aimed to identify brain mechanisms underlying visual and orthographic processing in children with DD compared to age-matched and reading-matched control groups. For the brain activation analysis, we found less activation in the left precuneus and greater activation in the right pre/postcentral gyrus for the DD group compared to the AC and RC groups in both the lexical and perceptual tasks, suggesting a common mechanism for visual and orthographic deficits. PPI analysis further revealed interaction effects between task and group, suggesting a task-specific deficit. First, the right pre/postcentral gyrus was less connected with the right ACC in the perceptual, but not the lexical task, for children with DD compared to both control groups. Second, the LMOG was less connected with the left IFG for children with DD compared to the AC and RC groups in the lexical task; however, the LMOG was more connected with the left IFG in the DD group compared to the AC group on the perceptual task. Lastly, the LMOG and right MOG were less connected with the RPHIP in children with DD compared to the control groups in only the perceptual task. Taken together, the brain activation analysis revealed an overlapping brain mechanism associated with orthographic and visual-perceptual deficits in the DD

TABLE 2 | Group comparisons for brain activation in the lexical – null and perceptual – null contrasts, along with the conjunction analysis.

Anatomical region	H	BA	Voxels	*x*	*y*	*z*	*Z*
			Lexical-null				
AC > DD							
Superior parietal lobule	L	7	162	−20	−68	54	4.62
Superior parietal lobule	R	7	30	28	−66	58	3.97
Postcentral	L	3	54	−32	−26	50	3.80
Middle frontal gyrus	L	6	28	−38	0	38	3.70
Middle frontal gyrus	L	8	25	−46	6	42	3.68
Superior temporal gyrus	L	22	31	−50	−46	10	3.57
RC > DD							
Inferior parietal lobule	L	7/40	31	−34	−58	46	3.88
Middle occipital gyrus	L	19	33	−32	−80	−2	3.72
DD > AC							
Precentral gyrus	R	4	176	40	−16	54	4.73
Culmen	L	–	32	−14	−52	−20	4.35
Inferior temporal gyrus	R	20	23	52	−10	−24	4.18
Postcentral gyrus	R	3/4	44	52	−14	56	3.95
Superior temporal gyrus	L	38	25	−42	16	−20	3.79
DD > RC							
Postcentral gyrus	R	3/4	128	52	−14	52	4.39
Precentral gyrus	R	4	153	40	−18	50	4.27
Postcentral gyrus	L	40	42	−64	−26	22	4.07
Inferior frontal gyrus	L	13	35	−36	12	−14	3.79
Postcentral gyrus	R	2/3	47	64	−22	38	3.71
AC > RC							
Cingulate gyrus	L	32	22	−2	16	40	3.90
RC > AC							
Middle temporal gyrus	L	21	26	−64	−28	−4	4.04
Inferior temporal gyrus	R	20	23	52	−8	−24	3.80
			Perceptual-null				
AC > DD							
Superior parietal lobule	R	7	85	30	−62	60	4.38
Fusiform gyrus	L	21	43	−18	−74	−16	3.96
Superior temporal gyrus	L	13	23	−58	−42	16	3.93
Precentral gyrus	L	4	82	−32	−24	54	3.90
Lentiform nucleus	L	–	40	−24	−18	6	3.84
Superior parietal lobule	L	7	136	−24	−68	54	3.83
Middle occipital gyrus	R	19	38	26	−66	2	3.75
Precuneus	R	7	30	12	−66	30	3.70
RC > DD							
Middle occipital gyrus	L	19	149	−36	−64	−14	4.61
Inferior occipital gyrus	L	19	132	−32	−80	−2	4.25
Precuneus	L	7	93	−18	−58	42	4.03
Cuneus	R	18	22	20	−100	−2	4.00
Precuneus	L	7	38	−14	−72	36	3.98
Precuneus	L	7	32	−26	−70	40	3.66
Superior parietal lobule	L	7	32	−34	−58	50	3.47
DD > AC							
–	–	–	–	–	–	–	–
DD > RC							
Postcentral gyrus	R	3	74	40	−22	50	3.95
AC > RC							

(Continued)

TABLE 2 | Continued

Anatomical region	H	BA	Voxels	*x*	*y*	*z*	*Z*
–	–	–	–	–	–	–	–
RC > AC							
–	–	–	–	–	–	–	–
Conjunction of lexical and perceptual							
AC > DD and RC > DD							
Precuneus	L	7	34	−16	−62	46	3.02
DD > AC and DD > RC							
Precentral gyrus	R	4	20	38	−18	50	3.19

H, hemisphere; L, left, R, right; BA, Brodmann Area.

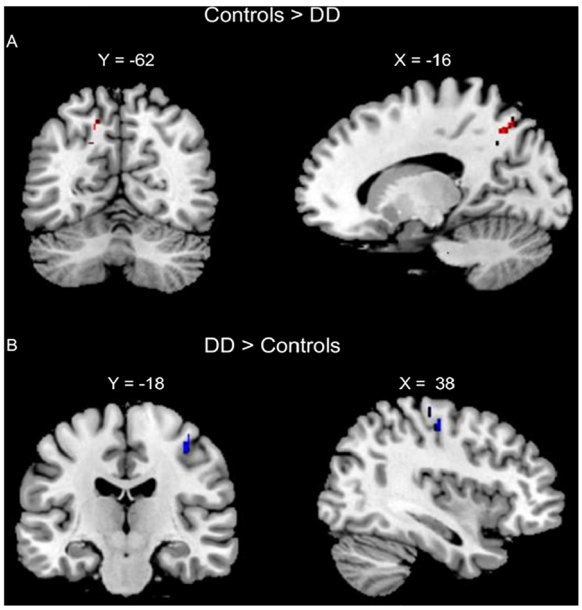

FIGURE 2 | Conjunction analyses of group comparisons in brain activation for the lexical and perceptual tasks. **(A)** Conjunction of AC > DD for the lexical task, RC > DD for the lexical task, AC > DD for the perceptual task, and RC > DD for the perceptual task (left precuneus, in Red). **(B)** Conjunction of DD > AC for the lexical task, DD > RC for the lexical task, DD > AC for the perceptual task, and DD > RC for the perceptual task (right pre/post central gurus, in Blue).

group. However, the PPI analysis revealed task specific deficits during visual and orthographic processing. For the first time, we identified brain mechanisms that are specific for visual-perceptual deficits, specific for orthographic processing deficits and shared by both visual and orthographic deficits.

Universal Brain Mechanisms of Visual Deficits and Orthographic Deficits

We found that the left precuneus showed decreased activation in children with DD compared to the AC and RC groups for both the lexical and the perceptual tasks. This suggests a universal deficit in orthographic and visual-perceptual processing in dyslexia, which may be related to a deficit in visual attention (Vidyasagar and Pammer, 2010). A previous study reported decreased activation in the left SPL in children with DD, extending to the left precuneus in a complex visual spatial task (Peyrin et al., 2011). The difference found between DD and control groups in the previous study was in the left SPL/precuneus (−15, −56, 48), which is proximal to the peak in the precuneus (−16, −62, 46) in the current study. Therefore, reduced activation in the left precuneus might implicate deficient visual attention that is important in both visual symbolic and orthographic processing. This finding lends support to that of Boros et al. (2016), which demonstrated a similar neural deficit in a letter detection and a symbol string detection task in children with DD. Boros et al. (2016) reported task-universal underactivation in the left visual word-form area of the ventral pathway in children with DD compared to controls. In contrast, we found a universal underactivation in the left precuneus within the dorsal visual pathway in DD across both the lexical and perceptual tasks. The orthographic task in the study conducted by Boros et al. (2016) required participants to identify a single letter in a string of five letters, while the perceptual task required the subjects to detect a single symbol from a string of five symbols. The different tasks and stimuli in the two studies may explain the differences in spatial locations. Our task required the participant to make a same/different judgment on Chinese characters and Tibetan symbols, which may involve a more holistic visual processing, while their detection task likely required a more fine-grained analytic visual processing. However, both studies suggest a universal deficit in linguistic and non-linguistic visual processing. Therefore, even though the current study was conducted in Chinese speaking children, the finding of universal deficits underlying visual perceptual and orthographic processing should not be specific to Chinese readers.

Alternatively, our finding is consistent with previous magnocellular studies, which show reduced brain activation in the left precuneus during visual motion detection and other magnocellular tasks (Peyrin et al., 2011; Reilhac et al., 2013). In summary, we found a universal deficit in linguistic and non-linguistic visual stimuli processing in children with DD, which may be due to deficits in visual attention, or related to magnocellular function abnormality.

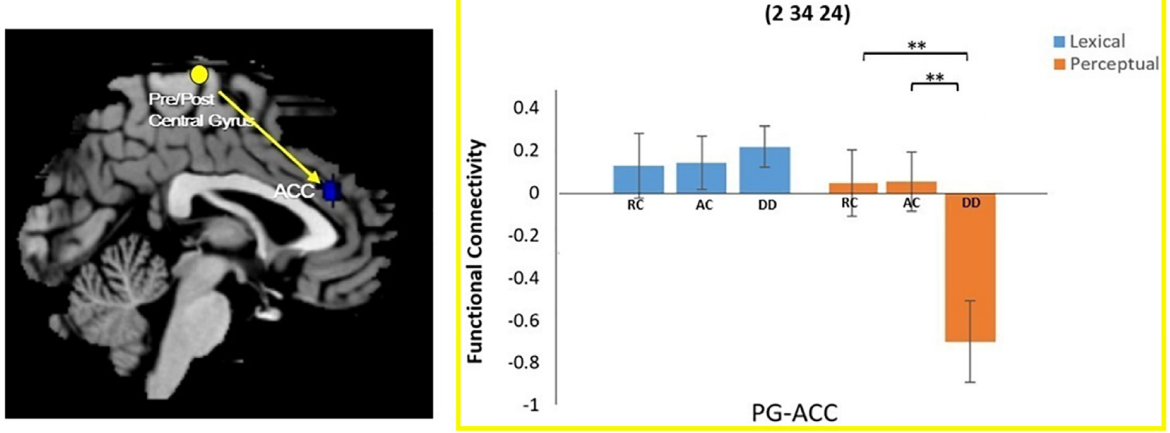

FIGURE 3 | Group × task interaction effect on functional connectivity between the right pre/postcentral gyrus and the right anterior cingulate cortex (ACC). DD had weaker functional connectivity than AC and RC only for the perceptual task. There was no group difference in the lexical task. $^{**}P < 0.01$.

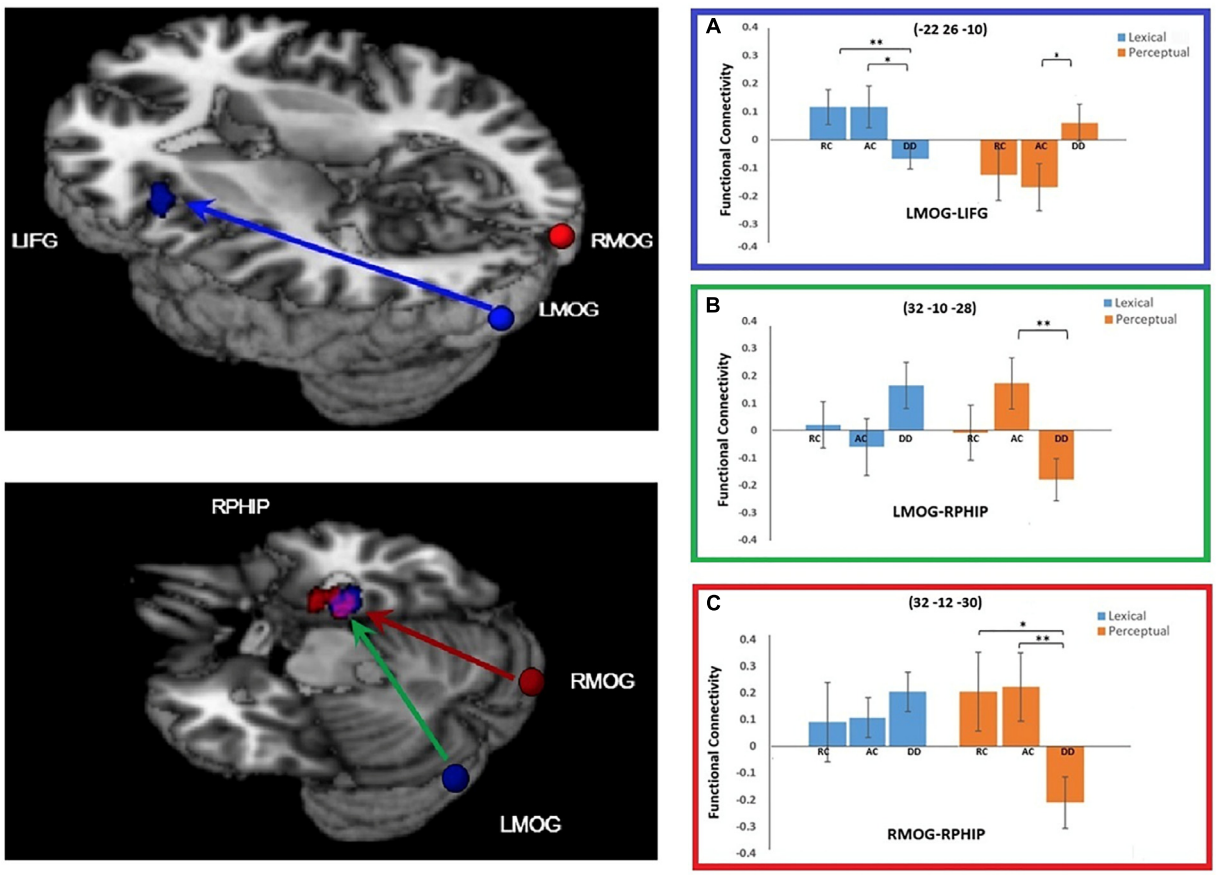

FIGURE 4 | Group × task interaction effects on functional connectivity of the seed regions left middle occipital gyrus (LMOG) and right middle occipital gyrus (RMOG). **(A)** Group × task interaction effect on functional connectivity between the LMOG and the left inferior frontal gyrus (IFG) (in Blue). DD had weaker functional connectivity than AC and RC for the lexical task, and stronger connectivity than AC for the perceptual task. **(B,C)** Group × task interaction effect on functional connectivity between the two seed regions (LMOG and RMOG) and the right parahippocampal gyrus (RPHIP), respectively. From LMOG to RPHIP (in Green), DD had weaker functional connectivity than AC but not RC for the perceptual task. There was no group difference for the lexical task. From the RMOG to the RPHIP (in Red), DD had weaker functional connectivity than RC and AC for the perceptual task. There was no group difference for the lexical task. The interaction effect for the LMOG and the RMOG overlapped at the RPHIP (in purple). $^{*}P < 0.05$, $^{**}P < 0.01$.

Finally, we found an overlap in the increased brain activation at the right pre/postcentral gyrus in the DD group compared to the AC and RC groups in both tasks. A previous study found that children with DD have greater activation of the right pre/postcentral gyrus during an auditory rhyming task than AC and RC groups (Cao et al., 2017). The group difference peak in that task (20, 40, −20) was proximal to the group difference peak in the current study (20, 38, −18). Cao et al. (2017) posited that the enhanced activation of the right pre/postcentral gyrus indicated neural compensation due to an increased reliance on language articulation during auditory rhyming judgment in the DD group. The current study extends previous findings and suggests that the observed neural compensation exists even in non-linguistic tasks. This is consistent with evidence from previous meta-analysis studies which found increased activation of the right pre/postcentral gyrus in those with DD for language, symbol, and number processing (Paulesu et al., 2001; Richlan et al., 2009, 2011). With this in mind, it is possible that children with DD tend to rely on articulation, even for non-linguistic stimuli such as symbols or numbers by saying the name of symbols/shapes, or numbers, which may be to compensate for poor verbal memory.

Moreover, these deficits seem to be associated with dyslexia *per se*, rather than deficient reading because the younger reading-matched control children showed a similar pattern as the older control children. Previous studies with only one AC group cannot exclude the possibility that brain differences observed were actually due to lower reading skill in DD than controls, as intervention studies have found that when reading ability is improved, brain activation patterns become more similar to controls (Simos et al., 2002; Shaywitz et al., 2004). Having two control groups allows researchers to identify brain mechanisms specifically underlying dyslexia instead of low reading ability. However, this does not mean that the brain mechanisms we found are the cause of dyslexia rather than a consequence of dyslexia. As Huettig et al. (2018) argued, the difference between individuals with DD and controls might be a secondary consequence of suboptimal reading experiences including both quantitative and qualitative differences in reading (Huettig et al., 2018). This argument holds true even when children with DD are compared to reading-matched controls, because both the quantity and quality of reading is different in younger reading-matched control children and children with DD. In the current study, children with DD showed faster reaction times than AC and RC, but relatively lower accuracy than the controls. It suggests that children with DD tended to compromise accuracy for faster reaction time, which might be a secondary consequence of suboptimal reading experience. Therefore, the brain differences observed between children with DD and controls might be due to the children with DD using different strategies. In summary, our findings suggest that DD is associated with deficient visual-perceptual processing located at the left precuneus, which might be a cause of dyslexia, or a result from suboptimal reading experience by children with DD.

Specific Deficits in Visual Perceptual Processing

In the current study, we found that the functional connectivity between the right pre/postcentral gyrus and right ACC was reduced in children with DD compared to the AC and RC groups in the perceptual task, but not in the lexical task. As part of the limbic system, the ACC region is responsible for the complex cognitive operations required for executive control (see a meta-analysis by Margulies et al., 2007), such as bilingual language switching (Abutalebi and Green, 2007) and task-related motor control (Paus et al., 1993). Therefore, the findings of the current study might indicate that the DD group had a possible disassociation between executive control (in the right ACC) and somatosensory/motor processing (in the right PG) during the perceptual task, which may be the underlying mechanism of the visual perceptual deficit. However, in the lexical task, there is an increased demand for executive control due to higher task difficulty than the perceptual trials, and children with DD appear to be capable of maintaining the connection between the right ACC and right pre/postcentral gyrus when the task is harder.

Next, the current study found that the LMOG and right MOG were less connected with the RPHIP in the DD group compared to the AC and RC groups in the perceptual task, but not the lexical task. The parahippocampal gyrus is known to be associated with perceiving the local visual environment in visual navigation (Epstein and Kanwisher, 1998; Park et al., 2011), which processes the layout of local space. It is also involved in processing the semantics of the visual environment (Bonner et al., 2015). The current findings suggest a weaker association between the bilateral visual cortex and the parahippocampal visual network during visual symbol processing in the perceptual task for the children with DD. This further suggests that the visual deficit in DD might be due to the reduced connections between different visual regions.

Specific Deficit for the Lexical Task

The current study found reduced functional connectivity between the LMOG and the left IFG for the DD group compared to RC and AC groups in the lexical task. In the perceptual task, the DD group showed increased functional connectivity between these two regions compared to AC, but not RC. The LMOG is commonly understood to be responsible for visuo-orthographic processing during written word tasks (Zhang et al., 2013; Cao et al., 2017), while the left IFG plays an important role in phoneme segmentation and manipulation (Booth et al., 2007; Cone et al., 2008). It appears that our finding suggests a reduced interaction between orthography and phonology in DD which is consistent with previous studies (Booth et al., 1999, 2000; Plaut and Booth, 2000; Desroches et al., 2010; Cao et al., 2017). For instance, a behavioral study showed that, compared to typical readers, children with DD had reduced orthographic interference effects (shorter reaction times in responding to orthographically similar words compared to orthographically dissimilar words) in an auditory rhyming task (Zecker, 1991), suggesting less activation of orthography during the phonology task. Subsequently, an fMRI study found

that children with DD show less activation in the left fusiform gyrus (a region related to orthographic processing) during auditory rhyming tasks compared to typical readers (Desroches et al., 2010). Weak phonological activation was also found during visuo-orthographic tasks in DD. For example, adults with dyslexia show less activation in the superior temporal gyrus (a region related to phonological processing) during visual word rhyming tasks compared to typical readers (Paulesu et al., 1996). Furthermore, studies have revealed reduced functional connectivity between the left IFG and the left fusiform gyrus in dyslexia during auditory rhyming (Cao et al., 2017), visual rhyming (Cao et al., 2008), phonological-lexical decision (Schurz et al., 2015), visual-lexical decision (van der Mark et al., 2011), and silent reading (Schurz et al., 2015). Our finding is consistent with these findings. Moreover, we further demonstrated that this reduced connectivity between the LMOG and left IFG is only present in the linguistic task. In the perceptual task, children with DD exhibited greater connectivity between LMOG and left IFG than the AC group, which suggests that this connectivity may be more specialized for connecting orthography to phonology in children with typical reading ability while children with DD show a more diffuse pattern across tasks for this connection.

CONCLUSION

The present study examined the brain mechanisms involved in visual and orthographic deficits in dyslexia compared to age-matched and reading-matched controls. We found that children with DD had less activation in the left precuneus and greater activation in the right pre/postcentral gyrus compared to AC and RC in both the lexical and perceptual tasks. This suggests a shared mechanism of visual and orthographic deficits in DD. The PPI analysis, however, revealed a task-specific deficit. Children with dyslexia showed reduced connectivity between the LMOG and left IFG in the lexical task, suggesting a weaker connection between orthography and phonology. Furthermore, the children with dyslexia showed reduced connectivity between the bilateral MOG and the right parahippocampal gyrus only in the perceptual task, suggesting a disconnection between different regions in the visual system. In summary, the present study found, both common and specific mechanisms for visual deficits and orthographic deficits in DD, which sheds new light on understanding the visuo-orthographic deficit in developmental dyslexia.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Boards at Michigan State University and Beijing Normal University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Boards at Michigan State University and Beijing Normal University.

AUTHOR CONTRIBUTIONS

XY: data collection, data analysis, and paper writing. GS paper writing and editing. YL: PPI analysis. YD: data collection. FC: study design, supervision of study conduction, data analysis, and paper writing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2018.00490/full#supplementary-material

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BRIEF RESEARCH REPORT
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Corticobulbar Tract Injury, Oromotor Impairment and Language Plasticity in Adolescents Born Preterm

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Children born preterm are at risk of impairments in oromotor control, with implications for early feeding and speech development. In this study, we aimed to identify (a) neuroanatomical markers of persistent oromotor deficits using diffusion-weighted imaging (DWI) tractography and (b) evidence of compensatory neuroplasticity using functional MRI (fMRI) during a language production task. In a cross-sectional study of 36 adolescents born very preterm (<33 weeks' gestation) we identified persistent difficulties in oromotor control in 31% of cases, but no clinical diagnoses of speech-sound disorder (e.g., dysarthria, dyspraxia). We used DWI-tractography to examine the microstructure (fractional anisotropy, FA) of the corticospinal and corticobulbar tracts. Compared to the unimpaired group, the oromotor-impaired group showed (i) reduced FA within the dorsal portion of the left corticobulbar tract (containing fibres associated with movements of the lips, tongue, and larynx) and (ii) greater recruitment of right hemisphere language regions on fMRI. We conclude that, despite the development of apparently normal everyday speech, early injury to the corticobulbar tract leads to persistent subclinical problems with voluntary control of the face, lips, jaw, and tongue. Furthermore, we speculate that early speech problems may be ameliorated by cerebral plasticity – in particular, recruitment of right hemisphere language areas.

Keywords: preterm birth, oromotor control, tractography, MRI, language lateralization

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INTRODUCTION

Our understanding of the impact of preterm birth on the cerebral white matter has been furthered by diffusion-weighted imaging (DWI) (Ment et al., 2009; Pandit et al., 2013; Travis et al., 2015a; Pecheva et al., 2017). Furthermore, altered diffusion metrics in specific white matter tracts have been demonstrated in relation to long-term cognitive outcome (Northam et al., 2012b; Travis et al., 2015b, 2016) and neurological function (see Ment et al., 2009 for a review). Non-speech oromotor control is known to be impaired in this population, including problems with sucking, weaning to solid food (Slattery et al., 2012; Sanchez et al., 2017) and eating difficulties persisting up to the age of 6 years (Samara et al., 2010).

However, the specific neural correlates of oromotor control have rarely been examined, and studies have mainly relied on gross clinical MRI measures in younger populations (Sanchez et al., 2017).

A large proportion of children with prematurity-related brain injury have long-lasting oromotor difficulties (Northam et al., 2012a). These children struggle with the deliberate control of the jaw, lips, face, and tongue during the speech and non-speech movements. We have demonstrated that, on DWI, this impaired subgroup shows reduced fractional anisotropy (FA, a measure of water diffusivity) in the posterior limb of the internal capsule of the left cerebral hemisphere. This suggests motor tract involvement but does not identify which specific pathways have been compromised. We previously found that left corticobulbar tract injury (specifically the dorsal portion, which contributes to the control of the lips, tongue, and larynx) predicted dysarthria and oromotor dysfunction after traumatic brain injury in childhood (Liegeois et al., 2013). We therefore applied the same diffusion tractography method in the previously reported group of adolescents born preterm, who are at risk of bilateral periventricular white matter injury (Guo et al., 2017), and hypothesised that persistent oromotor impairment would be associated with reduced FA in the left corticobulbar tract.

Despite relatively normal everyday speech in adolescence, abnormal early speech development (e.g., late onset, poor speech quality) was reported by parents in many of the children with oromotor impairments – and these children were also more likely to have received speech and language therapy (Northam et al., 2012a). Given the early timing of the injury there should be considerable potential for cerebral plasticity (Jacola et al., 2006; Tillema et al., 2008; Staudt, 2010) and we therefore hypothesized that the absence of an overt speech disorder might reflect reorganization of language to the right cerebral hemisphere. We used functional MRI (fMRI) during a verb generation task to estimate the degree of interhemispheric reorganization in language-associated frontal and temporal brain regions. Having already reported language outcomes in relation to MRI/DWI findings in this cohort (Northam et al., 2012b), here we explored the relationship between language lateralization during a verb generation task (Northam et al., 2012b) and oromotor skills in the subgroup who had both fMRI and diffusion MRI data.

MATERIALS AND METHODS

Participants

Thirty-six adolescents (13 males, mean age 16 ± 1 years) born preterm (mean gestation age 27 weeks, range 26–31; mean birthweight 1060 g, range 591 g to 2243 g) out of a cohort of 50 as part of a previous study (Northam et al., 2012a) had undergone (i) a speech and oromotor assessment and (ii) MRI scanning including a high angular resolution diffusion imaging (HARDI). Of this sample, 25 had injury on cranial ultrasound at birth (15 minor, 10 major) and four had cerebral palsy (one bilateral, three predominantly unilateral).

Ethical approval for the study was obtained from Great Ormond Street Hospital for Children/Institute of Child Health Research Ethics Committee. All parents or participants gave written informed consent.

Definition of Oromotor Impairment

Eleven of the 36 adolescents were previously classified as having an oromotor impairment (two mild-moderate, and nine severe who scored 60–91%) on the Focal Oromotor Control (FOC) subtest from the Verbal Motor Production Assessment for Children (Hayden and Square, 1999). They, however, showed no impairment in speech sound production during everyday speech warranting a diagnosis of motor speech disorder. This was assessed using the Connected Speech and Language subtest, where motor precision is evaluated during the spontaneous description of a story based on four sequenced pictures. The VMPAC is a standardized tool which assesses neuromuscular control of the articulators during speech and non-speech ("oromotor") movements with high reliability. The FOC subtest assesses deliberate control of the jaw, lips, face, and tongue. Participants are required to execute movements (e.g., tongue protrusion, smiling, blowing) and speech sounds in isolation and in sequence (e.g., /a/ /m/ /u/).

The VMPAC was administered by a trained administrator (GN) at the time of MRI acquisition according to the specific guidelines established in the video accompanying the VMPAC manual. GN and AM had three training sessions to confirm correct administration. Following training, each testing session was video recorded. These recordings were rated by a speech and language pathologist (AM) with over 20 years' experience in the field of differential diagnosis of motor speech disorders, including in children born pre-term and numerous other neurological and neurodevelopmental populations. The assessment was rated for impaired facial symmetry, tone, and smoothness of movement.

Diffusion MRI

An eddy-current-nulled twice-refocused EPI sequence with high-angular resolution was acquired (b-value = 3000 s/mm^2, TE = 128 ms, 60 diffusion-weighted directions, in-plane resolution 2.1 mm × 2.1 mm, 3 mm slice thickness, 37 contiguous axial slices, acquisition time ∼9 min). Further diffusion imaging protocol details can be found elsewhere (Northam et al., 2012a,b).

Tractography of the Corticobulbar and Corticospinal Tracts

DWI datasets were pre-processed using the MRTrix software suite (Tournier et al., 2012). Tractography methods were as described in Liegeois et al. (2013) and performed in native space using a probabilistic streamlines algorithm[1]. Two components of the corticobulbar tract were tracked using spherical seed ROIs placed in the axial plane (radius 7 mm). The seed region for the CST was centered in the white matter adjacent to the precentral gyrus (at the level of the hand "omega"). The ROI for the dorsal corticobulbar tract was placed 15 mm inferior to the hand area, and the ventral corticobulbar tract was centered another 15 mm inferiorly. For all three tracks, an inclusion ROI

[1] http://www.mrtrix.org/

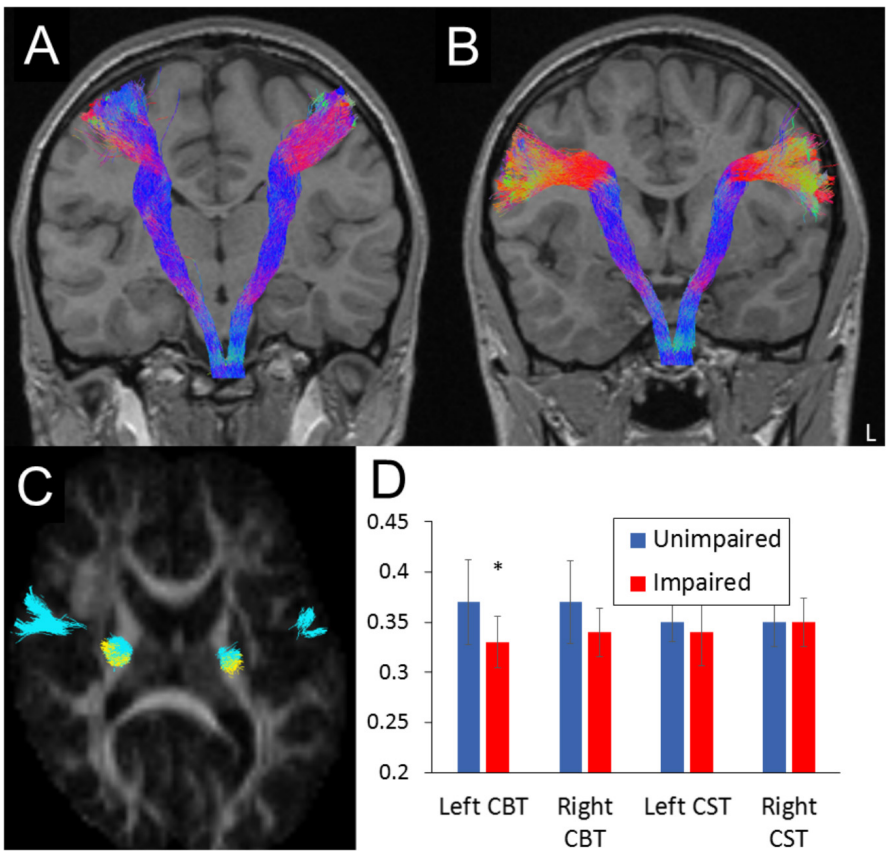

FIGURE 1 | Illustrative examples of **(A)** corticospinal and **(B)** dorsal corticobulbar tract tractography reconstruction in a participant. Tracts are projected on a T1-weighted MRI scan in coronal plane to allow view along the full tract length. Axial cross section **(C)** illustrates partial overlap of the two tracts (blue, corticobulbar or CBT; yellow, corticospinal or CST) at the level of the posterior limb of the internal capsule. L, left hemisphere. **(D)** Group differences in mean FA for each tract (error bars represent SDs; * statistical difference $p < 0.01$).

was manually placed at the level of the pons (Liegeois et al., 2013, see **Supplementary Figure S1A**). We set the maximum number of streamlines generated at 100,000, with a maximum of 1,000 streamlines retained. A binary mask of all voxels containing selected streamlines was created for each of the six tracks. Mean FA was extracted within each mask. An example case is shown in **Figures 1A–C**.

Language Lateralization on fMRI

Details of the fMRI protocol are provided elsewhere (Northam et al., 2012b). Briefly, participants were asked to generate single verbs, without vocalization, associated with single words presented via earphones (task condition). Two runs of ten task/rest cycles were completed by each participant. Lateralization indices (LI) were calculated within defined regions of interest, including an extended Broca's area (pars triangularis and opercularis, premotor cortex, and middle frontal gyrus), the temporal lobes (inferior, middle, and superior gyri combined) and the cerebellum. As fMRI-derived lateralization indices are threshold dependent, they were calculated at multiple statistical thresholds using a bootstrapping method as implemented in the LI-toolbox (Wilke and Lidzba, 2007). Indices range from +1 (complete left lateralization) to −1 (complete right lateralization). Atypical lateralization in Broca's region was defined by a LI value <0.2 (Pahs et al., 2013).

Statistical Analyses

Fractional anisotropy values were compared between groups using univariate analyses of covariance (age as a covariate). Spearman's correlations were used to assess the relationship between track measures and oromotor scores. LI were compared between impairment groups using independent sample *t*-tests. A binary logistic regression was computed to identify imaging predictors of oromotor impairment.

RESULTS

Clinical and Neuropsychological Characteristics

Participants with focal oromotor control (FOC) impairment had greater degree of neurological and imaging abnormalities than those without impairment (see **Supplementary Table S1**), together with lower IQ and language test scores.

Group Differences in Motor Tracts

The oromotor-impaired group showed reduced FA within the left-dorsal CBT compared to the unimpaired group (**Figure 1D**) [$F(1,30) = 7.97$, $p = 0.009$; 95% confidence interval (CI) of the mean difference 0.012–0.073; partial eta squared = 0.215). This reduction remained significant when controlling for full scale IQ ($F = 5.47$, $p = 0.027$, partial eta squared = 0.17] or CELF language scores ($F = 5.22$, $p = 0.03$, partial eta squared = 0.157). No other tract differences were found (all $p > 0.07$), although the reduction in the left ventral CBT approached significance ($p = 0.074$). Mean FA from within the left dorsal ($\rho = 0.54$, $p = 0.001$, see **Supplementary Figure S1C**) and ventral ($\rho = 0.36$, $p = 0.041$) CBT correlated positively with scores on the FOC subtest across the whole sample.

To determine the most robust predictors of oromotor impairment, we entered the following predictor variables into a forward binary logistic regression: abnormal neurological examination, abnormality on conventional MRI, mean FA from left posterior limb of the internal capsule (as used previously, Northam et al., 2012a) and FA in left-dorsal CBT. A test of the full model against the constant revealed that the only significant independent predictor of FOC impairment was mean FA in the left-dorsal CBT ($B = -39.43$, $SE = 16.72$; Exp(B) < 0.0001, 95% CI for Exp(B) = <0.001 to 0.001), correctly classifying 75% of the sample. The final model was statistically significant (Chi Square = 55.59, $p = 0.018$), and explained a large proportion of variance (Nagelkerke $R = 0.34$). Removal of the term led to a significant change in −2 log likelihood ratio ($p = 0.002$). Given the small number of participants with impairments, these results have to be interpreted with caution.

fMRI Language Lateralization

In the preterm group, activation for the generate > listen contrast was detected (random effect analysis, $P < 0.05$, corrected for multiple comparisons) in the left inferior frontal regions extending into the precentral and middle frontal gyrus, the superior temporal gyrus, and the right cerebellum (see **Supplementary Figure S1B**). Two example cases of children with major bilateral brain injury (hemorrhagic parenchymal infarction grade 4) are shown in **Figure 2**. Case A with intact oromotor function shows typical left-sided lateralization, as seen in 88% of this group. In contrast, case B with oromotor impairment shows strong recruitment of the right inferior frontal and temporal cortices, seen in 64% of this group (Fisher's exact: $p = 0.003$). This pattern is also reflected in the mean LI (**Figure 2C**), showing lower values in Broca's region ($t_{df = 34} = 3.91$, $p < 0.001$) and temporal lobes ($t_{df = 34} = 3.10$, $p = 0.004$), but not the cerebellum ($p = 0.152$) in those with oromotor impairment relative to those without. There was a positive correlation between FA in the left CBT (dorsal and ventral combined) and LI values derived from Broca's region ($\rho = 0.383$, $p = 0.030$).

DISCUSSION

Using DWI-tractography in a group of adolescents born preterm, we have identified an association between subclinical oromotor

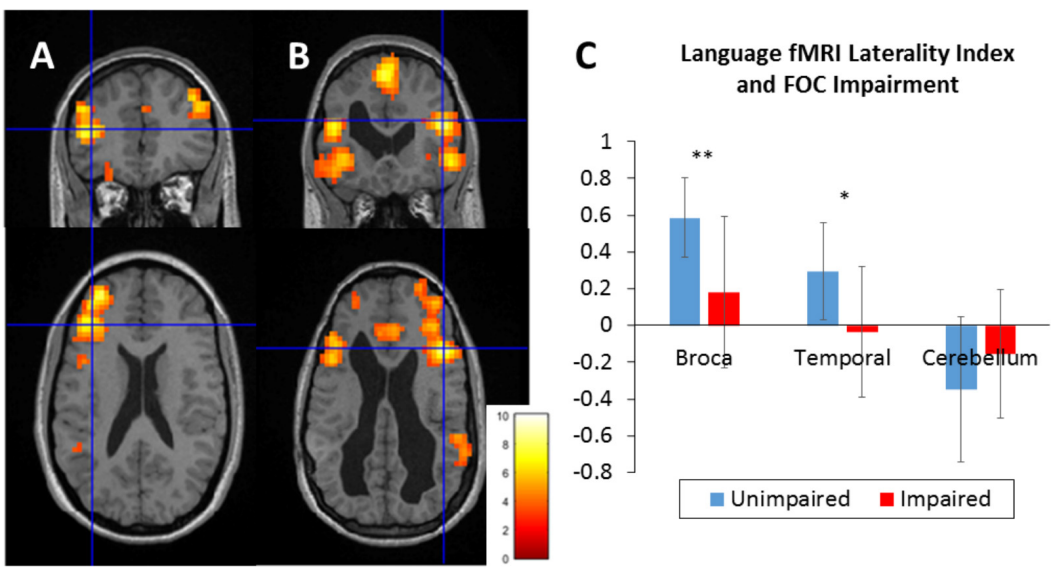

FIGURE 2 | fMRI language laterality in two example cases **(A)** – without oromotor impairment, **(B)** – with oromotor impairment, and **(C)** mean laterality indices in focal oromotor impairment groups. Both cases had sustained major preterm birth-related brain injury (still visible as enlargements of the lateral ventricles). Maps represent single subject activation during a verb generation task (thresholded at $p < 0.001$, color bar shows z-values). Left hemisphere is displayed on the left. Crosshair indicates inferior frontal activation peak. In case **(A)** with bilateral hemorrhagic lesion in the frontal cortex (left < right) shows left lateralization (Broca's laterality index = +0.6). In case **(B)** (slurred speech at 4 years, now resolved) with bilateral hemorrhagic lesion in the frontal cortex (left > right) language was represented bilaterally (laterality index = –0.1). **(C)** Group differences in laterality indices in regions of interest (Broca's region, temporal lobe, and cerebellum). Error bars represent SD; statistical difference: $^{**}p < 0.001$, $^{*}p < 0.01$.

impairment and the microstructural integrity of the primary motor pathway. We focused on the dorsal component of the corticobulbar tract, as this is known to originate from the primary motor representations of the larynx, lips, jaw, and tongue (Takai et al., 2010; Liegeois et al., 2016). This anatomically constrained approach provided a much better predictor of oromotor problems than less specific measures of internal capsule integrity (shown previously, Northam et al., 2012a) in line with other studies indicating a relationship between limb motor outcome and the microstructure of motor tracts in preterm individuals (Groeschel et al., 2014).

We also demonstrated (using an fMRI language task) that the presence of oromotor impairment and left corticobulbar tract injury is associated with greater recruitment of Broca's homolog in the right hemisphere. Moreover, we identified a positive relationship between the severity of left corticobulbar tract damage and the degree of language reorganization. The apparent reorganization of both motor speech and language regions to the right hemisphere suggests functional co-dependence between the two during language development. However, we cannot exclude that prenatal brain injury affected both systems in the left hemisphere, given their anatomical proximity.

Our findings agree with previous studies suggesting that early periventricular injury is associated with atypical language representation (Staudt et al., 2001). In those children with persistent oromotor impairments and atypical speech development, we would interpret this as a compensatory mechanism. In support of this view, inter-hemispheric plasticity has been shown to diminish the behavioral impact of lesions on language development in children following neonatal stroke (Northam et al., 2018).

Importantly, the potential for interhemispheric plasticity following brain injury appears to depend on the timing of the lesion. For instance, children with dysarthria following traumatic left corticobulbar tract damage have been found to have typical left hemisphere language lateralization (Morgan et al., 2013). The later timing of the injury in these children (from 3 to 16 years) may account for the lack of interhemispheric reorganization, as the potential for structural and functional plasticity is maximal in infancy. This view is also in keeping with recent evidence in childhood stroke, showing poorer language outcomes and less right hemisphere reorganization for injuries occurring after the age of 5 years (Ilves et al., 2014; Lidzba et al., 2017a,b).

Although we have identified clear evidence of oromotor impairments in the preterm group – for instance when performing sequential kissing and smiling movements or producing randomly arranged speech sounds (e.g., /a//m//u/) – we describe this as "subclinical" since these unusual combinations do not occur frequently in everyday speech. However, what is unclear is the developmental impact of such subtle speech-motor difficulties in preterm children. Although the problems in our cohort were modest at the time of assessment (adolescence), it has been suggested that there may be a link between oromotor control problems and disruption of early language development (Alcock, 2006; Krishnan et al., 2013). For instance, FA differences have been identified in the left corticobulbar tract in children with developmental speech disorders of unknown origin (Morgan et al., 2018). Although in our cohort, detailed speech, and language assessments were not undertaken in childhood, parental reports indicate that impaired participants were more likely to have received speech and language therapy – or to have displayed some form of atypical speech development (e.g., late onset, poor speech quality/tongue control; Northam et al., 2012a). It seems plausible that such problems might lead to "knock-on" effects on early cognitive development, education, and subsequent school performance. There may therefore be an argument for early identification of these children to enable timely intervention. Overall, our findings highlight the need for a prospective longitudinal study examining early speech and oromotor development in infants born preterm, with and without corticobulbar tract injury.

In conclusion, we provide further evidence (see also Liegeois et al., 2013) that early injury to the left corticobulbar tract is detrimental to the development of oromotor control. We have also shown that despite apparently normal everyday speech, persistent deficits are nevertheless detectable many years later during novel oromotor tasks. Moreover, we have demonstrated recruitment of the right hemisphere language areas in these individuals – and suggest that this may be a compensatory mechanism contributing to the favorable long-term speech outcomes in preterm children.

DATA AVAILABILITY STATEMENT

The datasets for this manuscript are not publicly available because participants and guardians have not given consent for data sharing. Requests to access the datasets should be directed to TB (t.baldeweg@ucl.ac.uk).

AUTHOR CONTRIBUTIONS

GN contributed to study design, acquired and analyzed the data, and wrote the manuscript. AM contributed to study concept and design, study supervision, provided speech/oromotor diagnosis, and critically revised the manuscript for intellectual content. SF performed the tractography analysis. TB contributed to study concept and design, study supervision, data analysis, and critically revised of manuscript for intellectual content. FL contributed to study concept and design, analysis of data, study supervision, and wrote the manuscript.

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SUPPLEMENTARY MATERIAL

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FIGURE S1 | (A) Seed spherical regions (7 mm radius) of interest and target pons region (yellow) used for the tractography reconstructions of the motor tracts (see Liegeois et al., 2013, for details). The center of the spherical seed for the corticospinal tract is placed on the precentral white matter in the "hand knob." The centers of the dorsal and ventral corticobulbar seed spheres are located 15 and 30 mm ventrally to the hand center, but more anteriorly to follow the course of the precentral white matter. The target inclusion region in the pons (in yellow on the sagittal and coronal views of color coded FA maps, see arrows) is delineated on an axial slice to ensure it covers the cross section of the pyramidal tract. **(B)** Functional MRI activation for the Generate > Listen contrast (covertly generating single verbs vs. listening to bursts of amplitude-modulated white noise) in the preterm group. Results are projected onto an inflated single subject template (dspmview toolbox) at $p = 0.05$, family-wise error (FWE) correction. The color bar indicates T-value. Left hemisphere is on the left. Activated clusters included the left inferior frontal region (peak at −38, 22, 2) extending into the precentral and middle frontal gyri, the supplementary motor area and anterior cingulate cortex (peak at −6, 4, 56), the right cerebellum (peak at 38, −66, 30), left (peak at −58, −22, 4), and right superior temporal gyri (peak at 60, −32, 6) as well as the right anterior insular/opercular cortex (peak 40, 20, 2). **(C)** Relationship between focal oromotor scores and corticobulbar tract FA in the whole group.

TABLE S1 | Clinical and neuropsychological characteristics of focal oromotor impairment groups.

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frontiers in Human Neuroscience

ORIGINAL RESEARCH
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White Matter Plasticity in Reading-Related Pathways Differs in Children Born Preterm and at Term: A Longitudinal Analysis

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Children born preterm (PT) are at risk for white matter injuries based on complications of prematurity. They learn to read but on average perform below peers born full term (FT). Studies have yet to establish whether properties of white matter pathways at the onset of learning to read are associated with individual variation later in reading development in PT children. Here, we asked whether fractional anisotropy (FA) at age 6 years is associated with reading outcome at age 8 years in PT children in the same pathways as previously demonstrated in a sample of FT children. PT (n = 34, mean gestational age = 29.5 weeks) and FT children (n = 37) completed diffusion MRI and standardized measures of non-verbal IQ, language, and phonological awareness at age 6 years. Reading skills were assessed at age 8 years. Mean tract-FA was extracted from pathways that predicted reading outcome in children born FT: left arcuate fasciculus (Arc), bilateral superior longitudinal fasciculus (SLF), and left inferior cerebellar peduncle (ICP). We explored associations in additional pathways in the PT children: bilateral inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus. Linear regression models examined whether the prediction of reading outcome at age 8 years based on mean tract-FA at age 6 years was moderated by birth group. Children born PT and FT did not differ significantly in tract-FA at age 6 years or in reading at age 8 years. Sex, socioeconomic status, and non-verbal IQ at age 6 years were associated with reading outcome and were included as covariates in all models. Birth group status significantly moderated associations between reading outcome and mean tract-FA only in the left Arc, right SLF, and left ICP, before and after consideration of pre-literacy skills. Microstructural properties of these cerebral and cerebellar pathways predicted later reading outcome in FT but not in PT children. Children born PT may rely on alternative pathways to achieve fluent reading. These findings have implications for plasticity of neural organization after early white matter injury.

Keywords: prematurity, diffusion MRI, longitudinal study, reading development, tractography, white matter microstructure

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INTRODUCTION

Neuroplasticity can be defined as the ability of the brain to reorganize itself. Neuroplasticity is essential for recovery from injury or disease and is also fundamental for normal development from infancy to adulthood and for learning at any age. As an example of plasticity, studies have found that children with extensive pre- or perinatal injury to left hemisphere cortical brain regions that typically serve these functions can, nonetheless, develop normally after initial delays (Levine et al., 1987; Marchman et al., 1991; Feldman et al., 1992, 2002). White matter is comprised of myelinated and unmyelinated axons that connect distant regions of the brain. A growing literature suggests that white matter contributes to neuroplasticity because white matter responds dynamically to experience (Sampaio-Baptista and Johansen-Berg, 2017). Recent studies have demonstrated that properties of white matter circuits are associated with measures of human cognition (e.g., Fink et al., 2010; Van Hecke et al., 2010; Caligiuri et al., 2015). Specifically, white matter microstructure has been linked to learning to read (Ben-shachar et al., 2007; Vandermosten et al., 2012a; Wandell and Yeatman, 2013; Travis et al., 2016a). We recently demonstrated that properties of specific white matter pathways at the onset of learning to read predicted later reading skills in a sample of children born full term (FT) (Borchers et al., 2019a). Children born preterm (PT) prior to 32 weeks gestation have been shown to have distinctive patterns of white matter microstructure as a consequence of PT birth and its complications (Volpe, 2009). In this study, in order to explore neuroplasticity in relation to white matter, we sought to determine whether similar white matter-reading associations would be found in a longitudinal study of school-aged children born PT.

White matter injury is a major component of the encephalopathy of PT preterm (PT) birth (Volpe, 2009). The immature white matter in neonates born PT is highly susceptible to injury due to hypoxia ischemia and inflammation (Back et al., 2007; Khwaja and Volpe, 2007; Volpe, 2009). These early insults affect primarily the myelin-producing cells, or oligodendrocyte precursors, and result in cell maturation arrest, cell death, and myelination failure (Back et al., 2007; Khwaja and Volpe, 2007). Even in the absence of obvious white matter injury on conventional magnetic resonance imaging (MRI), differences in the microstructure of major cerebral white matter pathways have been detected in children born extremely or very PT compared to children born near or at term, using diffusion magnetic resonance imaging (dMRI) at near term equivalent age. However, the findings have been inconsistent across studies; the PT groups have been found to have lower fractional anisotropy (FA) in some studies (Anjari et al., 2007; Knight et al., 2018), but higher FA (Giménez et al., 2008) or both higher and lower FA as a function of tract in other studies (Rose et al., 2008). Group differences on cerebral white matter pathways persist into childhood and adolescence (Nagy et al., 2003; Groeschel et al., 2014; Travis et al., 2015a) though again the results vary as a function of white matter tract and participant age. These white matter changes are likely to have implications for cognitive skills and may influence learning. Other complications of PT birth include cerebellar injury, which may also have implications for cognitive and related functioning (Brossard-Racine et al., 2015). The white matter connections between the cerebellum and cerebrum may also be altered after PT birth (Travis et al., 2016b).

We chose to study white matter microstructure and reading in children born PT for many reasons. First, reading development provides a unique opportunity to examine learning-dependent plasticity of white matter pathways in humans. Reading is typically acquired over a long period of time after instruction and many hours of practice. Second, understanding the neurobiology of reading is an educational and public health priority. Our society is becoming ever more literacy-driven. If children do not learn to read fluently, their opportunities for a fulfilling and integrated life are at risk. Third, individual differences in reading are associated with variations in white matter microstructure in samples of otherwise healthy children.

During reading, the brain integrates signals from dispersed cortical regions that process visual, phonological, and semantic information in a left-lateralized network of occipitotemporal, temporoparietal, and inferior frontal cortices (Price, 2012). In weak or impaired readers, this network of cortical regions is different, with lower levels of activation in posterior regions and greater activations in inferior frontal regions (Shaywitz et al., 2006). Functional imaging also finds, in children who respond positively to interventions, patterns of activation that begin to approach that of unimpaired readers (Simos et al., 2002; Temple et al., 2003; Gaab et al., 2007). Individual variation in the microstructural properties of several cerebral and cerebellar pathways, as measured by dMRI has been shown to correlate with reading-related skills in typically developing children and adolescents (Beaulieu et al., 2005; Ben-shachar et al., 2007; Wandell and Yeatman, 2013). White matter-reading correlations were found in the left arcuate fasciculus (Arc) and branches of the superior longitudinal fasciculus (SLF) (Vandermosten et al., 2012a; Yeatman et al., 2012a; Travis et al., 2016a). These pathways are considered to be part of the dorsal stream in cognitive models of language and reading and are thought to be involved in auditory-to-motor mapping, phonological processing, repetition, and the processing of complex sentences (Ben-shachar et al., 2007; Hickok and Poeppel, 2007; Dick and Tremblay, 2012; Skeide and Friederici, 2016). Additionally, a significant relationship between properties of the left inferior fronto-occipital fasciculus (IFOF) and performance on non-word reading suggested that this tract may be involved in highly demanding tasks translating orthography to phonology (Rollans et al., 2017). Correlations of white matter microstructure and reading were also found in the left inferior longitudinal fasciculus (ILF) (Yeatman et al., 2012a) and bilateral uncinate fasciculus (UF) (Travis et al., 2016a). The IFOF, ILF, and UF pathways are considered to be part of the ventral stream of the language and reading network and are thought to be involved in semantic and visual-orthographic processing (Friederici and Gierhan, 2013; Gil-Robles et al., 2013). The cerebellum is also known to play an important role in reading (Fiez and Petersen, 1998). White matter microstructure of the cerebellar peduncles, tracts connecting cerebellum to

cerebrum, have also been implicated in reading performance (Travis et al., 2015b).

Studies have demonstrated that diffusion metrics of reading-related pathways at younger ages predict reading proficiency at older ages (Hoeft et al., 2011; Yeatman et al., 2012a; Myers et al., 2014). A recent study of children with a range of reading abilities showed that FA of the dorsal pathways, including the left Arc and the left and right SLF, and the left inferior cerebellar peduncle (ICP) at age 6 years was associated with reading outcome at age 8 years (Borchers et al., 2019a). Observations in this study were powerful because the associations to later reading persisted even after consideration of demographic covariates (sex and socioeconomic status) and individual variation in pre-literacy skills (language abilities and phonological awareness), all of which were correlated with reading outcome. Taken together, these previous longitudinal studies have established a predictive role for both dorsal and ventral stream language pathways, as well as cerebellar pathways, in predicting reading development in healthy FT children. Less is known about the predictive value of these pathways in children born PT.

Previous studies and meta-analyses confirm that children born PT are at-risk for poor reading outcome later in life (Aarnoudse-Moens et al., 2009; Kovachy et al., 2015). Studies have also suggested that white matter microstructure of tracts associated with reading or reading-related skills are different in PT and FT children. For example, in a dMRI study, the SLF was found to be associated with reading in a group of 16-year old adolescents born PT but not in peers born FT (Frye et al., 2010). A different study, also assessing 16-year old adolescents born PT and FT found that the PT group relied more on bilateral white matter tracts than did the FT group (Mullen et al., 2011). In a study of children born PT and FT across a wide age range, concurrent associations of reading and white matter metrics were found in segments of dorsal and ventral pathways (Travis et al., 2016a). However, the direction of association was different between the two birth groups suggesting that plasticity changes after PT birth lead to different neural organization in order to accomplish learning to read. In a different cohort of 6-year old children born PT and FT, pre-literacy skills were associated with microstructural properties of the left Arc (Dodson et al., 2018). Though the direction of associations was similar in the children born PT and FT, the associations were weaker in the PT group. However, associations of language and white matter properties of the right UF, a pathway within the ventral stream, were moderated by birth group status: positive associations were found in children born FT but not in children born PT (Dodson et al., 2018). These findings further support the view that variations in the underlying neurobiology of pre-literacy skills reflect plasticity and reorganization following early white matter injury, resulting in a different neural implementation of reading skills.

In this study we sought to examine whether microstructural properties of dorsal and cerebellar white matter pathways at age 6 years are associated with reading outcome at age 8 years in a sample of children born PT, as we have previously demonstrated in a sample of children born FT (Borchers et al., 2019a). We further sought to determine if the prediction is found above and beyond the contribution of demographic and pre-literacy skills at age 6 years. In addition to the dorsal and cerebellar pathways previously implicated in prediction, we included ventral stream pathways (IFOF, ILF, and UF) to determine if the microstructural properties of these pathways are associated with later reading. If the pattern of associations in PT children parallels the one seen in FT children, the findings would imply similar neural correlates of reading across birth groups, despite the fact that children born PT are at risk for white matter injuries and have previously shown different values of white matter diffusion metrics. In contrast, distinct patterns of associations in PT compared to FT children might suggest important variations in how the brain adapts to reading in children born PT.

MATERIALS AND METHODS

Participants

Children born PT and FT were enrolled in the study at age 6 years, and followed up at age 8 years, as part of a longitudinal study that examined the neural basis of reading. The FT group (Borchers et al., 2019a) was defined as birth at $\geq$37 weeks gestational age or birth weight $\geq$2,500 g. PT birth was defined as $\leq$32 weeks gestational age because these are children at high risk for white matter injury (Volpe, 2009) and decrements in reading ability (Aarnoudse-Moens et al., 2009; Kovachy et al., 2015). Children were excluded from the study if they had any neurological or medical condition (other than prematurity or its complications) that might impact learning to read, including genetic disorders, significant hearing loss or visual impairment, intelligence quotient $\leq$ 80, and non-English speakers. The final sample included 37 FT children (15 males; mean age at time 1: 6 years 2 $\pm$ 2 month; mean age at time 2: 8 years 1 $\pm$ 2 month) and 34 PT children (22 males; mean age at time 1: 6 years 2 $\pm$ 2 month; mean age at time 2: 8 years 2 $\pm$ 2 month). To characterize the birth groups, at age 6 years, parents completed a comprehensive demographic and health questionnaire. Socioeconomic status (SES) was measured using a modified version of the Hollingshead Four Factor Index of Socioeconomic Status (Hollingshead, 1975). Children were classified as 'bilingual' if a parent reported that their child could speak a language other than English. All children were competent in English, attended English-speaking schools for at least two years prior to enrollment, and completed all assessments in English. Children were categorized as having a family history of reading delay if any first-degree relatives (mother, father, or siblings) were diagnosed or suspected of having a reading disorder.

Neurocognitive Assessment at Age 6 and 8 Years

We followed the same protocol for neurocognitive assessments as described in Borchers et al. (2019a). At age 6 years, children completed standardized assessments of phonological awareness (Comprehensive Test of Phonological Processing, CTOPP; Wagner et al., 1999), language [Clinical Evaluation of Language Fundamentals – Fourth Edition (CELF-4); Semel et al., 2004], and non-verbal IQ [Weschler Abbreviated Scale

of Intelligence-II (WASI-II); Wechsler and Hsiao-pin, 2011] as potential predictor variables for later reading. At age 8 years, children's reading proficiency was assessed using the Gray Oral Reading Tests – Fifth Edition (GORT-5; Wiederholt and Bryant, 2012). The GORT requires children to read aloud stories of increasing difficulty and subsequently answer questions about the passage. The Oral Reading Index, our primary outcome variable, measures reading fluency, comprised of accuracy and rate of reading, and comprehension.

MRI Acquisition and Analyses

Imaging parameters and methods for dMRI data preprocessing, analyses of subject's motion, and individual native-space tractography have been described in several previous publications (Dodson et al., 2018; Borchers et al., 2019a; Bruckert et al., 2019) and are briefly summarized below.

MRI scans were obtained at age 6 years using a 3T MRI scanner (GE MR750 Discovery, GE Healthcare, Milwaukee, WI, United States) with a 32-channel head coil. High resolution T1-weighted images were collected with a 3D fast-spoiled gradient (FSPGR) sequence (TR = 7.24 ms; TE = 2.78 ms; FOV = 230 mm × 230 mm; acquisition matrix = 256 × 256; 0.9 mm isotropic voxels; orientation = sagittal). Diffusion data were collected with a dual-spin echo, echo-planar imaging sequence with full brain coverage (TR = 8300 ms; TE = 83.1 ms; FOV = 220 mm × 220 mm; acquisition matrix = 256 × 256; voxel size: 0.8594 mm × 0.8594 mm × 2 mm; orientation = axial) using a *b*-value of 1000 s/mm^2, sampling along 30 isotropically distributed diffusion directions. Three additional volumes were acquired at $b = 0$ at the beginning of each scan.

The open-source software mrDiffusion[1] implemented in MATLAB R2014a (Mathworks, Natick, MA, United States) was used to pre-process the diffusion data. We quantified the degree of relative head motion in each participant by calculating the magnitude of motion correction (in voxels) in the x-y-z plane of each volume relative to the prior volume. For each diffusion scan, we counted the number of volumes with translational motion of 1 voxel or more. We then calculated the mean number of volumes with ≥1 voxel of relative motion across the entire sample ($M = 1.37$, $SD = 3.18$). Participants who deviated from this mean by more than three standard deviations were excluded from analyses. This procedure led to the exclusion of two participants (1 PT). Group comparisons were performed to ensure that children born FT and PT did not differ in their average relative head motion [$t(69) = 1.58$, $p = 0.118$, $d = 0.36$].

In the remaining participants, to correct for participant's motion, each diffusion weighted image was registered to the mean of the three non-diffusion (b0) images using a rigid body transformation (Rohde et al., 2004). The mean b0 image was registered to the participant's T1-weighted image, which had been aligned to the canonical ac-pc orientation. The combined transform that resulted from motion correction and alignment to the T1 anatomy was applied to the raw data once, and the transformed images were resampled to 2 mm × 2 mm × 2 mm isotropic voxels. Following robust tensor fitting and outlier rejection based on the RESTORE procedure (Chang et al., 2005), FA maps were generated using the standard formula (Mukherjee et al., 2008).

Cerebral and cerebellar white matter pathways were tracked and segmented using the open source software Automated Fiber Quantification (AFQ; Yeatman et al., 2012b). AFQ uses a three-step procedure to identify white matter pathways in the native space of each child: (i) Whole-brain tractography was performed using a deterministic streamline tracking algorithm (Mori et al., 1999; Chang et al., 2005), with a fourth-order Runge–Kutta path integration method. Tractography was seeded from each voxel in a white matter mask (FA > 0.2). Tracking proceeded in all directions until FA values dropped below 0.15, or until the angle between the last path segment and next step direction was greater than 30°; (ii) Automatic tract segmentation was done using a way-point region of interest (ROIs) approach as described by Wakana et al. (2007). Template ROIs were defined in MNI space and warped to native space by applying a non-linear transformation (Friston and Ashburner, 2004); and (iii) Automatic tract refinement was achieved by comparing each candidate fiber to an established fiber tract probability map (Hua et al., 2008) and removing streamlines that pass through regions of white matter having a low probability for belonging to the tract under analysis.

We selected pathways for analysis *a priori* based on our previous findings, documenting associations between the mean tract-FA of these pathways at age 6 years and reading outcome at age 8 years in the subsample of children born FT (Borchers et al., 2019a) (**Figure 1A**). These pathways included: left Arc, left and right SLF, and left ICP. We also included the left and right IFOF, ILF, and UF (**Figure 1B**) to examine whether ventral stream pathways are associated with later reading in children born PT. Individual tractograms (fiber renderings) of each pathway were visually inspected in each child prior to any statistical analysis, to ensure that the tract generally conformed to anatomical norms for location and shape and did not include many aberrant fibers. We successfully identified the tracts in all children with the following exceptions: the left AF could not be tracked in one FT child and the left ICP could not be tracked in one FT and three PT children.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS software (version 23.0, IBM Corp., 2015). Statistical significance was set at $p < 0.05$. The Shapiro–Wilk test was used to assess whether our neurocognitive and neurobiological data were normally distributed. With the exception of SES and mean tract-FA of the left Arc, all data were normally distributed. We chose to do parametric tests for all associations. Bonferroni correction was applied to these zero-order associations to account for multiple comparisons.

Demographic Characteristics of Children Born PT and FT

We compared children born PT and FT on four continuous (age, gestational age, birthweight, SES) and four categorical (sex, language status, grade, family history of reading delay)

[1]https://github.com/vistalab/vistasoft/tree/master/mrDiffusion

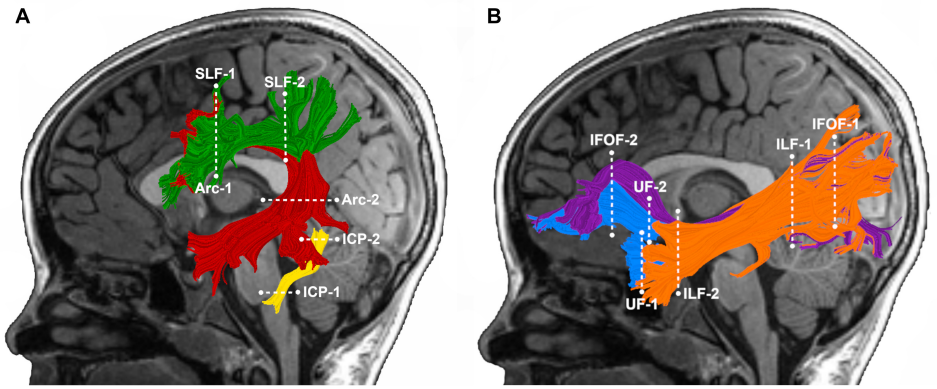

FIGURE 1 | Tractography of cerebral and cerebellar white matter pathways. Left hemisphere tract renderings are displayed on a mid-sagittal T1 image from a representative child in our group. Right hemisphere tract renderings not shown. Dashed lines represent the location of the regions of interest (ROIs) used to segment each pathway from the whole-brain tractogram. **(A)** Dorsal stream and cerebellar pathways: the left arcuate fasciculus (Arc) is displayed in *red*, the left superior longitudinal fasciculus (SLF) in *green*, and the left inferior cerebellar peduncle (ICP) in *yellow*. **(B)** Ventral stream pathways: the left inferior frontal occipital fasciculus (IFOF) is displayed in purple, inferior longitudinal fasciculus (ILF) in *orange* and the left uncinate fasciculus (UF) in *blue*.

demographic measures using two-tailed independent *t*-tests or chi-square analyses, respectively. We further compared the two groups on their standardized measures of non-verbal IQ, language, and phonological awareness as well as mean tract-FA obtained at age 6 years and reading outcome at age 8 years using two-tailed independent *t*-tests. Two-tailed independent *t*-tests were also used to evaluate possible confounding effects at age 6 years with reading outcome at age 8 years by comparing the Oral Reading Index in the following subgroups: male vs. female, monolingual vs. bilingual. The Mann–Whitney *U*-test was used to compare reading outcome between subgroups with uneven distributions: kindergarten vs. first grade and positive vs. negative family history of reading delay. We computed Pearson correlations to assess the degree of associations between reading outcome at age 8 years and each of the following at age 6 years: SES, non-verbal IQ, language, and phonological awareness.

Hierarchical Linear Regression Models

We conducted a series of hierarchical linear regression models to assess the contribution of mean tract-FA of the selected tracts at age 6 years to reading outcome at age 8 years. Demographic variables and neurocognitive measures that showed significant subgroup differences or associations with reading outcome were included as covariates in all models. We first measured whether there was a main effect of each white matter pathway and then whether birth group status moderated the prediction of mean tract-FA to later reading outcome. We repeated the series of regression models to assess the unique contribution of each white matter pathway after consideration of language and phonological awareness – two pre-literacy skills that were previously associated with reading outcome in FT children (Borchers et al., 2019a). The variance inflation factor (VIF) was calculated to assess multicollinearity of each model. We considered VIF values less than 10 to indicate that there was no concern for multicollinearity (Field, 2013).

RESULTS

Characteristics of PT and FT Children

Group characteristics and statistical comparisons between PT and FT children are summarized in **Table 1**. By design, children born PT had significantly lower gestational age and birthweight than their FT peers. Overall, the two groups were well-matched on age, ethnicity, language status, and grade. The PT group had significantly more boys, but significantly fewer children with a family history of reading delay compared to the FT group. While children born PT and FT were on average from high SES backgrounds, SES was significantly lower in the PT group. Within the PT group, four had intrauterine growth restriction, 29 children had respiratory distress syndrome, of which five were classified as severe and required mechanical ventilation; six developed evidence of chronic lung disease, requiring supplemental oxygen beyond 36 weeks gestation. A total of 27 children had hyperbilirubinemia requiring phototherapy. Twelve children had abnormalities on cranial ultrasound; nine had intraventricular hemorrhage Grade II or less, two had mild dilatation of the ventricles, one had white matter injury and one had parenchymal injury. A total of 18 children had near term MRI scans and seven had abnormal findings, of which five had evidence of white matter changes or enlarged ventricles. However, no child had frank cystic lesions.

Children born PT and FT scored within the normal range on all cognitive, pre-literacy, and reading assessments (**Table 1**). While the two groups did not significantly differ in phonological awareness at age 6 years or reading outcome at age 8 years, PT children had significantly lower mean scores on language and non-verbal IQ compared to their FT peers. We found no significant differences in mean tract-FA of any white matter pathway.

To determine whether demographic variables or neurocognitive measures at age 6 years were important

TABLE 1 | Characteristics of the sample (significant *p*-values are printed in bold).

N = 71	Full Term (*n* = 37) *M* (*SD*) or *n* (%)	Preterm (*n* = 34) *M* (*SD*) or *n* (%)	*t* or χ^2	*p*	*d*
Demographic measures					
Age of test 1	6.2 (0.2)	6.1 (0.2)	0.60	0.548	0.12
Gestational age at birth (wks)	39.5 (1.5)	29.5 (2.4)	21.16	**<0.001**	4.98
Birth weight (grams)	3,298 (399)	1,336 (468)	19.05	**<0.001**	4.51
Males # (%)	15 (41%)	22 (69%)	4.15	**0.042**	n/a
Bilingual # (%)	19 (51%)	11 (32%)	2.62	0.105	n/a
Kindergarten # (%)	25 (68%)	26 (76%)	0.69	0.405	n/a
FH of reading delay # (%)	8 (22%)	1 (3%)	5.59	**0.018**	n/a
SES[1]	58.2 (10.0)	52.3 (14.2)	2.01	**0.049**	0.48
Neurocognitive measures					
IQ[2]	112.3 (16.0)	101.3 (13.4)	3.12	**0.003**	0.74
Language[3]	113.2 (12.8)	102.5 (10.8)	3.79	**<0.001**	0.90
Phono awareness[4]	113.5 (11.8)	110.1 (13.0)	1.15	0.255	0.27
Reading outcome[5]	102.2 (13.2)	97.6 (10.9)	1.61	0.112	0.38
Mean tract-fractional anisotropy					
Arc-L[6]	0.49 (0.03)	0.47 (0.03)	1.98	0.052	0.67
SLF-L[7]	0.42 (0.04)	0.43 (0.04)	−0.73	0.467	0.25
SLF-R[7]	0.47 (0.05)	0.48 (0.04)	−0.64	0.525	0.22
ICP-L[8]	0.43 (0.04)	0.44 (0.04)	−1.26	0.212	0.25
IFOF-L[9]	0.49 (0.03)	0.50 (0.04)	−0.76	0.445	0.18
IFOF-R[9]	0.50 (0.03)	0.50 (0.03)	−1.18	0.240	0.29
ILF-L[10]	0.43 (0.02)	0.43 (0.03)	0.40	0.688	0.10
ILF-R[10]	0.43 (0.02)	0.43 (0.03)	−0.54	0.589	0.13
UF-L[11]	0.43 (0.02)	0.42 (0.04)	0.85	0.401	0.20
UF-R[11]	0.45 (0.02)	0.44 (0.03)	1.57	0.123	0.38

[1]Socioeconomic status, measured with the Hollingshead Index at age 6 years; [2]Non-verbal Intelligence Quotient, measured with the WASI-II at age 6 years; [3]Core Language Index, measured with the CELF-4 at age 6 years; [4]Phonological Awareness Composite, measured with the CTOPP at age 6 years; [5]Oral Reading Index, measured with the GORT-5 at age 8 years; [6]Arcuate fasciculus; [7]Superior longitudinal fasciculus; [8]Inferior fronto-occipital fasciculus; [9]Inferior cerebellar peduncle; [10]Inferior longitudinal fasciculus; [11]Unciate fasciculus. L, left; R, right.

contributors to reading at age 8 years, we examined subgroup differences in, and correlations with reading outcome (**Supplementary Tables S1, S2**). Across children born PT and FT, girls scored significantly higher than boys on reading outcome (**Supplementary Table S1**). Therefore, sex was entered as a covariate in all regression models. Reading outcome did not differ between children who were monolingual vs. bilingual, between children enrolled in kindergarten vs. first grade at age 6 years, or between children with vs. without a family history of reading delay. Thus, we did not covary for these variables in subsequent regression models despite the difference in proportion of children with a family history of reading delay in each birth group. Across the entire sample, reading outcome at age 8 years was significantly correlated with SES, non-verbal IQ, language, and phonological awareness skills at age 6 years (**Supplementary Table S2**).

Based on these preliminary subgroup and correlation analyses, sex, SES, and non-verbal IQ were consistently entered as covariates in all regression models. Language and phonological awareness were added as behavioral predictor variables in the second round of regression models. Correlations between reading outcome and demographic variables, pre-literacy skills, and mean tract-FA ranged from −0.12 to 0.61 (**Supplementary Tables S2, S3**). For all subsequent regression models the VIF values were equal or less than 4.0. Thus, there was no cause for concern regarding multicollinearity.

Associations Between White Matter Pathways and Reading Outcome

Table 2 shows the results of multiple regression models predicting reading outcome at age 8 years by mean tract-FA of the left Arc, left and right SLF, and left ICP at age 6 years controlling for sex, SES, and non-verbal IQ. R^2 change and adjusted R^2 change values in models 1B-I reflect the increase in explained variance associated with the addition of the main effect of tract or the interaction term of tract × birth group relative to the preceding model with tract only. *Models 1A-1I* demonstrated that non-verbal IQ at age 6 years was the only consistent covariate that explained significant unique variance in reading outcome. When controlling for all covariates, birth group was not a significant predictor variable of reading outcome (*Model 1A*). The entire model accounted for 23.3% of the variance in reading outcome. FA of the left Arc did not significantly contribute to reading outcome (*Model 1B*). However, when we entered the interaction between mean tract-FA of the left Arc and birth group in *Model 1C* we found a significant increase of 5.4% in variance accounted for. As illustrated in **Figure 2A**, the

TABLE 2 | Prediction of reading outcome at age 8 years by mean tract-FA of the left Arcuate (Arc-L), left and right superior longitudinal fasciculus (SLF-L, SLF-R) and left inferior cerebellar peduncle (ICP-L) at age 6 years, controlling for sex, socioeconomic status (SES), and non-verbal intelligence (IQ) in the preterm and full term groups.

	Model 1A	Model 1B	Model 1C	Model 1D	Model 1E	Model 1F	Model 1G	Model 1H	Model 1I
Sex	4.1 (2.8)	4.1 (2.8)	4.2 (2.7)	2.9 (2.7)	2.7 (2.6)	3.8 (2.7)	4.6 (2.6)	4.1 (2.7)	3.3 (2.6)
SES	0.2 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
IQ	**0.2 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.3 (0.1)[b]**	**0.3 (0.1)[b]**
Group	−0.1 (2.8)	1.1 (2.9)	**94.8 (41.8)[a]**	−1.4 (2.7)	50.7 (26.5)	−0.9 (2.8)	**72.6 (26.1)[b]**	−0.7 (2.8)	**78.6 (28.7)[b]**
Arc-L	–	87.2 (44.7)	**198.2 (65.7)[b]**	–	–	–	–	–	–
Arc-L × group	–	–	**−193.8 (86.3)[a]**	–	–	–	–	–	-
SLF-L	–	–	–	**92.9 (32.2)[b]**	**154.8 (44.5)[c]**	–	–	–	–
SLF-L × group	–	–	–	–	−122.2 (61.9)	–	–	–	–
SLF-R	–	–	–	–	–	**69.7 (29.0)[a]**	**134.0 (35.7)[c]**	–	–
SLF-R × group	–	–	–	–	–	**-**	**−154.1 (54.5)[b]**	–	–
ICP-L	–	–	–	–	–	–	–	**84.3 (35.2)[a]**	**170.2 (45.5)[c]**
ICP-L × group	–	–	–	–	–	–	–	**-**	**−181.4 (65.3)[b]**
Δ R^2	–	4.3%	5.4%[a]	8.7%[b]	3.9%	**6.3%[a]**	**7.8%[b]**	**6.3%[a]**	**7.6%[b]**
Total R^2	**23.3%[c]**	**27.2%[c]**	**32.6%[c]**	**32.0%[c]**	**35.9%[c]**	**29.6%[c]**	**37.4%[c]**	**33.2%[c]**	**40.8%[c]**
Adjusted R^2	**18.7%[c]**	**21.5%[c]**	**26.2%[c]**	**26.8%[c]**	**29.9%[c]**	**24.2%[c]**	**31.5%[c]**	**27.7%[c]**	**34.8%[c]**

Data are unstandardized coefficients (SE). [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$. R^2 change (Δ R^2) values in models 1B, D, F, and H are in reference to model 1A. Δ R^2 values in models 1C, E, G, and I reflect the increase in variance accounted for by the interaction term in relation to the preceding model with the main effect for that tract. Significant values are printed in bold.

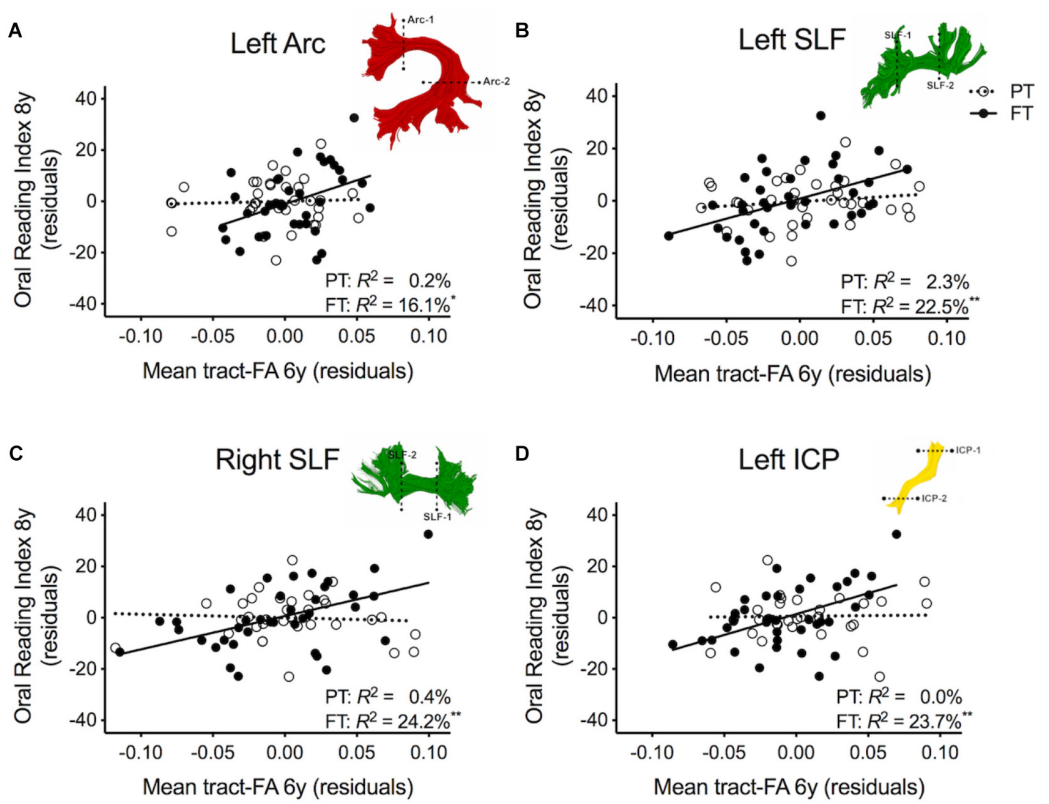

FIGURE 2 | Regression residuals of mean tract-FA of the dorsal stream and cerebellar pathways at age 6 years and reading outcome at age 8 years in children born preterm (PT, open circle, dotted line) and full term (FT, filled circles, solid line) after controlling for sex, socioeconomic status, and non-verbal IQ. Subplots **(A–D)** show a significant interaction indicating that associations between reading outcome and mean tract-FA of the left Arcuate (Arc), left and right superior longitudinal fasciculus (SLF), and left inferior cerebellar peduncle (ICP) differed between birth groups. Δ R^2 values reflect the increased variance accounted for by the corresponding pathway in children born PT or FT.

prediction of the left Arc to reading outcome was different in the two groups: in children born FT, mean tract-FA was positively associated with reading outcome, while mean tract-FA was not associated with reading outcome in children born PT. *Models 1C-1I* demonstrated a similar pattern of associations. In all three cases, FA of the tract made a significant contribution to the variance in reading outcome, adding 6.3–8.7% to the variance accounted for. However, the interaction of mean tract-FA with birth group was significant (*Models 1G and 1I*) or trending toward significance (*Model 1E, p* = 0.053) in all remaining cases, explaining approximately 3.9–7.8% additional variance. The associations between reading outcome at age 8 years and mean tract-FA of the left SLF, right SLF, and left ICP at age 6 years was again positive in the FT, but absent in the PT group (**Figures 2B–D**).

Table 3 shows the second round of regression analyses, the results of adding pre-literacy skills to the models. *Model 2A* showed that the combined contribution of covariates, language, and phonological awareness improved the prediction of reading outcome, accounting for 42.4% of the variance. With the addition of pre-literacy skills to the model, non-verbal IQ was no longer a unique predictor of reading outcome. However, language and phonological awareness were significant predictors. Similar to *Model 1A*, birth group status did not explain significant variance in reading outcome at age 8 years, even after the addition of pre-literacy skills at age 6 years to the model. Overall, the pattern of results was similar with pre-literacy skills included in the models as in the first round of analyses. The interaction terms of mean tract-FA of the left Arc, left and right SLF, and left ICP remained significant and added 3.9–10.3% unique variance (*Model 2C, 2G,* and *2I*). The exception was *Model 2E*, in which the interaction between the left SLF and birth group was no longer approaching significance. However, we found a significant main effect of the left SLF accounting for 4.7% of the variance in reading outcome across both birth groups ($p = 0.021$) (*Model 2E*). In children born PT and FT, mean tract-FA of the left SLF at age 6 years was positively associated with reading outcome at age 8 years (**Figure 3B**). In the remaining dorsal tracts, associations were positive in the FT and non-significant in the PT groups (**Figures 3C,D**).

Since PT and FT children differed in their proportion of children with a family history of reading delay, regression models might have been unduly influenced by these children. We therefore, re-ran the regression models excluding children with a family history of reading delay ($n = 9$; 1 PT). The pattern of associations between the selected white matter pathways at age 6 years and reading outcome at age 8 years remained the same – before and after consideration of pre-literacy skills (**Supplementary Tables S4, S5**).

In order to assure that we did not miss any potential associations between mean tract-FA of other reading-related pathways and reading outcome in the PT group, we conducted a final round of regression analyses including the left and right IFOF, ILF, and UF. We did not find any main effects of these ventral pathways controlling for sex, SES, and non-verbal IQ at age 6 years or any significant interactions tract with birth group (**Table 4**, **Figures 4A–F**). After pre-literacy skills were added to the models, the interaction of mean tract-FA of the left UF and birth group (Model *4K*) approached significance ($p = 0.055$) explaining 3.5% of the variance in reading outcome (**Table 5**).

TABLE 3 | Prediction of reading outcome at age 8 years by mean tract-FA of the left Arcuate (Arc-L), left and right superior longitudinal fasciculus (SLF-L, SLF-R) and left inferior cerebellar peduncle (ICP-L) at age 6 years, controlling for sex, socioeconomic status (SES), non-verbal intelligence (IQ), language, and phonological awareness (Phono aware) in the preterm and full term groups.

	Model 2A	Model 2B	Model 2C	Model 2D	Model 2E	Model 2F	Model 2G	Model 2H	Model 2I
Sex	0.9 (2.5)	1.1 (2.6)	1.3 (2.5)	0.3 (2.5)	0.2 (2.4)	0.6 (2.5)	1.3 (2.2)	1.5 (2.6)	1.2 (2.5)
SES	0.1 (0.1)	0.0 (0.1)	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)	0.0 (0.1)	0.1 (0.1)	0.0 (0.1)
IQ	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)	0.0 (0.1)	0.1 (0.1)	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)
Language	**0.4 (0.1)[a]**	**0.4 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.4 (0.1)[b]**	**0.5 (0.1)[c]**	0.2 (0.2)	0.3 (0.1)
Phono aware	**0.3 (0.1)[a]**	0.2 (0.1)	0.2 (0.1)	**0.2 (0.1)[a]**	0.2 (0.1)	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.3 (0.1)[a]**	0.2 (0.1)
Group	1.1 (2.6)	1.7 (2.8)	**81.3 (38.0)[a]**	0.2 (2.5)	37.1 (24.3)	0.6 (2.5)	86.5 (22.2)[c]	0.0 (2.7)	**60.1 (27.9)[a]**
Arc-L	–	35.8 (43.6)	**132.5 (62.6)[a]**	–	–	–	–	–	–
Arc-L × group	–	–	**−164.7 (78.4)[a]**	–	–	–	–	–	–
SLF-L	–	–	–	**69.9 (29.4)[a]**	**115.2 (41.6)[b]**	–	–	–	–
SLF-L × group	–	–	–	–	−86.6 (56.8)	–	–	–	–
SLF-R	–	–	–	–	–	**62.4 (25.8)[a]**	**138.2 (30.3)[c]**	**–**	**–**
SLF-R × group	–	–	–	–	–	**-**	**−179.2 (46.0)[c]**	**-**	**-**
ICP-L	–	–	–	–	–	**-**	**-**	**72.1 (33.0)[a]**	**136.6 (43.7)[b]**
ICP-L × group	–	–	–	–	–	**–**	**–**	**–**	**−137.3 (63.3)[a]**
Δ R^2	–	0.6%	**3.9%[a]**	4.7%[a]	1.9%	**4.9%[a]**	**10.3%[c]**	**4.4%[a]**	**4.0%[a]**
Total R^2	**42.4%[c]**	**42.7%[c]**	**46.6%[c]**	**47.2%[c]**	**49.1%[c]**	**47.3%[c]**	**57.7%[c]**	**46.1%[c]**	**50.1%[c]**
Adjusted R^2	**37.0%[c]**	**36.2%[c]**	**39.6%[c]**	**41.3%[c]**	**42.5%[c]**	**41.5%[c]**	**52.2%[c]**	**39.7%[c]**	**43.2%[c]**

Data are unstandardized coefficients (SE). [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$. R^2 change (Δ R^2) values in models 2B, D, F, and H are in reference to model 2A. Δ R^2 values in models 2C, E, G, and I reflect the increase in variance accounted for by the interaction term in relation to the preceding model with the main effect for that tract. Significant values are printed in bold.

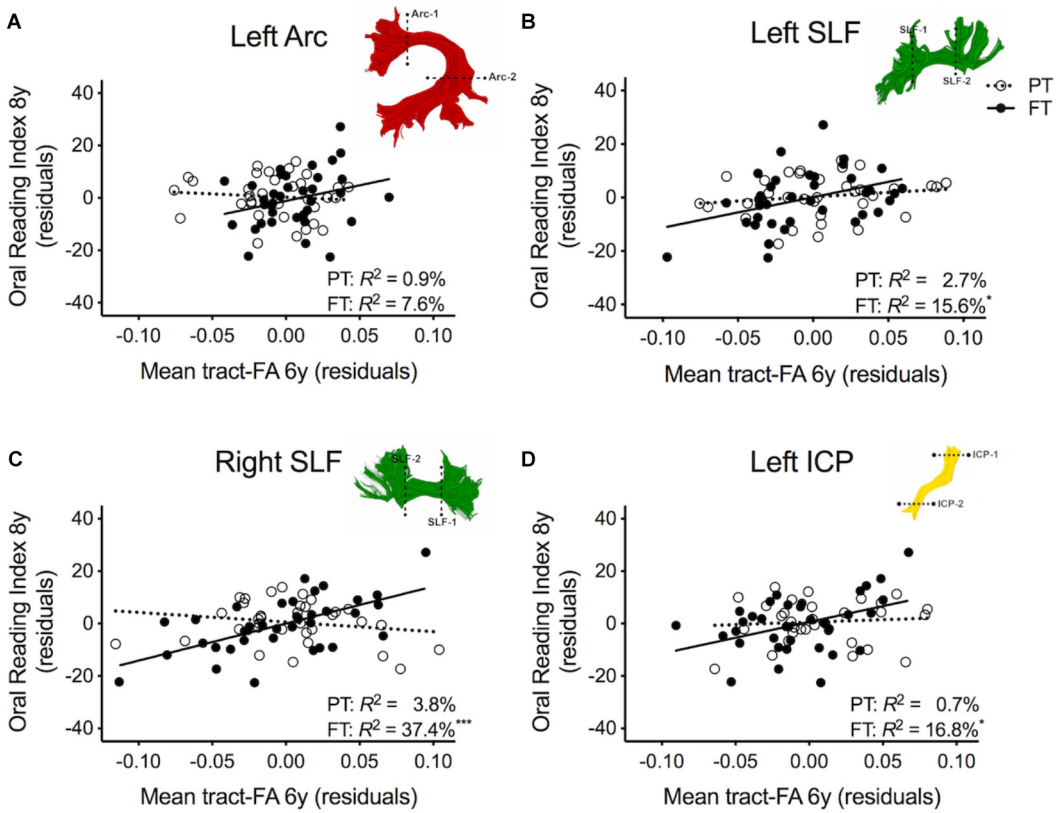

FIGURE 3 | Regression residuals of mean tract-FA of the dorsal stream and cerebellar pathways at age 6 years and reading outcome at age 8 years in children born preterm (PT, open circle, dotted line) and FT (filled circles, solid line) after controlling for sex, socioeconomic status, non-verbal IQ, language, and phonological awareness. Subplots **(A,C,D)** show a significant interaction indicating that associations between reading outcome and mean tract-FA of the left Arcuate (Arc), right SLF, and left ICP differed between birth groups. Subplot **(B)** shows that the association between reading outcome and mean tract-FA of the left SLF was not significantly different between birth groups. ΔR^2 values reflect the increased variance accounted for by the corresponding pathway in children born PT or FT.

Neither the interaction with birth group nor the main effect of the left or right IFOF, left or right ILF, or left or right UF added significant variance to the model after consideration of pre-literacy skills (**Table 5**, **Figures 5A–F**).

DISCUSSION

This study demonstrated that brain-reading relations were different in children born PT and FT. Individual differences in white matter properties of the left Arc, left and right SLF, and left ICP at age 6 years were associated with reading outcome at age 8 years in children born FT (Borchers et al., 2019a). Despite comparable levels (between birth groups) of mean tract-FA of these four selected pathways and similar reading scores, we found that birth group moderated the associations between FA at age 6 years and reading outcome 2 years later. Mean tract-FA of these pathways was not associated with reading outcome in children born PT. The pattern of results did not change after excluding nine children with a family history of reading delay. We did not find associations between mean tract-FA of the ventral pathways, including the left and right IFOF, ILF, and UF, and later reading outcome in either birth group. The distinct pattern of associations suggests that the neural basis of learning to read may be different in children born PT and FT. Variation in the neural substrates of reading may reflect the ability of the PT brain to recover from or compensate for neural consequences of PT birth, allowing these children to achieve reading skills within the normal range. The findings, thus, suggest that plasticity after white matter changes related to PT birth may be associated with changes in brain wiring supporting reading.

White Matter Plasticity in Children Born PT

We know that children born PT are at risk for white matter injury (Back and Rosenberg, 2014; Back, 2017). Before significant advances in neonatal care, cystic lesions within the periventricular zone were the most common form of white matter injury during PT birth (Gano et al., 2015). Today, non-cystic lesions within similar white matter regions predominate (Back et al., 2007; Volpe, 2009). Imaging studies have established that children born PT show differences in microstructural properties of major white matter pathways compared to their FT peers in the neonatal period (Anjari et al., 2007; Giménez et al., 2008; Rose et al., 2008), and also

TABLE 4 | Prediction of reading outcome at age 8 years by mean tract-FA of the left and right inferior frontal-occipital fasciculus (IFOF-L, IFOF-R), inferior longitudinal fasciculus (ILF-L, ILF-R), and uncinate fasciculus (UF-L, UF-R) at age 6 years, controlling for sex, socioeconomic status (SES), and non-verbal intelligence (IQ) in the preterm and full term groups.

	Model 3A	**Model 3B**	**Model 3C**	**Model 3D**	**Model 3E**	**Model 3F**	**Model 3G**	**Model 3H**	**Model 3I**	**Model 3J**	**Model 3K**	**Model 3L**	**Model 3M**
Sex	4.1 (2.8)	4.6 (2.8)	4.6 (2.8)	4.1 (2.8)	3.7 (2.9)	4.1 (2.8)	4.1 (2.8)	3.7 (2.8)	3.7 (2.8)	4.2 (2.9)	5.3 (2.9)	4.9 (2.8)	4.7 (2.9)
SES	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
IQ	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**	**0.2 (0.1)[a]**
Group	−0.1 (2.8)	−0.4 (2.9)	24.8 (44.5)	−0.4 (2.9)	29.8 (49.3)	**−0.1 (2.9)[a]**	37.2 (42.1)	−0.4 (2.9)	20.7 (52.4)	−0.1 (2.9)	−63.2 (39.9)	0.8 (2.9)	14.5 (49.4)
IFOF-L	–	36.7 (44.5)	69.7 (73.5)	–	–	–	–	–	–	–	–	–	–
IFOF-L × group	–	–	−51.0 (90.0)	–	–	–	–	–	–	–	–	–	–
IFOF-R	–	–	–	33.7 (47.9)	65.2 (70.3)	–	–	–	–	–	–	–	–
IFOF-R × group	–	–	–	–	−60.7 (98.8)	–	–	–	–	–	–	–	–
ILF-L	–	–	–	–	–	4.4 (48.5)	61.6 (80.7)	–	–	–	–	–	–
ILF-L × group	–	–	–	–	–	–	−86.9 (97.8)	–	–	–	–	–	–
ILF-R	–	–	–	–	–	–	–	58.0 (56.4)	91.4 (100.6)	–	–	–	–
ILF-R × group	–	–	–	–	–	–	–	–	−49.1 (121.8)	–	–	–	–
UF-L	–	–	–	–	–	–	–	–	–	1.4 (44.3)	−93.5 (74.2)	–	–
UF-L × group	–	–	–	–	–	–	–	–	–	–	148.5 (93.6)	–	–
UF-R	–	–	–	–	–	–	–	–	–	–	–	67.8 (49.7)	88.7 (90.5)
UF-R × group	–	–	–	–	–	–	–	–	–	–	–	–	−30.8 (111.2)
ΔR^2	–	0.8%	0.4%	0.6%	0.4%	0.0%	0.9%	1.2%	0.2%	0.0%	2.9%	2.1%	0.1%
Total R^2	**23.3%[c]**	**24.1%[b]**	**24.5%[b]**	**23.9%[b]**	**24.3%[b]**	**23.3%[b]**	**24.3%[b]**	**24.5%[b]**	**24.7%[b]**	**23.3%[b]**	**26.2%[b]**	**25.5%[b]**	**25.5%[b]**
Adjusted R^2	**18.7%[c]**	**18.3%[b]**	**17.4%[b]**	**18.0%[b]**	**17.3%[b]**	**17.4%[b]**	**17.2%[b]**	**18.7%[b]**	**17.7%[b]**	**17.4%[b]**	**19.3%[b]**	**19.7%[b]**	**18.6%[b]**

Data are unstandardized coefficients (SE). [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$. R^2 change (ΔR^2) values in models 3B, D, F, H, J, and L are in reference to model 3A. R^2 change values in models 3C, E, G, I, K, and M reflect the increase in variance accounted for by the interaction term in relation to the preceding model with the main effect for that tract. Significant values are printed in bold.

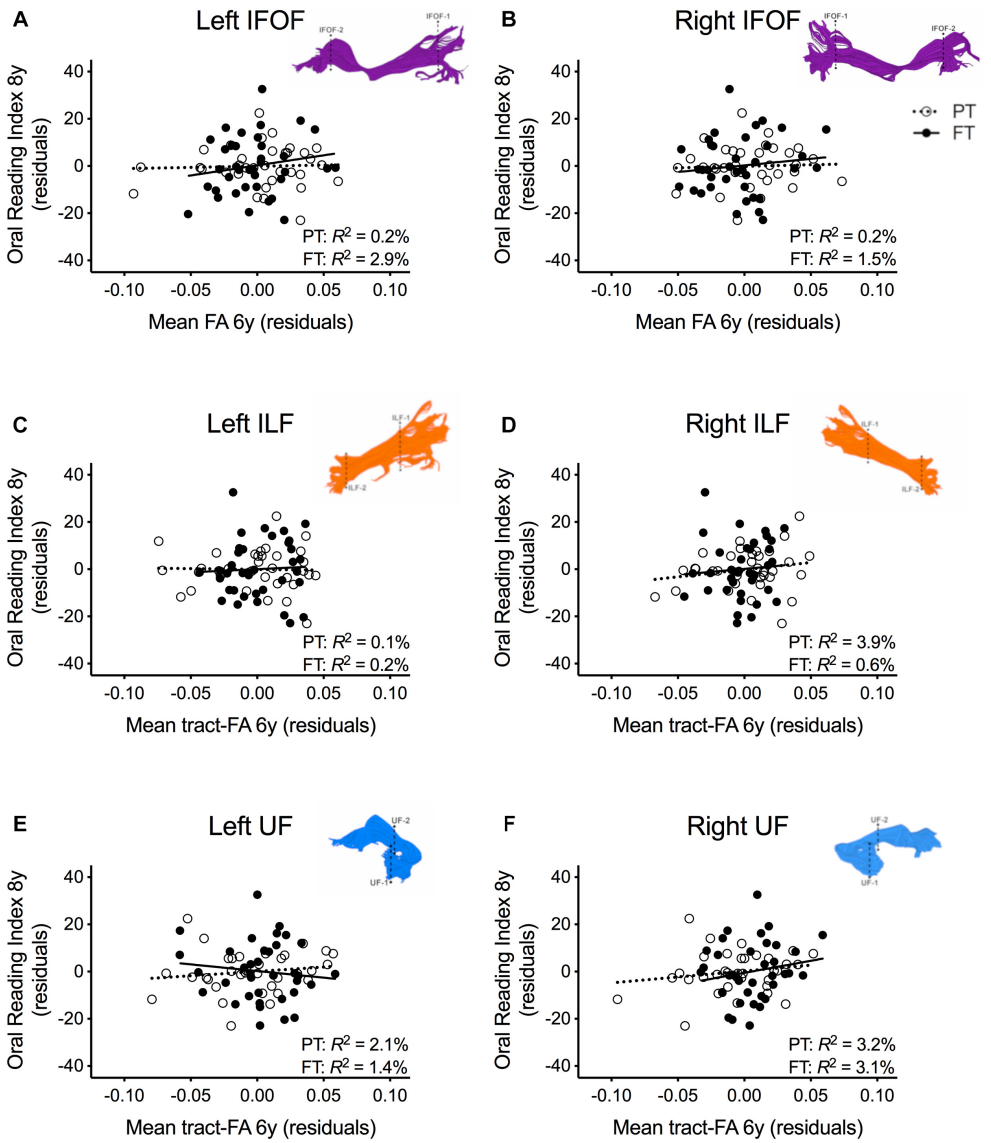

FIGURE 4 | Regression residuals of mean tract-FA of the ventral stream pathways at age 6 years and reading outcome at age 8 years in children born preterm (PT, open circle, dotted line) and FT (filled circles, solid line) after controlling for sex, socioeconomic status, and non-verbal IQ. Subplots **(A–F)** show no significant associations between reading outcome and mean tract-FA of the left and right inferior frontal occipital fasciculus (IFOF), ILF, and UF. Δ R^2 values reflect the increased variance accounted for by the corresponding pathway in children born PT or FT.

persisting into childhood (Nagy et al., 2003; Andrews et al., 2010; Dodson et al., 2017), adolescence (Nagy et al., 2003; Vangberg et al., 2006; Groeschel et al., 2014; Travis et al., 2015a), and adulthood (Allin et al., 2011; Eikenes et al., 2011). Studies vary in terms of the direction of group differences, which may be the result of differences in study samples, imaging methods, or analytic strategies. In any case, at the level of neurobiology, we have yet to learn whether white matter differences between children born PT and FT represent downstream effects of injury, long-term consequences of white matter dysmaturity, or reorganization of the PT brain. Such insights cannot be determined directly from diffusion scans taken at a single point in time and will require longitudinal imaging studies.

At the behavioral level, children born PT as a group experience long-term decrements in reading, but generally score within the normal range on standardized tests of reading (Aarnoudse-Moens et al., 2009; Lee et al., 2011; Kovachy et al., 2015). These results are behavioral indications of neural plasticity. The magnitude of group differences has been found to decrease for simple language functions (van Noort-van der Spek et al., 2012), though not for complex language functions (van Noort-van der Spek et al., 2012) or reading (Kovachy et al., 2015).

TABLE 5 | Prediction of reading outcome at age 8 years by mean tract-FA of the left and right inferior frontal-occipital fasciculus (IFOF-L, IFOF-R), inferior longitudinal fasciculus (ILF-L, ILF-R), and uncinate fasciculus (UF-L, UF-R) at age 6 years, controlling for sex, socioeconomic status (SES), non-verbal intelligence (IQ), language, and phonological awareness (Phono aware) in the preterm and full term groups.

	Model 4A	Model 4B	Model 4C	Model 4D	Model 4E	Model 4F	Model 4G	Model 4H	Model 4I	Model 4J	Model 4K	Model 4L	Model 4M
Sex	0.9 (2.5)	1.08 (2.6)	1.1 (2.6)	1.0 (2.6)	0.7 (2.6)	1.0 (2.6)	0.9 (2.6)	0.7 (2.6)	0.4 (2.6)	1.0 (2.6)	2.1 (2.6)	1.3 (2.6)	1.6 (2.7)
SES	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)	0.1 (0.1)	0.0 (0.1)	0.1 (0.1)	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)
IQ	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.1 (0.1)	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
Language	**0.4 (0.1)[a]**	**0.4 (0.1)[a]**	**0.4 (0.2)[a]**	**0.4 (0.1)**	**0.3 (0.2)[a]**	**0.4 (0.1)[a]**	**0.4 (0.1)[a]**	**0.3 (0.1)[a]**	**0.4 (0.1)[a]**	**0.4 (0.1)[a]**	**0.4 (0.1)[a]**	**0.3 (0.2)[a]**	**0.4 (0.2)[a]**
Phono aware	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	0.3 (0.1)	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**	**0.3 (0.1)[a]**
Group	1.1 (2.6)	1.1 (2.6)	7.6 (40.0)	1.0 (2.7)	24.0 (44.3)	1.2 (2.6)	46.3 (36.9)	0.9 (2.6)	61.8 (46.6)	1.2 (2.6)	−68.0 (34.8)	1.4 (2.7)	−25.3 (45.1)
IFOF-L	–	10.0 (39.9)	18.7 (66.3)	–	–	–	–	–	–	–	–	–	–
IFOF-L × group	–	–	−13.2 (81.0)	–	–	–	–	–	–	–	–	–	–
IFOF-R	–	–	–	14.1 (42.6)	38.5 (63.5)	–	–	–	–	–	–	–	–
IFOF-R × group		–	–	–	−46.3 (88.9)	–	–	–	–	–	–	–	–
ILF-L	–	–	–	–	–	8.3 (42.7)	77.6 (70.8)	–	–	–	–	–	–
ILF-L × group	–	–	–	–	–	–	−105.2 (85.9)	–	–	–	–	–	–
ILF-R	–	–	–	–	–	–	–	45.1 (49.9)	140.7 (88.2)	–	–	–	–
ILF-R × group	–	–	–	–	–	–	–	–	−141.5 (108.0)	–	–	–	–
UF-L	–	–	–	–	–	–	–	–	–	2.3 (39.0)	−102.3 (64.9)	–	–
UF-L × group	–	–	–	–	–	–	–	–	–	–	163.1 (81.9)	–	–
UF-R	–	–	–	–	–	–	–	–	–	–	–	27.6 (45.7)	−15.1 (85.3)
UF-R × group	–	–	–	–	–	–	–	–	–	–	–	–	60.4 (101.7)
ΔR^2	–	0.1%	0.0%	0.1%	0.3%	0.0%	1.4%	0.7%	1.5%	0.0%	3.5%	0.3%	0.3%
Total R^2	**42.4%[c]**	**42.5%[c]**	**42.5%[c]**	**42.5%[c]**	**42.8%[c]**	**42.5%[c]**	**43.8%[c]**	**43.2%[c]**	**44.7%[c]**	**42.4%[c]**	**45.9%[c]**	**42.8%[c]**	**43.1%[c]**
Adjusted R^2	**37.0%[c]**	**36.1%[c]**	**35.1%[c]**	**36.2%[c]**	**35.4%[c]**	**36.1%[c]**	**36.6%[c]**	**36.9%[c]**	**37.6%[c]**	**36.1%[c]**	**38.9%[c]**	**36.4%[c]**	**35.8%[c]**

Data are unstandardized coefficients (SE). [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$. R^2 change (ΔR^2) values in models 4B, D, F, H, J, and L are in reference to model 4A. R^2 change values in models 4C, E, G, I, K, and M reflect the increase in variance accounted for by the interaction term in relation to the preceding model with the main effect for that tract. Significant values are printed in bold.

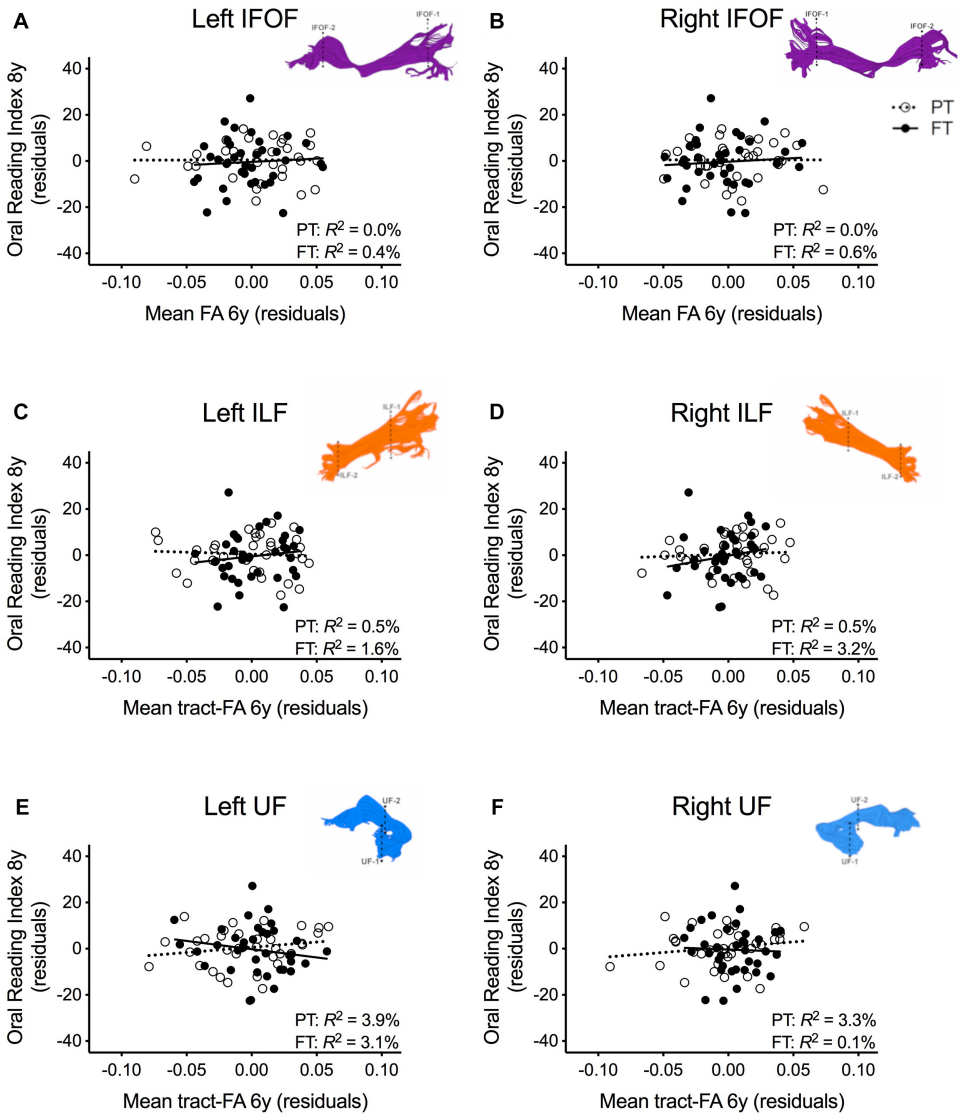

FIGURE 5 | Regression residuals of mean tract-FA of the ventral stream pathways at age 6 years and reading outcome at age 8 years in children born preterm (PT, open circle, dotted line) and FT (filled circles, solid line) after controlling for sex, socioeconomic status, non-verbal IQ, language, and phonological awareness. Subplots **(A–F)** show no significant associations between reading outcome and mean tract-FA of the left and right inferior frontal occipital fasciculus (IFOF), ILF, UF. Δ R^2 values reflect the increased variance accounted for by the corresponding pathway in children born PT or FT.

Structural and functional imaging studies have implicated impaired connectivity as relevant to reading and language difficulties after PT birth (Gozzo et al., 2009; Northam et al., 2012). An alternative frame is to consider white matter differences as an index of neuroplasticity after early injury and/or dysmaturity (Sampaio-Baptista and Johansen-Berg, 2017). Mullen et al. (2011) found that receptive vocabulary and rapid naming skills were correlated with diffusion metrics obtained from bilateral dorsal pathways in their PT group, suggesting that the PT participants relied heavily on the right hemisphere pathways. The FT comparison group in that study showed no significant associations of white matter metrics and reading (Mullen et al., 2011). Constable et al. (2013) used functional connectivity to interrogate cerebellar-cerebral connections and found increased connectivity was associated with receptive vocabulary and verbal comprehension in the PT sample. Findings from both of these studies, as the authors stated, may represent either a delay in maturation of white matter microstructure in the PT sample or the engagement of alternative neural pathways for language in PT adolescents. Yeatman and Feldman (2013) were able to document the use of alternate pathways for language and reading in a child born PT. In this case, a 12-year old girl who had been born PT and diagnosed with periventricular leukomalacia, a condition characterized by severe

damage to the white matter primarily surrounding the ventricles, was lacking the Arc and SLF bilaterally. Despite early language delays, the child achieved average scores on expressive language, sentence repetition, and reading (Yeatman and Feldman, 2013). Analyses suggested that she relied on intact ventral connections between the temporal and frontal lobes through the extreme capsule and UF rather than major dorsal pathways. All of these reports emphasize that white matter integrity is likely an important component of impaired performance and also a factor promoting plasticity in children born PT.

White Matter Pathways Were Associated With Later Reading in Children Born FT

The association of mean tract-FA to later reading outcome in FT children is consistent with many other studies. In typically developing children, diffusion metrics of the left AF and left SLF have been associated with various reading skills across different ages (Yeatman et al., 2011; Vandermosten et al., 2012b; Myers et al., 2014; Gullick and Booth, 2015; Travis et al., 2016a) Both pathways are thought to represent the dorsal stream in cognitive models of language and reading, linking inferior frontal with superior temporal cortices (Hickok and Poeppel, 2004; Scott and Wise, 2004) which have been implicated in phonological awareness and other pre-literacy skills (Houdé et al., 2010).

The association of the right SLF with later reading is in line with studies of developmental reading disorders. Among children with a familial risk for dyslexia, those children who subsequently developed into good readers showed faster white matter development in the right SLF compared to those who developed into poor readers (Wang et al., 2017). In addition, Hoeft et al. (2011) demonstrated that diffusion metrics of the right SLF predicted future reading gains in children with dyslexia but not in typical readers. Both studies suggest that the development of the right SLF may be a potential compensatory mechanism for white matter alterations within the left hemisphere, allowing children who are at risk for dyslexia to achieve fluent reading (Hoeft et al., 2011; Wang et al., 2017).

We have demonstrated that the right SLF is also associated with later reading outcomes in FT children (Borchers et al., 2019a). Because the right SLF was not associated with language or phonological awareness skills in that study, we proposed that the associations may reflect other skills that are involved in learning to read, such as executive function skills (Blair and Razza, 2007; Frye et al., 2009).

Cerebellar pathways have been recently implicated in reading. Travis et al. (2015b) reported associations between diffusion metrics of the cerebellar peduncles and reading in older children and adolescents. We have also shown that FA of the left ICP at age 6 years makes important contributions to reading outcome at age 8 years, even after consideration of preliteracy skills (Borchers et al., 2019a). Together, these studies suggest that cerebellar pathways contribute to cognitive processes that are integral to reading development. Because the ICP mostly contains afferent fibers from the spine and the olivary nucleus to the cerebellum, and efferent fibers from the cerebellum to the vestibular nuclei (Naidich and Duvernoy, 2009), our results may seem somewhat surprising. However, proficient reading is likely to also depend on implicit learning and feedback processes which support the execution of new perceptual and motor skills, such as oculomotor control and articulation (Stein et al., 2000; Velay et al., 2002). The ICP could mediate these processes and thus facilitate the fine-tuning and automatization of core functions of reading.

White Matter Pathways Were Not Associated With Later Reading in Children Born PT

In contrast to children born FT, we did not observe any significant associations between mean tract-FA of the dorsal or ventral pathways and later reading outcome in children born PT. While null findings are exceedingly common and represent potentially important discoveries, they are difficult to interpret. One possible explanation is that the size of our PT group may have been adequate only to detect very strong correlations at 5% alpha (two-tailed). Given that we had sufficient power to find significant associations in our FT group, however, we expected to also have sufficient power to find associations in the PT group, which was of similar size.

Another explanation for the lack of findings may be that children born PT rely on a different set of white matter pathways to achieve proficiency in reading accuracy, fluency, and comprehension. However, we did not find any associations with mean tract-FA of the left and right IFOF, ILF, and UF. Since we examined a comprehensive set of white matter pathways implicated in reading including dorsal, ventral, and cerebellar pathways, we think that this explanation is unlikely. Alternatively, children born PT may involve a larger network in which no specific pathway is predominant for reading. In a recent study, we assessed how different domains of cognitive function, often impacted by PT birth, were associated with reading outcome in children born PT relative to children born FT (Borchers et al., 2019b). While verbal skills (phonological awareness, language) at age 6 years were associated with reading outcome in both children born PT and FT, non-verbal cognitive skills (executive function, non-verbal IQ) were only associated with reading outcome in children born PT. These findings suggest that children born PT rely on a broader set of cognitive skills to achieve reading proficiency than children born FT (Borchers et al., 2019b). Whether this broader set of cognitive skills may in turn be mediated by a larger network of white matter pathways is an important topic for future research.

It is also possible that children born PT represent a heterogeneous group, both in terms of behavior and white matter injury. In this study, the sample of PT children did not differ from the sample of FT children either in reading outcome or mean tract-FA. In addition, the PT group was generally of high SES and had relatively strong IQ scores compared to other samples of PT children (Bhutta et al., 2002). Therefore, these findings may not be representative of PT children of low SES and/or with lower IQ scores. We recognize that associations of reading outcome and mean tract-FA of white matter pathways may be present in a subset of PT children. However, because our sample was moderate in size and relatively homogeneous, we were not

able to consider subgroup analyses, such as comparing relations in extremely low gestational age (gestational age at birth less than 28 weeks) versus very low gestational age (gestational age at birth over 28 weeks).

Lastly, children born PT may rely on the same pathways as children born FT, but FA may be insensitive to their individual variation in reading outcome. FA is an indirect measure of white matter microstructure and influenced by a number of different tissue factors such as myelin thickness, axonal diameter, axon density, and crossing fibers (Beaulieu, 2002; Wheeler-Kingshott and Cercignani, 2009). Because hypoxia, ischemia, and inflammation associated with PT birth can affect white matter maturation (Back et al., 2007; Khwaja and Volpe, 2007; Volpe, 2009), FA may index a different or more diverse set of tissue factors in children born PT compared to children born FT. Ongoing studies are exploring these possibilities.

CONCLUSION

Microstructural properties of cerebral and cerebellar white matter pathways at age 6 years were associated with reading outcome 2 years later in children born FT, but not in children born PT. Our findings suggest that the two groups may have important differences in the neural basis of reading development. These differences may point to white matter plasticity after injury in children born PT, given that they learn to read, often within the normal range. Overall, this study highlights that there may be multiple routes to learning to read. Design of behavioral assessment and intervention should consider birth group status. The metrics we have used here, namely FA, may not be specific enough to detect recovery of function and differential development in children born PT. Future studies should integrate diffusion MRI with imaging methods that can provide direct measures of myelin content and axonal diameter (e.g., Assaf et al., 2008; Mezer et al., 2013) to assess and triangulate the associations between white matter pathways and reading abilities in children born PT.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Stanford University Institutional Review Board. In all cases, a parent or guardian provided written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Stanford University Institutional Review Board (#IRB-22233).

AUTHOR CONTRIBUTIONS

LB analyzed the data and drafted the initial manuscript. LRB and CD collected and analyzed the data, reviewed, and revised the manuscript. VM, KT, and MB-S contributed to conceptualization of data analysis, coordinated and supervised data analysis, critically reviewed the manuscript for intellectual content, and revised the manuscript. HF conceptualized and designed the study, selected the data collection instruments, coordinated and supervised data collection, assisted in the creating of the initial draft of the manuscript, critically reviewed the manuscript for intellectual content, and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2019.00139/full#supplementary-material

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Effects of Early Language Deprivation on Brain Connectivity: Language Pathways in Deaf Native and Late First-Language Learners of American Sign Language

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Previous research has identified ventral and dorsal white matter tracts as being crucial for language processing; their maturation correlates with increased language processing capacity. Unknown is whether the growth or maintenance of these language-relevant pathways is shaped by language experience in early life. To investigate the effects of early language deprivation and the sensory-motor modality of language on white matter tracts, we examined the white matter connectivity of language-relevant pathways in congenitally deaf people with or without early access to language. We acquired diffusion tensor imaging (DTI) data from two groups of individuals who experienced language from birth, twelve deaf native signers of American Sign Language, and twelve hearing L2 signers of ASL (native English speakers), and from three, well-studied individual cases who experienced minimal language during childhood. The results indicate that the sensory-motor modality of early language experience does not affect the white matter microstructure between crucial language regions. Both groups with early language experience, deaf and hearing, show leftward laterality in the two language-related tracts. However, all three cases with early language deprivation showed altered white matter microstructure, especially in the left dorsal arcuate fasciculus (AF) pathway.

Keywords: deaf, sign language, language deprivation, white matter pathway, diffusion tensor imaging

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INTRODUCTION

Human language is a highly complex cognitive system that relies on a distributed neural network. One crucial question regarding the neurobiology of human language is the role of language experience during development. Early neural plasticity allows environmental experience and learning to shape postnatal brain development (Huttenlocher, 2002) and is often limited to a critical period (Hensch, 2005). Although a similar critical period has been suggested for language development (Lenneberg et al., 1967), it remains unclear how experience within a critical time window contributes to language acquisition. The question is difficult to investigate because neural changes at different levels occur simultaneously during the first few years of postnatal development in typically developing children.

One approach to the question is to compare populations with different early language experience. Although spoken language is ubiquitous for children who hear normally, congenitally

deaf children do not have access to it from birth. Approximately 10% of the deaf children are born into deaf families who use sign language as their main communication method. Sign languages are natural languages with linguistic features similar to spoken languages (Stokoe, 1978; Klima and Bellugi, 1979), and the developmental milestones for sign language are similar to those of spoken languages (Reilly et al., 1990; Anderson and Reilly, 2002; Pichler, 2002; Mayberry and Squires, 2006). Deaf children with deaf parents who sign with them thus experience language from birth, like typically developing children with normal hearing. But their early language experience occurs via the visual-manual modality in contrast to the auditory-oral modality of hearing children's language experience. However, the majority of deaf children are born into hearing families. Some families learn sign language to communicate with their deaf children. Some families prefer to use oral communication with their deaf children, often using hearing compensation technologies such as cochlear implants or hearing aids, together with speech training. Under certain conditions, neither spoken language nor sign language is accessible to deaf children resulting in early language deprivation. Thus, congenitally deaf individuals vary in their early language environment, offering a rare opportunity to investigate the role of early language experience in the development of the neural language network. Research on this question is also crucial to raise the awareness of the potential negative sequelae of early language deprivation in deaf children.

Recent neurolinguistics models (Hickok and Poeppel, 2004, 2007; Parker and Brorson, 2005; Saur et al., 2008; Friederici, 2009; Price, 2012) have identified two information streams, the dorsal and ventral streams, as being crucial for maintaining the dynamic language network. The dorsal stream involves the temporal-parietal-frontal connections mainly via the superior longitudinal fasciculus (SLF) - arcuate fasciculus (AF) complex (Catani and Mesulam, 2008). The ventral stream runs through the extreme capsule (EmC) linking middle-posterior STG to the anterior IFG; the inferior fronto-occipital fasciculus (IFOF) that establishes the occipital-temporo-frontal connection; the inferior longitudinal fasciculus (ILF) connecting the occipital lobe and the temporal lobe; and the uncinate fasciculus (UF) connecting anterior temporal to inferior frontal areas (see Dick and Tremblay, 2012, for a review on the anatomy and functions of each fiber tract).

The dorsal stream is often considered to be responsible for an auditory–motor integration function, carrying acoustic speech signals from the auditory cortex to articulatory representations in the frontal lobe, while the ventral stream is more responsible for speech recognition, and involves structures in the superior and middle temporal lobe that are crucial for meaning and comprehension (Hickok and Poeppel, 2004, 2007; Saur et al., 2008). The dorsal stream has been identified in several studies as also being relevant to complex syntactic processing (Caplan et al., 1986; Wilson et al., 2011; Verhoeven et al., 2012; Meyer et al., 2014; Skeide et al., 2016). It is unclear if deficits at the syntactic level of language are secondary to deficits in other lower-level functions mediated by the dorsal pathways, such as auditory-motor integration and working memory. In addition, previous studies have consistently found a left-ward lateralization pattern, with greater volume, more streamlines, and greater microstructural integrity in the left AF compared to the right AF (Büchel et al., 2004; Catani et al., 2007; Glasser and Rilling, 2008; Ocklenburg et al., 2013; Takao et al., 2013; Eichert et al., 2018). This lateralization pattern is found in children and adolescents as well as in adults (Lebel and Beaulieu, 2009). Eichert et al. (2018) compared the laterality of dorsal AF with the ventral IFOF in humans and macaque monkeys. In humans, the dorsal AF but not the ventral IFOF pathway is left-lateralized, while neither tract is lateralized in macaques. Panesar et al. (2018) also found strong left-lateralized connectivity patterns for ILF in humans. Variability is observed in the exact laterality of UF across studies (Malykhin et al., 2008; Hasan et al., 2009; Yasmin et al., 2009; Danielian et al., 2010; Jahanshad et al., 2010; Ocklenburg et al., 2013; Takao et al., 2013). Less information on laterality is available for EmC.

These language-related pathways mature relatively late in development (Lebel et al., 2008, 2012; Brauer et al., 2011; Perani et al., 2011), and their degree of maturation correlates with language development. Compared to sensorimotor regions, language-related temporal and frontal regions in the left hemisphere show protracted myelination development (Pujol et al., 2006). Accelerated vocabulary development after the age of 18 months relates to a rapid myelination phase in the language-related regions. Children aged 5 to 9 years show a delayed gray matter thinning process in left IFG (Broca's area) and bilateral posterior temporal regions (Sowell et al., 2004). At age 7 children show immature AF-SLF and IFOF pathways compared to adults (Brauer et al., 2013), and the degree of maturation of the AF-SLF pathway from the ages of 3 to 10 years correlates with children's comprehension of complex sentences (Skeide et al., 2016). The protracted maturation of the language-related pathways might indicate an extended plastic period that can be shaped by language in the environment.

The majority of studies on language pathways have been conducted with hearing individuals who use spoken languages. To date few studies have directly examined the white matter pathways for sign language in deaf native signers. An empirical question is whether the sensory-motor modality of language affects the connectivity of the language network.

Existing studies on white matter connectivity in congenitally deaf individuals have generally found decreased white matter volume or altered white matter microstructure mostly restricted to auditory-related areas, such as bilateral Heschl's gyrus (HG), planum temporale (PT), and STG, but not in long range language pathways (Emmorey et al., 2003; Li et al., 2012; Hribar et al., 2014; Karns et al., 2017). One study comparing white matter microstructure in deaf and hearing individuals found additional differences in several language-relevant fiber tracts, such as bilateral SLF and left IFOF (Kim et al., 2009). One factor that may account for the inconsistencies across studies is variation in the developmental onset of language experience among deaf individuals. Because Kim and his collaborators did not report the language acquisition backgrounds of their deaf participants, it is possible that the differences they observed between the deaf and hearing participants were due to effects related to early language deprivation. Deaf individuals who first acquire language later

in life show low levels of language proficiency across levels of linguistic structure compared to deaf individuals who experience language from birth (Newport, 1990; Mayberry and Eichen, 1991; Mayberry and Lock, 2003; Boudreault and Mayberry, 2006; Mayberry et al., 2017). Deaf individuals who experienced language deprivation also show altered neural activation patterns compared to deaf individuals with typical language development (Mayberry et al., 2011, 2018; Ferjan Ramirez et al., 2014, 2016), for both lexical and sentence processing. Still, little is known about how early linguistic experience affects the connections between crucial language regions.

In the present paper, we investigate two contrasting factors in early language experience, namely, the sensory-motor modality of early linguistic experience, and the presence/absence of early linguistic exposure. We report the results of a diffusion tensor imaging (DTI) study with 12 hearing native speakers of English who were L2 learners of ASL, 12 deaf native signers of ASL who were L2 learners of English (mostly in the written form), and 3 deaf individuals who experienced extreme language deprivation throughout childhood and who experienced ASL as their first language in adolescence or early twenties.

There are two alternative hypotheses for the effects of the sensory-motor modality of language. One possibility is that deaf native signers establish both dorsal and ventral neural pathways for language processing, with the ultimate size and strength being indistinguishable from that of hearing speakers. Despite the modality difference, the neural correlates for sign language processing are very similar to those for spoken language processing. Lesion studies show that left perisylvian regions are required for sign language use (Hickok et al., 1998; Atkinson et al., 2005). In addition, neural imaging studies show that sign language tasks also activate fronto-temporal regions, especially the left IFG and the left posterior superior temporal lobe (Petitto et al., 2000; MacSweeney et al., 2002; Sakai et al., 2005; Mayberry et al., 2011; Leonard et al., 2012), which is similar to the language network reported for spoken language. Thus, it is likely that dorsal and ventral language pathways connecting IFG and the temporal cortex are also crucial for sign language processing. Alternatively, since sign languages use the visual modality to process linguistic information, there might be structural plasticity of language-related white matter connectivity, which may yield alternative pathways for sign language processing. If so, we would expect deaf native signers to show less robust connectivity for those pathways crucial for spoken language processing, such as AF-SLF and UF, but potentially more robust connectivity for pathways that link the visual cortex and the language regions, such as ILF and IFOF.

For the effects of early language experience, given that late L1 learners show deficits in morpho-syntactically complex structures (Newport, 1990; Mayberry and Eichen, 1991; Mayberry and Lock, 2003; Boudreault and Mayberry, 2006), we might expect to find main differences to be located within the dorsal pathways that are thought to be crucial for complex sentence development and processing. Alternatively, it is possible that both ventral and dorsal pathways are affected, considering the findings from Kim et al. (2009). Another less likely possibility is that development of the language pathways is solely biologically predetermined and unaffected by early language experience. If so, we would not observe any differences between late L1 learners and deaf native signers in terms of white matter connectivity.

MATERIALS AND METHODS

Participants

Twenty-seven adults participated in the study. The protocol was approved by the Institutional Review Board (IRB) of the University of California San Diego.

Two groups of deaf and hearing individuals with robust early language experience were scanned to examine the effects of sensory-motor modality in their early language experience. The group of deaf native signers consisted of twelve participants who were all born severely to profoundly deaf and acquired ASL as their first language from birth from their deaf parents (**Table 1**). The group of hearing participants consisted of twelve participants who were native English speakers and had taken 40 to 50 weeks of college-level ASL instruction (**Table 1**). All participants were right-handed adults with no history of neurological or psychological impairment. The hearing L2 signers speakers serve as a sensory-motor modality contrast for the deaf native signers. Like the native signers, they experienced language from birth albeit in the auditory-vocal modality instead of the visual-manual one. Because previous research has consistently shown insignificant white matter changes during young adulthood (Good et al., 2001; Brickman et al., 2006; Lebel and Beaulieu, 2011), we did not strictly control for age in these two groups. We compare the deaf native signers to the hearing L2 ASL signers, instead of monolingual English speakers, because the deaf native signers are all also bilingual in ASL and English (mostly in the written form).

Three individuals also participated in the current study as special cases, allowing us to examine how the presence/absence of early language experience affects the language pathways. These individuals were born deaf and experienced severe language deprivation throughout childhood. Their pseudonyms are Carlos, Shawna, and Martin. Due to various circumstances, these otherwise healthy deaf individuals were mainly raised

TABLE 1 | Summary of demographic information for each group.

Group	Number[1]	Age (sd)	L1 Modality	L1 Onset	L1 Duration (years)
Deaf native signers	12 (5)	33.33 (4.1)	Visuo-manual	Birth	Same as age
Hearing L2 signers	12 (11)	24.2 (3.9)	Auditory-oral	Birth	Same as age
Deaf late signers	Carlos	16	Visuo-manual	13	3
	Shawna	16	Visuo-manual	14	2
	Martin	51	Visuo-manual	21	30

[1]*Total number of participants in each group (female participants in the parentheses). For the deaf late signers, each special case is listed by pseudonym.*

at home with hearing, non-signing family members during childhood and so acquired neither spoken nor sign language and were illiterate. Carlos and Shawna began learning ASL at the age of 13 and 14, respectively, when they were immersed in the same sign language environment for the first time. They had fewer years of ASL exposure at the time of testing compared with Martin who began learning ASL in his 20 s and had 30 years of ASL experience at the time of testing.

Carlos was born into a hearing and non-signing family in another country and received no special services for deaf children, including schooling. He immigrated with family members to the United States at age 11. He was placed into a group home for deaf teenagers at age 13 years and 8 months, which was his first exposure to American Sign Language (ASL). At the time of scanning, he was 16 years and 10 months old, with 3 years and 2 months of daily exposure to ASL.

Shawna was raised by hearing and non-signing guardians and kept at home until the age of 12. She sporadically attended several schools, both deaf and mainstream, for a total of 16 months. At the age of 14 years and 7 months, she was placed into the same group home as Carlos, which marked her first language immersion experience. Shawna was 16 years and 9 months old at the time of scanning, with 2 years and 2 months of daily exposure to ASL.

Martin was born into a hearing and non-signing family in rural Mexico and attended no school until age of 21 when he learned some Mexican Sign Language at a school for deaf children. He immigrated to the United States at age 23, where he learned ASL. Since then, he has used ASL daily with deaf signers, including his wife, co-workers, and friends. At the time of scanning, he was 51 years old, with 30 years of sign language experience.

Elsewhere we have reported in detail on the language development and neurolinguistic processing of these case studies. Despite wide variation in their early home environments, these three cases of childhood language deprivation showed similar patterns of ASL acquisition (Ramírez et al., 2013; Cheng and Mayberry, 2019). They can comprehend some basic syntactic structures but show difficulties with morpho-syntax and complex sentence structures. Their neural activation patterns in response to single ASL signs primed with pictures was imaged with anatomically constrained Magnetoencephalography (aMEG). All three cases showed atypical localization patterns for single signs in comparison to deaf native and hearing L2 signers (Ferjan Ramirez et al., 2014, 2016; Mayberry et al., 2018).

Table 1 summarizes the demographic information of the deaf native signer group, the hearing L2 group, and each deaf individual with delayed L1 onset.

Image Acquisition

MRI scans were performed at the UCSD Radiology Imaging Laboratory on a General Electric 1.5 Tesla EXCITE HD scanner with an eight-channel phased-array head coil. Four scans were conducted, including one conventional three-plane localizer, one T1 weighted anatomical scan using IR-SPGR sequence with prospective motion (PROMO) correction, one diffusion-weighted scan using single-shot echo-planar sequence with isotropic 2.5 mm voxels and 30 diffusion gradient directions using *b*-value of 1000 s/mm2 (TE/TR 80.4 ms/14,300 ms), and one non-diffusion-weighted (T2) scan using fast spin echo sequence with prospective motion correction.

Image Processing and Fiber Tracking

For preprocessing, T1-weighted images were corrected for non-linear warping (Jovicich et al., 2006) and spatial sensitivity inhomogeneities (Hagler et al., 2009) using customized processing stream written in MATLAB. As for the diffusion-weighted images, we performed four pre-processing steps, including motion correction (Hagler et al., 2009), eddy current correction (Zhuang et al., 2006), b0 distortion correction (Chang et al., 2012), and gradient non-linearity correction (Jovicich et al., 2006).

We fit the diffusion tensors (DTs) and diagonalized the DT matrices using singular value decomposition to obtain three eigenvectors and their corresponding eigenvalues. We then calculated the fractional anisotropy (FA) ratio from the eigenvalues.

We used a probabilistic tract atlas (Hagler et al., 2009) to identify tracts of interest. We chose to use a probabilistic fiber tracking method instead of a deterministic method because it can better handle the problem of crossing fibers and stray fibers and avoids the subjectivity involved in manually selecting ROI seeds. This atlas has been used across different populations including healthy adults with an age range of 21 to 80 (Perry et al., 2009), epilepsy patients (Hagler et al., 2009), young children and adolescents with an age range of 3 to 20 (Jernigan et al., 2016), and typical and autistic toddlers with an age range of 1 to 4 years (Solso et al., 2016).

The atlas used manually identified three-dimensional maps of streamline fiber counts in 42 individuals together with their T1-weighted images to create co-registered, normalized, average fiber density maps, which provide probabilistic information about the locations and orientations of 23 fiber tracts. Fiber tracts were first manually identified for each individual in DTI Studio (Mori et al., 2005) using multiple ROIs to select a population of streamlines that followed the paths known from anatomy (Wakana et al., 2004), mainly following a 2-ROI approach with the addition of subsequent multiple 'NOT' ROIs to remove extraneous fibers that are not a part of the pathway. The goal is to reliably reconstruct fiber bundles that are anatomically accurate with a focus on the core of the fiber bundle. Next, normalized and averaged three-dimensional maps of streamline fiber counts were generated as fiber density maps and co-registered with the common T1 space. Cross-subject average tensors were calculated to provide information about the range of possible diffusion orientations at each location in atlas space. The atlas therefore provides probabilistic information about the locations and orientations of each fiber tract.

Based on previous studies (Hickok and Poeppel, 2004, 2007; Parker and Brorson, 2005; Saur et al., 2008; Friederici, 2009; Dick and Tremblay, 2012; Price, 2012), we selected four fiber tracts from the atlas as relevant long-range pathways for language, namely AF (the direct long segment of the SLF-AF complex), IFOF, ILF, and UF.

So far there is no consensus on the anatomical classification of the SLF-AF complex, and different subcomponents have been proposed, but their functions are still under debate. In the current study, we only looked at the long segment that directly connects the frontal and the temporal regions, as described in the delineation methods, because this is the classic dorsal AF pathway that has been extensively studied in terms of anatomical structures and functions.

One ventral pathway, EmC, was not included here. There are limited anatomical studies on the human EmC, and it is difficult to reliably reconstruct this fiber tract and delineate it from neighboring tracts such as the external capsule, IFOF, and UF. This pathway is not available in most major DTI atlases due to a lack of reliable means to identify it using the 2-ROI approach. Therefore, we omitted this pathway in the current study to ensure that we could delineate the correct fiber tracts.

Below we describe how the selected fiber tracts were manually delineated in DTI Studio based on the documentation from the probabilistic tract atlas.

The AF was manually delineated by the following steps. First, the most inferior axial slice in which the fornix could be seen as a single structure was identified. On the same axial slice, the anterior-posterior midpoint of the posterior limb of the internal capsule was identified, and a coronal slice at this midpoint was chosen. On this slice, an 'OR' ROI was selected by choosing the superolateral area just lateral to the posterior limb of the internal capsule including all superior and lateral gyri coming from this core. Next, the midpoint of the splenium of the corpus callosum in a coronal slice was identified, and an "AND" ROI was drawn around the entire ipsilateral hemisphere. In addition, "NOT" ROIs were selected to avoid fibers extending into the external capsule, fibers extending inferiorly through the brainstem, and fibers extending through the cingulum. Next, the anterior commissure was identified in an axial slice and the visible fibers lateral to the sagittal striatum were selected as an "AND" ROI, while 'NOT' ROIs were selected to avoid fibers extending superiorly to the parietal lobe and through the cingulum.

The IFOF was manually delineated by the following steps. First, the anterior-posterior midpoint in a coronal slice between the posterior edge of the splenium of the corpus callosum and the occipital pole was identified. An "OR" ROI was drawn around the occipital lobe, inferior to the parietal-occipital sulcus. Next, the most anterior edge of the genu of the corpus callosum was identified in a coronal slice, and an "AND" ROI was drawn around the entire ipsilateral hemisphere. In addition, "NOT" ROIs were selected to avoid fibers extending superiorly and posteriorly beyond the parietal-occipital sulcus and extending through the thalamus.

The ILF was delineated by the following steps. First, the most posterior coronal slice in which the cingulum was visible was selected, and an 'OR' ROI around the entire hemisphere was selected. Next, the most posterior coronal slice in which the temporal lobe was visibly distinct from the frontal lobe was selected, and an "AND" ROI was drawn around the entire temporal lobe. In addition, "NOT" ROIs were selected to avoid fibers extending to the contralateral hemisphere at the mid-sagittal line, fibers extending superiorly to the parietal lobe beyond the parietal-occipital sulcus, and fibers extending anteriorly that terminate in the frontal lobe.

The UF was delineated by the following steps. First, the most posterior coronal slice in which the temporal lobe was visibly distinct from the frontal lobe was selected, and an "OR" ROI was drawn around the entire temporal lobe, and another "AND" ROI was drawn around the external capsule. In addition, "NOT" ROIs were selected to avoid fibers extending posteriorly from the main bundle of the uncinate and short fibers at the temporal stem that did not fully extend into the temporal and frontal lobes.

Using Freesurfer (Dale et al., 1999), we first non-linearly morphed individual T1-weighted images to align with the atlas space using the method of discrete cosine transforms (Friston et al., 1995). Diffusion-weighted images were first rigid-body-registered to corresponding T1-weighted images resampled to atlas space, and then further registered using joint probability density function (JPDF) method (Leventon and Grimson, 1998). Next, *a posteriori* probability of a voxel belonging to a given fiber tract was estimated given the first eigenvector derived from DT calculations together with the location information (i.e., fiber probability given location alone) and the orientation information (i.e., fiber probability given the DT first eigenvector and the atlas average of DTs rotated and warped into single subject space) from the co-registered and normalized fiber density maps. A probability threshold (relative fiber probability >0.08) was applied following Hagler et al. (2009) to derive regions of interests (ROIs) for each target fibers. This threshold was determined in Hagler et al. (2009) by testing a range of thresholds and choosing the threshold that provided the smallest difference in fiber volumes between manually selected and atlas-derived fiber masks across all subjects and fibers. Finally, the weighted averages of FA was calculated for each fiber tract (Hua et al., 2008). More details of this automated white matter tracking method can be found in Hagler et al. (2009).

Figure 1 shows the locations of these fiber tracts in the left hemisphere found in a deaf native signer participant. We examined these tracts in both right and left hemispheres to examine for possible lateralization effects.

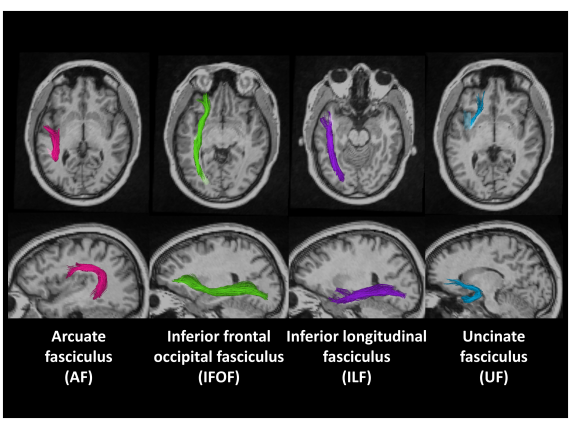

FIGURE 1 | Region of interests (ROIs) of four fiber tracts derived using probabilistic tract atlas in the left hemisphere of one deaf native subject.

Statistical Analyses

We used the lme4 package (Bates et al., 2012) in R (R Core Team, 2012) to conduct analyses of variance (ANOVA) tests between the deaf and hearing infant-language experience groups, using the mean FA values of each fiber tract of each individual. We also calculated the z-scores of mean FA for the deaf participants in R.

RESULTS

Effects of Early Language Modality

First, we investigated the effects of the sensory-motor modality of language by comparing the data from the deaf native signers with that of the hearing native English speakers, L2 signers. The deaf and hearing participants show very similar FA values in all fiber tracts in both hemispheres, with close median values and a similar degree of variance (**Figure 2**). Also, for both groups the FA values in the left hemisphere appear to be higher than those in the right hemisphere. We conducted an Analysis of Variance (ANOVA) test with FA value as the dependent measure, group as the between-subjects fixed effect, fiber tract and hemisphere as within-subjects fixed effects, and gender and age as between-subjects covariates. After controlling for gender ($F(1, 174) = 2.596$, $p = 0.108$) and age ($F(1, 174) = 2.924$, $p = 0.089$) effects, the results showed a significant difference among fiber tracts ($F(3, 174) = 60.770$, $p < 0.001$), a difference between hemispheres ($F(1,174) = 14.689$, $p < 0.001$) with lower FA in the right hemisphere, a trend toward interaction between fiber tract and hemisphere ($F(3, 174) = 2.389$, $p = 0.070$), but no difference between the groups ($F(1, 22) = 0.094$, $p = 0.759$), and no interactions between group and fiber tract ($F(3,174) = 0.261$, $p = 0.853$), group and hemisphere ($F(1, 174) = 0.036$, $p = 0.848$), or between group, fiber tract and hemisphere ($F(3,174) = 0.173$, $p = 0.914$).

These results indicate that, in general, there is left lateralization of language-relevant tracts in deaf and hearing participants alike, despite differences in the sensory-motor modality of their infant language experience. In addition, the trend for interaction between fiber tract and hemisphere suggests that the degree of lateralization might be slightly different for each fiber tract.

To examine the nature of this trend, we conducted ANOVA tests for each fiber tract with FA as the dependent measure, group as the between-subjects fixed effect, hemisphere as within-subjects fixed effects, and gender and age as between-subjects covariates. We found a strong left lateralization effect for AF ($F(1, 42) = 10.842$, $p = 0.002$) and ILF ($F(1, 42) = 8.832$, $p = 0.004$), but no lateralization effect for IFOF ($F(1, 42) = 2.210$, $p = 0.144$) and UF ($F(1, 42) = 0.004$, $p = 0.949$). Again, no group or interaction effects between group and hemisphere were observed in any of the tracts.

These findings confirm in the present data set that the dorsal AF shows left lateralization reported in the literature. In addition, we found one ventral pathway, ILF, to also show left lateralization, while the other two ventral pathways appear to be more bilateral. Crucially, these lateralization patterns are shared by both deaf and hearing participants, suggesting that language modality is not a factor in these laterality effects.

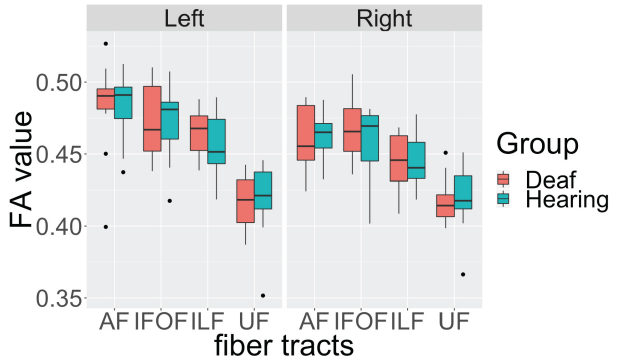

FIGURE 2 | Individual average fractional anisotropy (FA) values of hearing and deaf participants in arcuate fasciculate, AF, inferior frontal occipital fasciculus, IFOF, inferior longitudinal fasciculus, ILF, and uncinate fasciculus, UC, as a function of hemisphere showing no significant differences between the groups. The top of the box plot shows the higher quartile (25%), the black bar shows the median (50%), and the bottom of the box shows the lower quartile (75%); the black dots show outliers outside the 1.75 interquartile range.

One observation worth noting is that for the dorsal AF, two individuals from the deaf native signer group and one individual from the hearing speaker group, were below the 1.75 interquartile range of their respective group, but only in the left hemisphere. After examining their individual profiles, we noticed that these individuals all had higher FA values in the right hemisphere for the dorsal AF pathways. According to the literature (Catani et al., 2007; Lebel and Beaulieu, 2009), there are individual differences in the lateralization patterns of this pathway. Therefore, we speculate that these individuals show lower FA in the left hemisphere due to a right lateralization pattern.

Effects of Early Language Deprivation

Next, we investigated the effects of early language experience on language-relevant fiber tracts by first comparing the data from each of the three deaf case studies who matured without language to the deaf native signers and hearing native speakers who had language experience from birth. We used z-scores and interquartile ranges to estimate the differences between the language deprived cases and the two infant-language experience control groups. We then summarized the similarities and differences across these three cases.

Table 2 shows the z-scores of each deaf case study when calculated within the sample of both deaf native signers and hearing native speakers, 24 individuals in total who experienced language from birth. All three case studies showed decreased FA values in the dorsal AF pathway when compared to the language-from-birth control groups, while their FA values in the ventral pathways showed more individual variation.

Figure 3 shows the FA values of each deaf case in comparison to the interquartile range of the infant-language experience control group, including both deaf native signers and hearing native speakers. The FA values of all three late learners fell outside the infant-language experience control groups' 1.75 interquartile range for left dorsal AF pathway. Their FA values for AF in the right hemisphere were also lower than the infant-language

TABLE 2 | *z*-scores of three deaf case studies compared to the infant-language experience groups (N = 24).

Case name	AF		IFOF		ILF		UF	
	Left	Right	Left	Right	Left	Right	Left	Right
Carlos	−1.723*	−2.257*	0.083	−0.634	0.495	0.349	0.432	−0.544
Shawna	−0.903	−0.674	−0.343	0.462	0.735	1.391	1.898*	1.048
Martin	−1.110	−0.825	−0.7	−0.452	−2.65**	−1.652*	−0.777	−1.426

*One-tailed p-value < 0.05; **One-tailed p-value < 0.01.

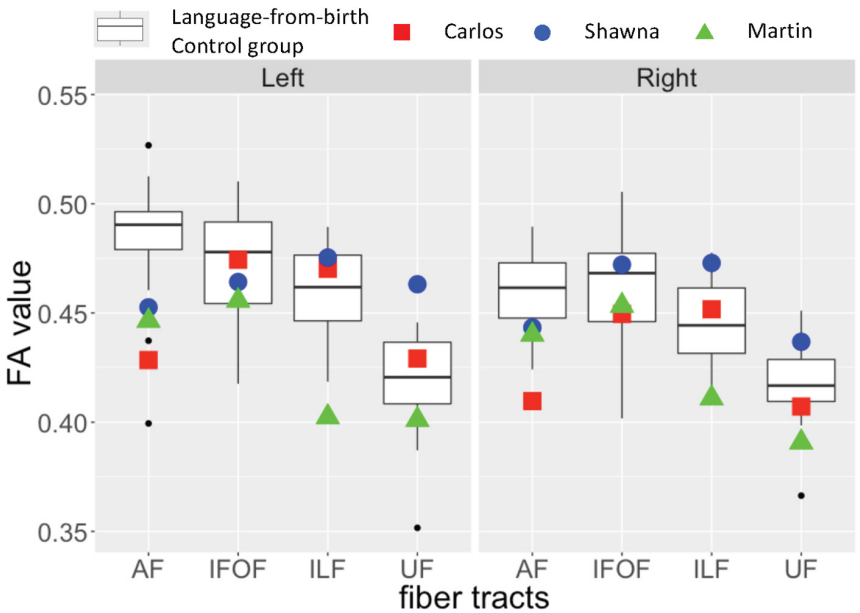

FIGURE 3 | Fractional anisotropy (FA) values for three deaf individuals with severe early language deprivation as a function of pathway and hemisphere. The box plots represent the distribution of FA values of the infant-language experience control groups (both native deaf signers and hearing native English speakers, N = 24); the plotted shapes show the values for each late L1 learner: Carlos – filled square; Shawna – filled circle; Martin – filled triangle (Carlos: AoA 13;8 with 3;2 years of experience; Shawna: AoA 14;7 with 2;2 years of experience; Martin: AoA 21 with 30 years of experience). The top of the box plot shows the higher quartile (25%), the black bar shows the median (50%) and the bottom of the box shows the lower quartile (75%); the black dots show outliers outside the 1.75 interquartile range.

experience control groups' interquartile range; only the FA values for Carlos fell outside the 1.75 interquartile range. As for the ventral pathways, the FA values of the case studies were either within normal range or showed more individual variations. Their FA values for bilateral IFOF were all within the interquartile range. For ILF, only the FA values for Martin were below the 1.75 interquartile range in both hemispheres. For UF, Shawna showed an FA value in the left hemisphere above the 1.75 interquartile range. Carlos showed normal FA values in both hemispheres. Martin showed FA values below the interquartile range in the left hemisphere and below the 1.75 interquartile range in the right hemisphere.

As discussed above in section "Effects of early language modality", some individuals from the infant-language experience control groups also showed decreased FA values in the left dorsal AF due to atypical lateralization patterns. Given that all three late learners showed slightly higher FA values in the left hemisphere for this pathway, and FA values in the right hemisphere that were closer to the interquartile range, we interpret their reduced FA values as revealing a lack of lateralization pattern due to early language deprivation in comparison to the outliers in the infant-language experience control groups who show right lateralization for these tracts.

DISCUSSION

With respect to the sensory-motor modality of language, we asked if deaf native signers and hearing native speakers would show similar microstructure of the language pathways despite differences in the sensory-motor modality of their early language. We observed no differences between the deaf and hearing groups for any of the four language-relevant pathways. This lack of differences supports the hypothesis that language modality does not affect the connectivity between major language regions when language acquisition begins in infancy.

Effects of neural cross modal plasticity due to sensory (auditory) deprivation among deaf individuals have been reported for some cognitive functions, such as general visuo-spatial working memory (Ding et al., 2015;

MacSweeney and Cardin, 2015; Cardin et al., 2018). With respect to language processing when a first language is acquired early on, however, the default language network is unaffected by language modality or sensory (auditory) deprivation (Petitto et al., 2000; MacSweeney et al., 2002; Sakai et al., 2005; Mayberry et al., 2011; Leonard et al., 2012). Our findings provide further evidence for the amodal nature of the language network when infants experience sufficient language during development and further extends them by showing that deafness *per se* does not affect development of the language pathways.

Our findings are also the first to demonstrate left lateralization of two language pathways, dorsal AF and ventral ILF, in deaf native signers, similar to the lateralization that has been consistently found for hearing native speakers (Büchel et al., 2004; Catani et al., 2007; Glasser and Rilling, 2008; Ocklenburg et al., 2013; Takao et al., 2013; Eichert et al., 2018; Panesar et al., 2018). We also found similar bilateral patterns for ventral IFOF and ventral UF in both the deaf and hearing control groups, findings that are also consistent with the literature (Kubicki et al., 2002; Ocklenburg et al., 2013; Takao et al., 2013; Hernando et al., 2015; Eichert et al., 2018).

Crucially, by comparing the data from the language-from-birth control group with that of the three case studies, we found specific effects of early language deprivation on the language pathways. Decreased FA values (below the 1.75 interquartile range) in the left dorsal AF pathway were observed in each of the three cases when compared to the language-from-birth control groups. Given the strong left lateralization patterns observed among the language-from-birth control groups, it appears that the lower FA values in left AF in each case study are due to reduced laterality.

These findings are also consistent with the literature on the relation between the dorsal pathway and the ability to learn and process complex linguistic structures. As explained in the introduction, the dorsal stream is often associated with syntactic processing performance as previously found for typically developing children (Skeide et al., 2016), children with specific language impairment (Verhoeven et al., 2012), and aphasic patients (Wilson et al., 2011). The present study extends these findings to deaf people with early language deprivation, suggesting that their limited syntactic performance may be associated with connectivity deficits in dorsal pathways.

As for the ventral pathways, we observed more individual variations. Martin showed decreased FA values (below the 1.75 interquartile range) in bilateral ILF and in right UF compared to the language-from-birth control groups, while Carlos and Shawna did not show such effects. There are several possibilities for the individual variation in these ventral pathways. One possibility is that the ventral pathways are not as sensitive to a lack of early language experience as the dorsal pathways and remain plastic even after puberty. Martin did not begin to learn language until the age of 21. Carlos and Shawna both began to learn language at the ages of 13 and 14, respectively. In a neuroimaging study of lexico-semantic processing, Carlos and Shawna showed some activation in perisylvian language areas to familiar ASL signs primed with pictures (Ferjan Ramirez et al., 2016). By contrast, Martin showed almost no activation in bilateral temporal language areas, despite performing nearly as accurately and quickly as the deaf native signers, hearing L2 signers, and the other case studies (Mayberry et al., 2018). Thus, it is possible that these individual differences reflect a gradient effect of the duration of language deprivation in childhood and adolescence on the development of the ventral language pathways that potentially mediate lexico-semantic processing. Another possibility for the lack of clear effects of early language deprivation across ventral pathways is that they can be shaped by non-linguistic experience. Because ventral pathways are often associated with constructing meaning, as well as other non-linguistic functions such as complex object processing, late L1 learners may have gradually established these pathways through non-verbal communication and conceptual learning through daily life experience despite the lack of language in the environment. Future studies with a larger sample size and longitudinal observations are required to test these hypotheses.

One caveat in interpreting the present results is that the age of all three late signers was either younger or older than that of the control groups, falling at either the lower or the higher ends of the age range of stable white matter microstructure. However, given the facts that the IFOF often shows a similar trajectory of FA change as a function of age compared to other tracts (Lebel et al., 2008), and that all three cases had normal FA values in bilateral IFOF, we interpret the differences between the cases and the control groups as being more likely due to early language deprivation than simply age.

Another caveat is that Carlos and Shawna only had 2 to 3 years of ASL experience at the time of scanning, so that further neural plasticity induced by late language acquisition might still be possible. We plan to conduct follow-up DTI scans to address this issue. Still, given their limited ultimate attainment of ASL after substantially longer years of exposure, we expect less plasticity in their language pathways even with increased years of language use.

Research has found that deaf children with no formal sign language input often develop their own gestural system to communicate with their family members known as homesign (Goldin-Meadow and Feldman, 1977; Goldin-Meadow and Mylander, 1998). Whether the sophistication of the homesign system the deaf child develops with the family is related to their subsequent sign language development is unknown. Martin reported communicating with a hearing sister with gesture when living at home (Mayberry et al., 2018). Neither Carlos nor Shawna were reported by the knowledgeable professionals working with them to use homesign when they were initially placed in a residential sign language situation (Ferjan Ramirez et al., 2014), but doing so may not have been communicatively useful for them. Although homesign has been found to share some linguistic properties with language (Bates et al., 2012), it has also been observed to be used primarily as an expressive means of communication by the deaf child whose family members may neither fully comprehend nor use it in the same way (Carrigan and Coppola, 2017), thus limiting its potential to circumvent the effects of a lack of linguistic experience for the developing child (Morford and Hänel-Faulhaber, 2011).

The present findings also provide an explanation for some inconsistencies in the literature on white matter connectivity in deaf individuals. Kim et al. (2009) identified more extensive regions with white matter deficits, including non-auditory regions within language-related pathways, while Li et al. (2012) and Karns et al. (2017) found differences only within auditory regions. By explicitly comparing deaf native signers and well-studied cases of extreme delay in the onset of language experience, our findings suggest that the variable results of previous studies are likely due to the diverse language backgrounds that would be characteristic of any randomly selected sample of deaf individuals. Given that Kim et al. (2009) did not report the language backgrounds of their deaf participants, and they also found FA deficits in language-related pathways such as SLF, it is highly probable that their deaf participants experienced language deprivation during childhood, similar to the cases we studied here.

Our findings also shed light on the potential mechanisms of critical period effects for language development. Previous studies have reported selective critical period effects on morphologically and syntactically complex structures (Newport, 1990; Mayberry and Lock, 2003; Boudreault and Mayberry, 2006; Cormier et al., 2012) as well as decreased functional activation in several language regions (Mayberry et al., 2011, 2018; Ferjan Ramirez et al., 2014, 2016). However, it remained unclear how these language and neural outcomes were being influenced by early language experience. The present study shows that the case studies who suffered language deprivation during childhood developed less robust connections between language regions, especially in the dorsal stream. Given the association between dorsal pathways and syntactic processing, a coherent interpretation of the linguistic and neural activation data across these studies is that early language experience is crucial for the growth of the dorsal stream for language processing, linking various functional language regions, and thus facilitating the acquisition and processing of complex syntactic structures. Missing the critical time window for linguistic experience appears to affect development of the dorsal stream, which, in turn, creates deficits in language and neural outcomes, especially with respect to complex morpho-syntactic structures.

To conclude, in the present study we examined white matter microstructure of two groups of individuals with infant language experience, deaf native signers and hearing native speakers who were L2 signers, with three individual cases of childhood language deprivation, individuals who had little access to any kind of language until puberty or after. Our findings indicated that these cases had altered microstructure in some language-related pathways, especially in the left AF, when compared to deaf native signers. At the same time, deaf native signers of ASL showed similar connectivity within language-related pathways compared with hearing native speakers of English. Together these findings suggest that full growth of the brain language pathways requires early language experience during childhood. Language experience in early life appears to be crucial for the language system to become robustly connected as observed in the canonical mature state, regardless of its sensory-motor modality.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The UCSD Human Research Protections Program (HRPP). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

QC contributed to the study concept and design, data analysis, and wrote the manuscript. AR contributed to the neuroimaging methods and image processing. EH contributed to the study concept and design, data collection, and study supervision. RM contributed to the study concept and design, data collection, study supervision, and revised the manuscript.

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CASE REPORT
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Linking Early Life Hypothalamic–Pituitary–Adrenal Axis Functioning, Brain Asymmetries, and Personality Traits in Dyslexia: An Informative Case Study

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Developmental dyslexia (DD) is a multi-system disorder, combining influences of susceptibility genes and environmental factors. The causative interaction between specific genetic factors, brain regions, and personality/mental disorders, as well as specific learning disabilities, has been thoroughly investigated with regard to the approach of developing a multifaceted diagnostic procedure with an intervention strategy potential. In an attempt to add new translational evidence to the interconnection of the above factors in the occurrence of DD, we performed a combinatorial analysis of brain asymmetries, personality traits, cognitive and learning skills, and expression profiles of selected genes in an adult, early diagnosed with DD, and in his son of typical development. We focused on the expression of genes, based on the assumption that the regulation of transcription may be affected by genetic and epigenetic factors. The results highlighted a potential chain link between neuroplasticity-related as well as stress-related genes, such as BDNF, Sox4, mineralocorticoid receptor (MR), and GILZ, leftward asymmetries in the amygdala and selective cerebellum lobules, and tendencies for personality disorders and dyslexia. This correlation may reflect the presence of a specific neuro-epigenetic component of DD, ensuing from the continuous, multifaceted difficulties in the acquisition of cognitive and learning skills, which in turn may act as a fostering mechanism for the onset of long-term disorders. This is in line with recent findings demonstrating a dysfunction in processes supported by rapid neural

adaptation in children and adults with dyslexia. Accordingly, the co-evaluation of all the above parameters may indicate a stress-related dyslexia endophenotype that should be carefully considered for a more integrated diagnosis and effective intervention.

Keywords: dyslexia, brain asymmetries, stress, hypothalamic–pituitary–adrenal (HPA) axis, neuroplasticity genes, BDNF, MR

INTRODUCTION

Developmental dyslexia (DD) is a multi-system neurodevelopmental disorder that affects the ability of individuals to acquire specific learning skills, such as reading, writing, and spelling, despite having normal intelligence, perception instruction, sensory abilities, motivation, and educational opportunities (Spironelli et al., 2008; Peterson and Pennington, 2012; Langer et al., 2017). In the DSM-5^{TM} handbook of differential diagnosis, the term DD is incorporated in an extensive designation, i.e., that of Specific Learning Disorder (SLD; American Psychiatric Association, 2013). In this article, we opt for the term DD since both the diagnostic elements and the bibliographic data are documented according to this terminology.

BACKGROUND

Personality and DD: Psycho-emotional and Behavioral Outcomes

As originally advocated by Pennington (2006), a new conceptualization of investigating the complex substrate of DD proposes that the association between genetic, neurological, cognitive, psycho-emotional, and behavioral factors as well as their potential involvement in the onset of the symptoms and their continuity during development could better clarify the underlying components of the disease (Zakopoulou et al., 2014; Perrachione et al., 2016; Zoccolotti et al., 2016). DD often shows co-occurrence [Kaplan et al., 2006; also named co-existence (Gillberg, 2010) or comorbidity (Ramus et al., 2013; Ashraf and Najam, 2017)] with other disturbances, and shares common genetic factors with other mental disorders (Grigorenko, 2001; Pennington, 2006). In the context of dyslexia research, the emerging relationship between continuous learning difficulties and personality traits (personality characteristics affecting a person's behavior, thoughts, and feelings across situations, such as openness to experience, agreeableness, and neuroticism) is of increasing interest (Mason and Mason, 2005; Swanson and Hsieh, 2009; Tsitsas, 2017). Several independent studies support the notion that the frustration and difficulties caused by learning problems *per se*, both at home and in school, create continuous fear of failure or actual failure, sadness, inadequacy, reduced happiness and self-esteem, anxiety, emotional vulnerability, embarrassment, defensive behaviors, as well as withdrawal (Huc-Chabrolle et al., 2010; Zakopoulou et al., 2013; Bonifacci et al., 2016; Mammarella et al., 2016). Similarly, high levels of tension, anxiety, and depression in students and adolescents with learning disorders (LD) have been reported (Wilson et al., 2009; Panicker and Chelliah, 2016), while Lufi and Awwad (2013) have documented a high probability of test anxiety for adults with LD. Moreover, a significantly lower level of psychosocial health was reported recently for children with LD (Matteucci et al., 2019), and further, in addition to anxiety, such children may have attentional biases specific to reading (Haft et al., 2019), a situation that may, in turn, perpetuate anxiety (Bar-Haim et al., 2007), emphasizing the importance of individualized interventions, considering the psycho- and socio-emotional difficulties in this population.

Stress-HPA Axis, Neuroplasticity, and Epigenetic Reprogramming

Epigenetic mechanisms play a crucial role in the adaptive regulation of gene expression during postnatal life (Rutten and Mill, 2009; Szulwach et al., 2011). Numerous studies investigating the multidisciplinary phenotype of DD support the notion that early or longitudinal experiences of stress (prenatal and antenatal maternal stress, adult social stress) interact with neuroendocrine effectiveness in stressful social behavior and cognitive ability (Gudsnuk and Champagne, 2012; Li et al., 2013; Hostinar et al., 2015; D'Souza et al., 2016). Stress is capable of altering neurotransmission and synaptic plasticity in hypothalamic–pituitary–adrenal (HPA) axis-associated brain regions such as those of the prefrontal cortex (PFC), hippocampus, and amygdala (Gardner et al., 2009; van Bodegom et al., 2017). These regions are all targets of stress hormones known to be involved in dyslexia (Van den Bergh, 2011; Vogel and Schwabe, 2016). Stress exposure activates the HPA axis, resulting in elevation of blood glucocorticoid (GC) levels. The HPA axis is essential for successful adaptation to stress, and its dysfunction, combined with chronic stress exposure, especially early in life, may act as a triggering mechanism that could lead to the development of psychopathology (McEwen and Gianaros, 2011; Buschdorf and Meaney, 2015). GCs bind to two receptor types in the brain, mineralocorticoid receptor (MR) and glucocorticoid receptor (GR), both of which reside in the cytosol and upon GC-binding translocate to the nucleus where they regulate transcription by binding to GC-responsive elements of target genes (Pearce and Yamamoto, 1993). MR and GR mediate the initiation and termination of the HPA axis stress response and modulate acquisition, consolidation, storage, and retrieval of stressful experiences (Sapolsky et al., 2000; Kino and Chrousos, 2004; Montaron et al., 2006; Reul et al., 2015). *GILZ* has been used as an HPA axis activity measure. Its expression in peripheral blood decreases in chronic stress and social defeat and is correlated with smaller hippocampal volumes (Frodl et al., 2012). BDNF (brain-derived neurotrophic

factor) is a key neurotrophic factor implicated in learning and memory, but also in neural plasticity in the amygdala (Rattiner et al., 2005; Cowansage et al., 2010). Mutations in its receptor have been shown to modulate acquisition and consolidation of fear learning (Musumeci et al., 2009). Adult neurogenesis, the birth of new neurons in the adult brain, is considered highly sensitive to environmental stressors (Karten et al., 2005) such as those specifically encountered in learning disabilities/dyslexia. The SoxC proteins play an important role in the genetic network controlling neuronal differentiation in adult neurogenesis, while Sox4 regulates the establishment of neuronal properties and specification of cell fate (Mu et al., 2012).

The Neural-Systems Framework-Brain Asymmetries

Previous neuroimaging studies using functional MRI (fMRI; Shaywitz et al., 2002, 2004) and positron emission tomography (PET; Paulesu et al., 2014) when investigating both children and adults with dyslexia compared to control subjects reported hypo-activity in the left inferior parietal lobe and/or hyperactivity in the left inferior frontal gyrus during phonological awareness tasks such as rhyming judgments. Moreover, original voxel-based morphometry (VBM) studies unequivocally established the involvement of the posterior cerebellum in dyslexia, namely, lobules V, VI, and VII in reading difficulties (Carreiras et al., 2007), Crus I and II in semantic processing, and VIIB in cognitive tasks (Ruz et al., 2005).

Atypical abnormalities of the activity in the left temporal–occipital brain area may play a major role in the recognition of words and the accomplishment of phonological tasks (Kita et al., 2013). These atypical brain activities might underpin impaired phonological awareness in people with dyslexia. However, results from recent studies suggest that the differences found in multiple regions of the dyslexic brains indicate that cerebellar function is not the primary cause of dyslexia, but is rather a fundamental neurodevelopmental abnormality (Perrachione et al., 2016). Various investigations on animals and humans (Kim et al., 2011) testing the performance in cognitive or emotional tasks confirmed a structural and widespread reciprocal connectivity (Freese and Amaral, 2009) between the amygdala, hypothalamus, and ventromedial prefrontal cortex (vmPFC) in the regulation of emotions and social behavior (Arnsten, 2009; Schumann et al., 2009). During threat or uncertainty, the amygdala is activated under tonic inhibitory control from the PFC, having as a result the PFC to be hypoactive (Hänsel and von Känel, 2008; Thayer and Lane, 2009). Structural and functional brain asymmetries have been found in a number of prefrontal areas, mostly in adolescents and males, suggesting that these asymmetries may render them more vulnerable to certain disorders such as autism and dyslexia (Huster et al., 2007; Whittle et al., 2008).

Aim of the Present Study

In this study, we examined whether early stress and stressful learning experiences may constitute underlying predisposing components in the occurrence of DD (Eckert, 2004), in the case of an adult man (GA) diagnosed early with DD, with reported difficulties in manipulating strong emotional situations, and impulsive behavior, even though he presented an endearing personality.

To confirm that GA fulfilled the diagnostic criteria for DD, the DAST test (Fawcett and Nicholson, 1998) was implemented. An "at-risk" profile for dyslexia was highlighted, indicating weaknesses in specific areas related to learning (phonological processing; processing speed; language processing; visual-spatial processing). Moreover, the psychological test MMPI, assessing personality traits and psychopathology (Hathaway and McKinley, 1951), was conducted to check for any possible co-existing disorders. According to this analysis, the psychological profile of the patient showed the characteristics of fearful people with poor self-image and intense anxiety, who find it hard to relax and overcome their fears.

The psychological assessment was complemented with MRI and three-dimensional surface rendering techniques. Taking into account previous evidence showing a reduction of gray matter in specific cerebellar regions associated with DD or other types of dyslexia, such as inferior frontal gyrus, precentral gyrus, medial occipital gyri, frontal and occipital lobes, insula and basal ganglia (Brambati et al., 2004; Zadina et al., 2006), a VBM analysis was performed to investigate potential global volumetric changes in relevant brain regions. This analysis revealed anomalous leftward anatomical asymmetries, consistent with other studies in dyslexic brains (Stoodley and Stein, 2011).

Stressful conditions and experiences have been associated with alterations of HPA axis- and neuroplasticity-related genes, such as the nuclear receptors MR and GR, and the neurotrophin BDNF *via* epigenetic mechanisms (de Kloet et al., 2005; Unternaehrer et al., 2012). In our analysis, we also included the genes for *Ube3A* (Ubiquitin-protein ligase E3A), a transcriptional coactivator of steroid hormone receptors associated with neurodevelopmental syndromes and psychological conditions (LaSalle et al., 2015), and *GILZ* (GC-induced leucine-zipper), a GR/MR-responsive gene that contributes significantly to neural activation and transmitter release and has been linked to HPA axis dysfunction and psychosocial stress (Srinivasan and Lahiri, 2017). Finally, we also monitored genes that are important for neuroplasticity and neurogenesis such as the aforementioned *BDNF* and *Sox4* (Bergsland et al., 2006; Mu et al., 2012). We compared the expression levels of the above genes using whole blood RNA from the patient and his 25-year-old son, a healthy individual, with normal reading ability. This test was repeated 1 year later. As detailed below, the results revealed significant and consistent differences in the mRNA levels of these genes between the two samples that could be related to potential pathological mechanisms underlying this disorder and may encourage the use of such genes as potential peripheral blood-based biomarkers.

GA Case History

GA is a 56-year-old man, right-handed, diagnosed early with DD. According to his medical history and physical

TABLE 1 | Scores of GA in the DAST and MMPI analyses.

The Dyslexia Adult Screening Test (DAST) GA's profile			
Tasks assessed	**Scores**	**"At Risk" Index scores**	**Interpreted scores**
Rapid Naming	40	—	Very Strong Indicator
One Minute Reading	68	–	Strong Indicator
Postural Stability	2	-	Indicator
Phonemic Segmentation	5	—	Very Strong Indicator
Two Minute Spelling	22	–	Strong Indicator
Backwards Span	5	-	Indicator
Nonsense Passage	82	-	Indicator
Nonverbal Reasoning	3	–	Strong Indicator
One Minute Writing	30	0	Normal Band
Verbal Fluency	11	-	Indicator
Semantic Fluency	33	+	Above Average
"At Risk" score		**14**	
"At Risk" Quotient (ARQ)		**1,2**	**Strong "At Risk" Indicator**

The Minnesota Multiphasic Personality Inventory (MMPI) GA's profile		
Raw scores and *T*-scores of MMPI scales		
	Raw scores	***T*-scores**
Validity Scales		
F (Infrequency)	8	53
L (Lie)	2	32
K (Correction)	9	40
Clinical Scales		
Hypochondriasis (Hs); Scale 1	12	46
Depression (D); Scale 2	18	41
Conversion Hysteria (Hy); Scale 3	15	43
Psychopathic Deviate (Pd); Scale 4	23	54
Masculinity-Femininity (Mf); Scale 5	26	51
Paranoia (Pa); Scale 6	11	54
Psychasthenia (Pt); Scale 7	29	**55**
Schizophrenia (Sc); Scale 8	26	50
Hypomania (Ma); Scale 9	25	**62**
Social Introversion (Si); Scale 0	28	50
Case Profile	**Code type: 9-7/7-9**	

DAST: very severe difficulties (—) were recorded in the tasks of Rapid Naming and Phonemic Segmentation, while serious problems (–) were pointed out in One Minute Reading, Two Minute Spelling, and Nonverbal Reasoning, respectively. Noticeable problems (-) were observed in Postural Stability, Backwards Span, Nonsense Passage, and Verbal Fluency. The "At Risk" Quotient (>1.0) indicates that GA is strongly at risk of dyslexia. MMPI: profile of the scores on all of the MMPI scales. The patient obtained low T-scores in two validity (L and K) and two clinical scales (D and Hy), while moderate T-scores were recorded in one validity (F) and eight clinical scales (Hs, Pd, Mf, Pa, Pt, Sc, Ma, and Si). The two-point code type was determined by the highest two scales (shown in bold). T-scores were moderately elevated for Psychasthenia and Mania scale; however, none of the clinical scales showed elevations above 70.

examination, GA was physically healthy, without any history of neurologic, psychiatric, or otherwise chronic diseases. The developmental history provided information about GA's significant, persistent difficulties in reading, writing, and spelling since school age, class repetition, and failure in the national, university entry, examinations. Despite his severe learning disabilities, GA managed to complete his studies and obtain a PhD, and today he is a well-known scientist. However, as became obvious from the clinical interview, his high academic performance was achieved as a result of persistent and intense effort.

GA was referred to the neurological clinic because of visual abnormalities without any coexistent pathology. The brain imaging data and his early life history suggested a complex profile, demanding a more detailed investigation.

An informed consent document was signed by GA and his son, in accordance with the principles of the Declaration of Helsinki.

MATERIALS AND METHODS

See **Supplementary File S1** for Materials and Methods.

RESULTS AND DISCUSSION

According to the DAST analysis, GA's profile indicates very severe difficulties (—) with Rapid Naming and Phonemic Segmentation together with serious problems (—) in One Minute Reading, One Minute Spelling, and Nonverbal Reasoning. Noticeable problems (-) were observed in Postural Stability, Backwards Span, Nonsense Passage, and Verbal Fluency. Relatively good performance (0) was recorded in Writing, while above average performance (+) was recorded in Semantic Fluency. The results ("At Risk" Quotient >1.0) indicate that GA is strongly at risk of dyslexia (**Table 1**), highlighting his impairments not only in reading and writing skills but also in other

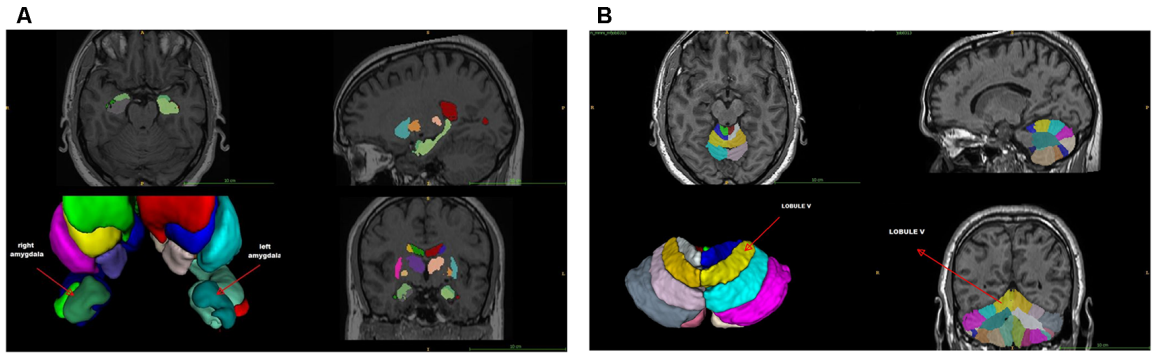

FIGURE 1 | (A) Voxel-based morphometry (VMB) analysis of the cerebrum. **(B)** VBM lobular analysis of the cerebellum. The location of lobule V is shown (arrow).

cognitive processes [(meta)phonological awareness, memory, reasoning; Callens et al., 2012; Tops et al., 2013]. Considering the MMPI profile, moderate and low *T* scores in specific scales revealed a personality profile, with mild symptoms of anxiety and tension [two-point code type: 9-7/7-9, corresponding to Mania scale (Ma) and Psychasthenia scale (Pt)], although without symptoms of hypo-mania (or mania), or other forms of psychopathology (**Table 1**). This is a relatively rare code type that describes people with phobias, who tend to be self-centered and often immature. They may have periods of impulsive-reckless behavior that are a frequent cause of difficulties in interpersonal relationships. These results were combined with the patient's history information and clinical characteristics, obtained in the context of a clinical interview.

The VBM analysis (**Supplementary Table S1**) revealed a smaller left amygdala volume compared to age- and sex-matched controls (GA: 0.03 vs. normal range 0.05–0.07), whereas the overall volume of the amygdala was close to the lowest normal value (GA: 0.08 vs. normal range 0.09–0.14). Indeed, the asymmetry index (calculated as the difference between right and left volumes divided by their mean) revealed a significant amygdala asymmetry (GA: +39.59 vs. normal range −16.41/+18.62; **Figure 1A** and **Supplementary Table S1**). No other significant differences were found (**Supplementary Table S1**). With regard to the cerebellum, the VBM lobular analysis showed that each lobule V was increased compared to controls (total; GA: 0.62 vs. normal range 0.21–0.42, right; GA: 0.32 vs. normal range 0.10–0.21, and left; GA: 0.30 vs. normal range 0.10–0.21; **Figure 1B** and **Supplementary File S2**). There was also an asymmetry in the volume of lobule Crus II, with the left one being smaller than the right (GA: +22.03 vs. normal range −22.45/+17.66; **Supplementary Figure S1** and **Supplementary File S2**). The left lobule VIIIB was increased and close to the upper limit compared to age- and sex-matched controls (GA: 0.39 vs. normal range 0.19–0.39), while there was an asymmetry between the right and left lobule VIIIB, with the right one being smaller than the left in this case (GA: −36.48 vs. normal range −25.39/+30.73). Both lobules X were decreased (total; GA: 0.08 vs. normal range 0.33–0.70, right; GA: 0.04 vs. normal range 0.16–0.34, and left; GA: 0.04 vs. normal range 0.17–0.35; **Supplementary File S2**).

The VBM findings reveal anomalous anatomical asymmetries, which support the argument that the cerebellum is one of the main regions associated with dyslexia with consistent differences between critical groups (Eckert, 2004; Stoodley and Stein, 2011; Vandermosten et al., 2016). More importantly, the results from the lobular analysis and the DAST are consistent with the findings of Stanberry et al. (2006), namely, that the asymmetries of lobules V, Crus II, VIIB, and X are involved in difficulties of postural stability, rapid naming, rapid reading, phonemic segmentation, and memory. They are also in line with other studies showing that working memory and fluid intelligence are associated with the dorsolateral prefrontal and anterior cingulate cortex, and that phonological processing, implicit learning, and rapid automatized naming are related to cerebellar asymmetries (Molinari et al., 2008; Stoodley and Stein, 2011, 2013).

Interestingly, although GA was diagnosed with dyslexia quite early, he achieved advanced degrees, indicating that the recorded brain asymmetries do not merely represent differences in reading experience, but rather they may actually contribute with a causative role in dyslexia (Vandermosten et al., 2016). Worthy of mention is that the emotional and/or behavioral characteristics of GA's profile are not classified in the clinical spectrum, indicating that: (i) the cerebellum asymmetries may be specific to his learning difficulties (Stoodley and Stein, 2011); and (ii) the amygdala asymmetries might reflect alterations in the expression of neuroplasticity genes, which could be triggered by the frustration that the persistent learning difficulties evoke as it has been previously suggested (Blair, 2010), affecting his behavior and stimulus reinforcement learning. However, it would have been certainly interesting to have access to information concerning earlier life periods of the subject examined, as to the form and degree of his dyslexia, because the data presented here only refer to adult findings (Shaywitz et al., 2002). Therefore, whenever possible, a temporal approach should be employed to correlate the critical developmental stages with the natural history of these patients.

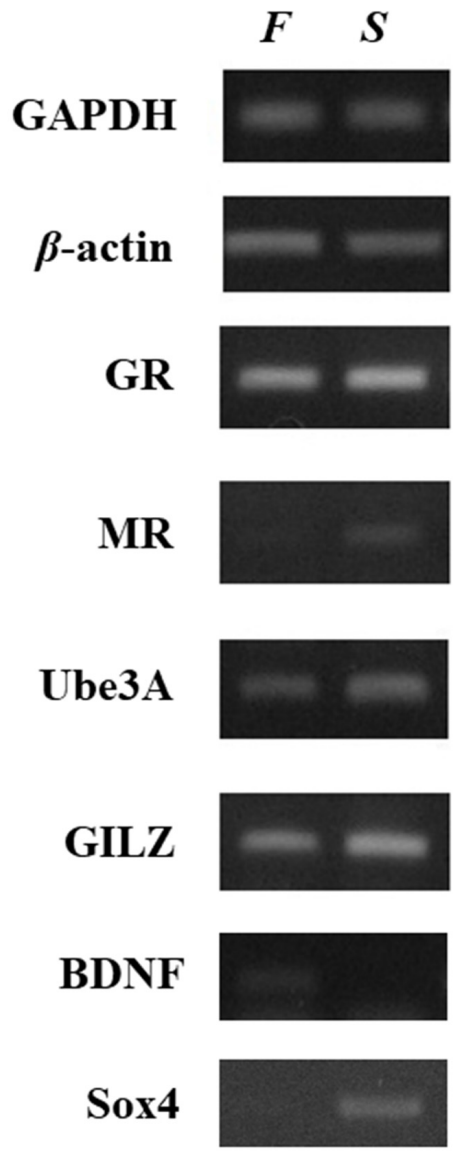

FIGURE 2 | Relative expression of selected neuroplasticity and stress-related genes between father and son. Gene expression was compared in whole blood RNA samples collected from the patient and his son. Relative gene expression levels were determined by semiquantitative reverse transcriptase-polymerase chain reaction (RT-PCR). The levels of *GAPDH* and *β-actin* were used as controls for cDNA normalization. Photographs provide one representative example of at least three different experiments that yielded consistent results. The mRNA levels of the genes encoding *MR*, *Ube3A*, *GILZ*, and *Sox4* were lower in the sample from the father (*F*) compared to the son (*S*). In contrast, the expression of *BDNF* was significantly higher in the father whereas glucocorticoid receptor (GR) showed no difference.

The investigation of the gene expression profile was performed by reverse transcriptase-polymerase chain reaction (RT-PCR) using self-designed specific primers (**Supplementary Table S2**). This analysis (**Figure 2**) showed that the mRNA levels of the genes tested differed remarkably between the two samples, with the exception of *GR*, which showed no difference between the patient and his healthy child. The mRNA levels of *MR*, *UBE3A*, *GILZ*, and *Sox4* genes were lower in the father than in the son. In contrast, the expression of *BDNF* was significantly higher in the father. Several studies have recognized the role of epigenetic mechanisms in altering the expression of genes involved in HPA axis function and neuroplasticity after stressful conditions and experiences. Although the data have to be extended to include the analysis of more cases, the differences in the expression profiles of the genes observed here could reflect long-term adaptation and adjustments to changes in the environment. In other words, the father may have acquired epigenetic alterations in critical genes for brain function. One of the most remarkable differences was the very low expression of MR in the blood of the patient although the GR levels were similar. As MR and GR activities oppose each other, the ratio of MR to GR is considered as a marker for stress resilience and vulnerability (Almeida et al., 2000). Provided that this is reflected in relevant brain regions, it may denote an imbalance between GR- and MR-mediated actions in the limbic system, which may lead to inadequate response to stress (de Kloet, 2013). It has been suggested that, during stress, MR provides a negative feedback signal, and low MR functionality may predispose individuals to increased stress susceptibility for psychiatric disorders (Harris et al., 2013). In addition, reduced MR expression in the limbic system may lead to a less favorable strategy to respond properly to a novel, stressful situation (ter Horst et al., 2012). Thus, decreased MR levels may affect stress-related learning and modify the cognitive appraisal of stressful situations (ter Heegde et al., 2015). Another gene, the mRNA levels of which were significantly lower in the father compared to the son, was that of *Sox4*, which may reflect impaired neurogenesis, and therefore insufficient supply with new neurons that could become integrated into pre-existing neuronal networks. The levels of BDNF mRNA were notably higher in the patient, possibly indicating chronic compensatory mechanisms to cope with stressful events (Autry and Monteggia, 2012; Zaletel et al., 2017).

The analysis of peripheral blood is emerging as a pertinent route for studying relevant gene expression changes in brain disease. For example, chromatin extracted from peripheral blood carries epigenetic marks that reflect individual life experiences. Such epigenetic biomarkers have been associated with various brain disorders, including schizophrenia (Gavin and Sharma, 2009), depression, aggressive behavior, or post-traumatic stress disorder (Rusiecki et al., 2012). Moreover, *GILZ* mRNA levels in peripheral blood mononuclear cells have been correlated with hippocampal volumes in patients with depression (Frodl et al., 2012). In addition, the methylation of the GR promoter in blood leukocytes has been associated with the history of various childhood adversities (McGowan et al., 2009; Tyrka et al., 2012), while acute psychosocial stress has been shown to alter the DNA methylation status of the *BDNF* gene in peripheral blood cells (Unternaehrer et al., 2012).

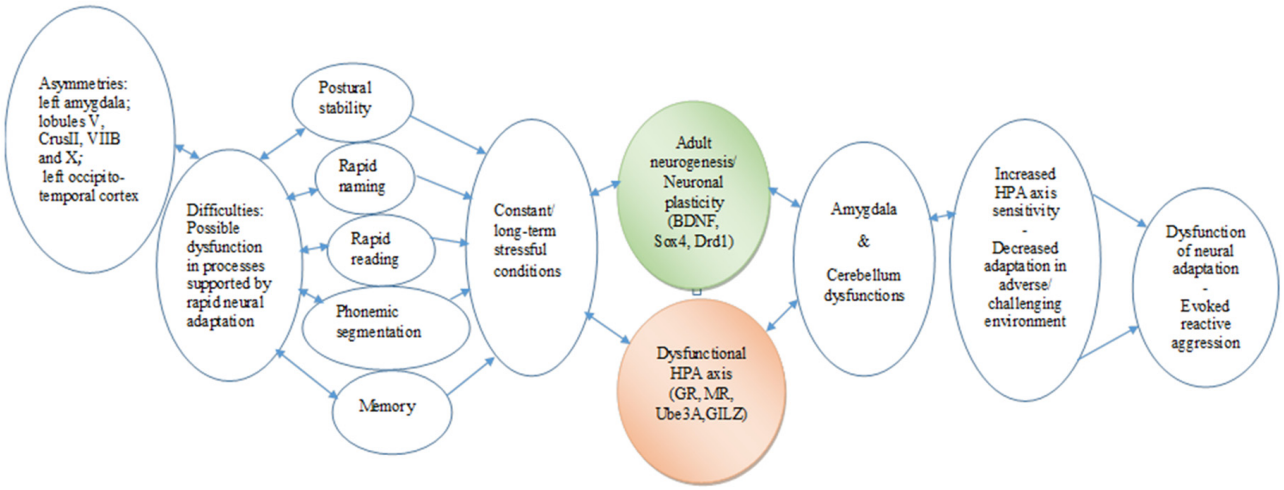

FIGURE 3 | Chain link of brain asymmetries, specific learning disabilities, neurogenesis, hypothalamic–pituitary–adrenal (HPA) axis, and psycho-emotional disorders. The proposed translational mechanism highlights the complex roles that specific brain and genetic asymmetries in constant interaction with the HPA axis may play in the expression and the management of learning disabilities. It also indicates the longitudinal potential consequences in cognitive and emotional development and in the behavioral adaptation of the individual from early childhood to adulthood (Hoeft et al., 2011). In essence, this chain link underscores the core roles of multifaceted associations between neurophysiological and epigenetic development, as well as the adaptation of cognitive and learning mechanisms.

CONCLUDING REMARKS

The data analyses on GA point to a dyslexic profile or endophenotype, characterized by altered stress response, MRI findings (asymmetries in the amygdala and specific cerebellar regions), and difficulties in coping with strong emotional and behavioral states. The case findings can be taken to indicate that the cerebellum asymmetries may negatively affect the skills of rapid reading and writing, phonological segmentation and sensorimotor functionality, possibly resulting in a blunted stress response. The asymmetries of the amygdala could indicate an impaired regulation system of the response to threatening stimuli (reading difficulties), which may result in reduced GR-mediated negative feedback on the HPA axis and allow reactive aggression. Given that the long-standing reading difficulties mirror threatening of frustrating conditions, they are considered as stress stimuli; as a result, the limited amygdala activity unable to manipulate negative emotions, supported by a corticosteroid receptor imbalance, might compromise adaptation and activate reactive aggression. In addition, a potential interplay between the dysfunction of particular lobules and amygdala should be taken into account, considering the dynamic changes in gene expression that may occur in the amygdala under threatening conditions, such as the learning difficulties. The significant differences in the expression profiles of the HPA axis and the neuroplasticity genes tested here may reflect long-term adjustments of transcriptional programs to the "threatening" learning environment (**Figure 3**). Thus, stress might be an important environmental factor that could act in concordance with genetic mutations or alone (epigenetically), resulting in DD endophenotypes and a variation of clinical phenotypes.

Thus, we propose that the present single case report suggests that, for a more integrated diagnosis and effective treatment, stress-related phenotypes should be carefully considered; in this direction, one should also bear in mind that epigenetic changes induced by environmental factors are dynamic and could be reversed with appropriate intervention processes. This interpretation is in line with current conceptualizations that, in the analysis of complex behaviors (for example, learning disabilities), different components such as cognitive processes, neural systems, and genetic and epigenetic factors should be co-estimated. While the in-depth description of a single case may be highly suggestive, future research involving a sizeable sample of informative individuals will be definitely required in order to reach firm conclusions on this interpretation.

DATA AVAILABILITY STATEMENT

All datasets analyzed for this study are included in the manuscript/**Supplementary files**.

ETHICS STATEMENT

The patient and his son provided us with written informed consent in accordance with the Declaration of Helsinki. They also gave their consent for the analysis, processing, and publication of the data. Since all described interventions were part of clinical practice, we did not consult the ethics committee for this study.

AUTHOR CONTRIBUTIONS

VZ, MS and TM conceived and designed the experiments and contributed reagents, materials and analysis tools. VZ, A-MV,

MD, ZP, DT, KP, GA, HB, VS, MS and TM performed the experiments. VZ, GA, HB, VS, PZ, GC, MS and TM analyzed the data. VZ, A-MV, MD, ZP, DT, GA, HB, VS, PZ, GC, MS and TM wrote the article.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2019.00327/full#supplementary-material

SUPPLEMENTARY FILE S1 | Materials and Methods.

SUPPLEMENTARY FILE S2 | Volumetry report: the raw data are shown, including a screenshot of the results.

FIGURE S1 | VBM lobular analysis of the cerebellum: the location of lobule Crus II is shown (arrow).

TABLE S1 | Volumetric brain analysis.

TABLE S2 | Primer sequences used for reverse transcription-PCR.

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Developmental Dynamic Dysphasia: Are Bilateral Brain Abnormalities a Signature of Inefficient Neural Plasticity?

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The acquisition and evolution of speech production, discourse and communication can be negatively impacted by brain malformations. We describe, for the first time, a case of developmental dynamic dysphasia (DDD) in a right-handed adolescent boy (subject D) with cortical malformations involving language-eloquent regions (inferior frontal gyrus) in both the left and the right hemispheres. Language evaluation revealed a markedly reduced verbal output affecting phonemic and semantic fluency, phrase and sentence generation and verbal communication in everyday life. Auditory comprehension, repetition, naming, reading and spelling were relatively preserved, but executive function was impaired. Multimodal neuroimaging showed a malformed cerebral cortex with atypical configuration and placement of white matter tracts bilaterally and abnormal callosal fibers. Dichotic listening showed right hemisphere dominance for language, and functional magnetic resonance imaging (fMRI) additionally revealed dissociated hemispheric language representation with right frontal activation for phonology and bilateral dominance for semantic processing. Moreover, subject D also had congenital mirror movements (CMM), defined as involuntary movements of one side of the body that mirror intentional movements of the other side. Transcranial magnetic stimulation and fMRI during voluntary unimanual (left and right) hand movements showed bilateral motor cortex recruitment and tractography revealed a lack of decussation of bilateral corticospinal tracts. Genetic testing aimed to detect mutations that disrupt the development of commissural tracts correlating with CMM (e.g., Germline DCC mutations) was negative. Overall, our findings suggest that DDD in subject D resulted from the underdevelopment of the left inferior frontal

gyrus with limited capacity for plastic reorganization by its homologous counterpart in the right hemisphere. Corpus callosum anomalies probably contributed to hinder interhemispheric connectivity necessary to compensate language and communication deficits after left frontal involvement.

Keywords: dynamic aphasia, congenital mirror movements, developmental cerebral anomalies, neuroimaging, brain stimulation

INTRODUCTION

Children and adults with language and literacy impairments (specific language impairment, dyslexia, and autism spectrum disorders) tend to have weaker cerebral lateralization than neurotypically developing individuals (de Guibert et al., 2011; Bishop, 2013; Ogawa et al., 2019). In addition, there are differences in the evolution of developmental and acquired disorders in children (Temple, 1997; Luyster et al., 2011). Perinatal language impairments and acquired childhood aphasias due to unilateral lesions of the dominant hemisphere rarely lead to pervasive deficits because efficient (adaptive) neural plasticity promotes recovery (Rauschecker et al., 2009; Yeatman and Feldman, 2013). By contrast, the presence of long-lasting deficits is the rule in specific language impairments and this has been related to bilateral brain abnormalities (Vargha-Khadem et al., 1998; Guerreiro et al., 2002; Rapin et al., 2003; Soriano-Mas et al., 2009). In this respect, there is evidence of how multiple brain systems may sustain the same function (e.g., degeneracy – Noppeney et al., 2004; Stefaniak et al., 2019), which may explain cases of resilience of language/cognitive functions to brain lesions. The idea of degeneracy exists both within subject, aiding to compensate the damage to a given network, and over subjects as in normal neurodevelopmental variation that can result, for instance, in differences in hemispheric lateralization (Biduła et al., 2017). However, the existence of multiple degenerate systems does not have to mean that such systems can become efficient, a situation that may be particularly true in cases of developmental malformations (i.e., Oberman et al., 2012; Zsoter et al., 2012; Mainberger et al., 2013). Specific language impairments are associated with reduced or reversed functional lateralization of language networks (see references in Luyster et al., 2011), suggesting that both cerebral hemispheres are engaged to compensate language deficits through adaptive neural plasticity. Thus, neural adaptation may be less efficient in cases of bilateral brain abnormalities and might represent an earlier neural marker for developmental language disorders by interfering with the continuous acquisition of skillful language functions (discourse, functional communication).

Many developmental language disorders are not associated with gross structural brain changes, but speech-language delay may also be associated to unilateral, bilateral or diffuse developmental cortical anomalies (e.g., perisylvian cortical dysplasia) (Graff-Radford et al., 1986; Guerreiro et al., 2000, 2002; Barkovich, 2010). There is an association between language delay and developmental abnormalities of the cortical mantle and white matter tracts (Andrade et al., 2015; Paldino et al., 2015, 2016). Nevertheless, the characterization of language delay and its relationship with gross developmental brain anomalies has not been clearly defined.

The syndrome of dynamic aphasia (DA) is a subtype of transcortical motor aphasia (TCMA) (Goldstein, 1917; Kleist, 1934; Luria, 1977; Berthier, 1999; Alexander, 2006) usually associated with acquired focal brain lesions (stroke, neoplasms) (Robinson et al., 1998) or slowly progressive degenerative disorders (e.g., primary progressive aphasia) (Esmonde et al., 1996; Robinson et al., 2006) involving the left frontal lobe, basal ganglia, or both. In the original formulation of DA, Kleist (1934) described it as a syndrome characterized by reduced drive to generate propositional speech despite the relative preservation of other language functions including spontaneous speech, object naming, word and sentence repetition, comprehension, and oral reading (Luria, 1966, 1970). Luria segregated DA into different subtypes, but he did not delineate the differences from one another (Lebrun, 1995). It was Lebrun (1995) who separated DA into three subtypes; one subtype corresponded to typical TCMA, another subtype resulted from what Luria called "spreading activation syndrome" (i.e., an impaired selection between competing verbal items that hampers verbal production), and the last type was described as a lack of drive to generate language.

In the present case study, we focus on the last type of DA referred to as "lack of drive to generate language." While all reported cases of DA were *acquired* (ADA) after brain injury or neurodegenerative disorders in adulthood (Alexander, 2006; Magdalinou et al., 2018), the case described herein resulted from developmental aberrations in both hemispheres mostly involving language-eloquent cortical regions and white matter tracts in a teenager male (subject D). Similar to other children and adolescents with developmental language disorders associated to bilateral cortical anomalies (Guerreiro et al., 2000, 2002), subject D was brought to our Unit by his mother complaining limited communicative ability. She claimed that "he does not speak spontaneously and is not communicative." This case can be endorsed to the category of Developmental Language Disorder (DLD) (American Psychiatric Association, 2013; Bishop et al., 2017). It was noticeable, however, that the language disturbance in subject D did not fulfill the criteria for any type of DLD reported up to now. Since it rather seems to be similar to one of the three variants described in ADA (lack of drive to generate language) (Kleist, 1934; Alexander, 2006), after performing a comprehensive testing, we classified the language disorder in subject D as *developmental dynamic dysphasia* (DDD). In this boy, DDD co-occurred with other neurodevelopmental disorders (mild left hemiparesis and congenital mirror movements - CMM) (Méneret et al., 2014) which in our view does not invalidate the diagnosis of DDD (see Bishop, 2017). In fact, the primary

complain was language delay and subject D had normal hearing by audiometry and an intellectual quotient (IQ) > 70 (see Guerreiro et al., 2002).

We performed a multimodal evaluation to identify the brain-cognitive profile of subject D including testing of cognitive, language, and motor functions. Multimodal neuroimaging included structural magnetic resonance imaging (MRI; high-resolution T_1-weighted image), functional MRI (fMRI) during four different tasks (phonemic fluency, semantic decision and left and right finger tapping) that allowed to evaluate functional cerebral dominance for language and motor functions, and diffusion tensor imaging (DTI)-Tractography of white matter tracts, that enabled the visualization of the language and motor pathways. In addition, transcranial magnetic stimulation (TMS) and genetic testing were performed to detect mutations that disrupt the development of commissural tracts (e.g., Germline DCC mutations).

MATERIALS AND METHODS

Case Description

Subject D was a 12-year-old right-handed boy with concurrent DDD and CCM who was brought by his mother to our Unit for language testing. She reported that subject D had "problems to verbally explain things... showing poor communication and sometimes making nonsense comments." She provided information about family history and her son's developmental milestones. The father of subject D was described as "shy and non-communicative." The parents and the brother of subject D were also right handed. Subject D was the second born of non-consanguineous parents. He was the product of a full-term pregnancy of 38 weeks. Maternal age at delivery was 30 years old. Delivery was normal and subject D's Apgar scores at 1 and 5 minutes after birth were 9 and 10, respectively. His birth weight was 3.500 g. Shortly after birth subject D developed a short-lived bilateral arm tremor that disappeared before hospital discharge 24 h later. Developmental milestones were slightly delayed for language, communication and motor functions.

During infancy, subject D was discovered to have several medical, neurological, ophthalmological and skeletal abnormalities. At 9 months of age he was operated on for bilateral inguinal hernia, and at 3 years-old he was operated of bilateral strabismus. CMM were discovered at age 4 in kindergarten. Skeletal and neurological exams at the ages of 8 and 12 years disclosed mild dorsal scoliosis, pectum carinatum and turricephaly. He also had mild developmental delay, mild left-sided hemiparesis, increased blinking and CMM of the opposite hand and foot during voluntary movements. Cognitive testing at school when subject D was 8.10 years, showed a verbal IQ of 73, below average performance in the Colored Raven Progressive Matrices (Raven et al., 1975) and limited vocabulary with impaired ability to define words. Subject D was right handed (+100) as assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971).

The study was performed in compliance with the Declaration of Helsinki. The parents of subject D signed a written informed consent for participation in the study and for the publication of the results. The protocol of this study was approved by the Ethical Research Committee Provincial of Malaga, Spain.

Cognitive and Intelligence Testing

Although subjects with *pure* cases of ADA with deficits confined to speech production have been described (Costello and Warrington, 1989; Gold et al., 1997; Robinson et al., 1998), others have more widespread speech and language deficits involving phonological, lexical and syntactical functions (mixed ADA) (Esmonde et al., 1996; Snowden et al., 1996; Raymer et al., 2002; Warren et al., 2003) and still others present with additional non-language cognitive deficits (Robinson et al., 2006; Caine et al., 2018; Magdalinou et al., 2018). Thus, the cognitive profile of DDD in subject D was also explored with tests tapping intelligence, concept formation and reasoning, memory, and executive functions.

Methods

Subject D was evaluated with the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 1974) and the Raven Colored Progressive Matrices (RCPM) (Raven et al., 1975). Memory was examined with the Test of Memory and Learning (TOMAL) (Reynolds and Bigler, 1994) and executive functions were tested with the Trail-Making Test (TMT) (Reitan, 1958; Arango-Lasprilla et al., 2017), the Hayling Sentence Completion Test (HSCT) (Burgess and Shallice, 1997; Abusamra et al., 2007; Cartoceti et al., 2008), the Wisconsin Card Sorting Test (WCST) (Grant and Berg, 1948; Heaton et al., 2009) and the Stroop Test (Stroop, 1935).

Results

Table 1 shows the results of the cognitive evaluation. On the WISC, subject D performed in the inferior range in all three IQ scores and his performance was also impaired on the RCPM. Subject D's learning and memory functions were also impaired with slightly lower scores in the verbal memory index than in the non-verbal memory index. On all tests tapping executive function, subject D had impaired performance. Analysis of the pattern of performance of subject D on the HSCT provided information on the mechanism underlying DDD. He was impaired in the two sections of the sentence completion task (HSCT) exclusively due to omissions and prolonged response times (>20 *s*). While he could successfully complete many open-ended sentences (0.73) in the sensible completion Section 1, he was totally unable to choose a word unrelated to both the syntactic and semantic context of the frame sentence in the unrelated completion Section 2, producing no responses to any sentence.

Orientation, Perception and Motor Tests

Methods

Several tests were administered to evaluate these skills. These included the Right-Left Orientation (RLO), Tactile Form Perception (TFP), Finger Localization (FL), and Judgment of Line Orientation (JLO) (Benton et al., 1983).

TABLE 1 | Cognitive testing.

Tests	Subject *D*'s scores	Performance descriptor	Normative data
Intelligence			
Verbal IQ	77	Inferior	
Performance IQ	76	Inferior	
Full Scale IQ	78	Inferior	>5th%ile
Raven Colored Progressive Matrices (max: 36)	26	BA	25th%ile
Memory			
Test of Memory and Learning (TOMAL)			
Verbal memory index	73	BA	100 ± 15
Non-verbal memory index	81	BA	100 ± 15
Composite memory index	74	BA	100 ± 15
Executive function			
Trail-Making Test			
Part A (sec/errors)	58/1	BA	<5th%ile
Part B (sec/errors)	109/1	BA	<5th%ile
Hayling Sentence Completion Test [α]			
Section 1 – sensible completion (max:	11/4*	A	–
15)/errors	0/15	BA	–
Section 2 – unrelated completion/errors			
Wisconsin Card Sorting Test (64 cards)			
Categories	3	BA	>16th%ile
Correct responses	46	–	
Perseverations	18	SBA	45th%ile
Stroop Test			
Word reading (score/errors)	46/0	BA	<25th%ile
Naming colors (score/errors)	38/1	BA	25th%ile
Word-Color	18	BA	
Interference	−2.81	BA	

[α] *The Argentinian version by Abusamra et al. (2007) was used. *All errors were omissions in both Sections. Data from healthy children show that errors in Section 1 are around 1.9% and responses in Section 2 are 58% correct (Cartoceti et al., 2008).*

Results

On the RLO, he showed a flawless performance when he was asked to orient in his own body (12/12) but showed a severe confronting person defect (1/8). In the TFP, he had normal performance with the preferred right hand (9/10) and mildly impaired tactile perception with the non-preferred left hand (7/10) (Spreen and Gaddes, 1969). On the FL, he demonstrated no deficit in the identification of single fingers both with hidden hands (20/20) and with visible hands (19/20), but a mildly impaired performance on identifying two simultaneously touched fingers when the hand was hidden (11/20), particularly for the left hand (4/10). Overall, the total score is mildly impaired in this task (total: 50/60; age-matched controls from Wake, 1957: mean = 54.4; n = 70). Subject D had average performance on the JLO test (21/30; age-matched controls: 24.7 ± 3.8, Benton et al., 1983).

Language Testing

Auditory Processing, Word Semantics, Receptive Vocabulary, Reading and Spelling

Methods

Auditory processing and word semantics were assessed with several subtests of the Spanish version (EPLA) of the Psycholinguistic Assessments of Language Processing for Aphasia (PALPA) (Kay et al., 1992; Valle and Cuetos, 1995). These included Non-word Minimal Pairs (PALPA 1), Word Minimal Pairs (PALPA 2), Repetition: Syllable Length (PALPA 7), Repetition: Non-words (PALPA 8), Repetition: Imageability × Frequency (PALPA 9), Sentence Repetition (PALPA 12), Digit Production/Matching span (PALPA 13) and Spoken Word-Picture Matching (PALPA 47). The receptive vocabulary ability was examined with the Peabody Picture Vocabulary-III (Dunn et al., 2010). Oral reading and spelling to dictation were tested also using PALPA subtests. Oral reading was tested for Letter Length (PALPA 29), Imageability × Frequency (PALPA 31), Grammatical Class (PALPA 32), and Grammatical Class × Imageability (PALPA 33), Morphological Endings (PALPA 34), Regularity (PALPA 35), and Non-words (PALPA 36). Spelling to dictation was tested for Letter Length (PALPA 39), Imageability × Frequency (PALPA 40), Morphological Endings (PALPA 43), Regularity (PALPA 44) and Non-words (PALPA 45). The PALPA has been originally designed for use with people with acquired disorders and hence it does not include developmental norms (Kay and Terry, 2004). One requisite for the diagnosis of ADA is that comprehension, naming and transcoding (repetition and oral reading) should be relatively spared or remarkably less impaired than spontaneous speech (Luria, 1966, 1977). Therefore, to be confident that performance on language domains in subject D was not so affected as spontaneous speech, subtests of the PALPA were compared with adult norms for Spanish speaking subjects (Valle and Cuetos, 1995). Results on these subtests were classified as "average" when scores were within 2 standard deviations or less from the mean (scores between 0.96 and 1.0 relative to normative data); "slightly below average" (scores between 0.90 and 0.95 relative to normative data), and "below average" (scores < 0.90).[1] Scores on the Peabody Picture Vocabulary-III were compared with age-matched normative data (Dunn et al., 2010).

Results

Table 2 shows the results on tasks tapping auditory processing, word semantics and receptive vocabulary. Most scores on PALPA subtests (18 out of 21) ranged from average (12/21) to slightly below average (6/21) and only a few scores were below average (3/21). Subject D performance on Non-word Minimal Pairs (PALPA 1) and Word Minimal Pairs were preserved obtaining better scores in the latter. Scores in Repetition: Syllable Length (PALPA 7) and Repetition: Non-words (PALPA 8) were flawless and almost intact in the Repetition: Imageability × Frequency (PALPA 9) subtest where subject D only performed 4 errors

[1] In the validation of the Spanish version of the PALPA, healthy subjects performed almost at ceiling. Thus, standard deviations were low indicating that the data points tended to be close to the mean and that failing only one item in a given test placed the scores of subject *D* two standard deviations below the mean.

TABLE 2 | Language testing.

Tests	Subject *D*'s scores (proportion)	Performance descriptor	Normative data[1]
Auditory Processing: Comprehension Tests			
Non-word minimal pairs (PALPA 1)			
Same (*n* = 28)	24 (0.86)	BA	27.45 ± 0.99
Different (*n* = 28)	25 (0.89)	A	27.09 ± 1.24
Word minimal pairs (PALPA 2)			
Same (*n* = 28)	25 (0.89)	A	27.54 ± 1.27
Different (*n* = 28)	26 (0.93)	SBA	27.68 ± 0.76
Auditory Lexical Decision: Imag x Freq (PALPA 5)			
High imageability-High frequency (*n* = 20)	20 (1.0)	A	20.00 ± 0.00
High imageability-Low frequency (*n* = 20)	19 (0.95)	SBA	20.00 ± 0.00
Low imageability-High frequency (*n* = 20)	19 (0.95)	SBA	19.95 ± 0.21
Low imageability-Low frequency (*n* = 20)	13 (0.65)	BA	19.41 ± 1.15
Non-words (*n* = 80)	73 (0.91)	SBA	78.18 ± 1.95
Spoken Word-Picture Matching (n = 40) (PALPA 47)	39 (0.97)	A	39.45 ± 1.67
Peabody Picture Vocabulary Test	135	BA	30th%ile
Auditory Processing: Repetition Tests			
Repetition: Syllable Length (PALPA 7) (n = 24)	24 (1.0)	A	23.8 ± 0.23
Repetition: Non-words (PALPA 8) (n = 24)	24 (1.0)	A	22.9 ± 0.64
Words, Imag x Freq (PALPA 9)			
High imageability-High frequency (*n* = 20)	20 (1.0)	A	20.00 ± 0.00[1]
High imageability-Low frequency (*n* = 20)	20 (1.0)	A	19.82 ± 0.65
Low imageability-High frequency (n = 20)	20 (1.0)	A	19.68 ± 1.02
Low imageability-Low frequency (*n* = 20)	19 (0.95)	SBA	19.27 ± 1.93
Non-words (n = 80)	76 (0.96)	A	77.68 ± 3.35
Repetition: Sentences (PALPA 12) (n = 36)	34 (0.94)	A	–
Digit Production (PALPA 13)	4	SBA	5.91 ± 0.67
Matching Span (PALPA 13)	5	A	6.18 ± 1.34

All test are from PALPA unless specified; [1]Normative data from Valle and Cuetos (1995). The "performance descriptors" have been obtained by comparison with normative data as follows: A indicates average, SBA slightly below average, and BA below average (see further details in text).

TABLE 3 | Oral reading and spelling.

Tests	Subject *D*'s scores (proportion)	Performance descriptor	Normative data[1]
Oral Reading			
Oral Reading: Letter Length (PALPA 29)	24 (1.0)	A	23.95 ± 0.21
Oral Reading: Imag x Freq (PALPA 31)			
High imageability-High frequency (*n* = 20)	20 (1.0)	A	19.95 ± 0.21
High imageability-Low frequency (*n* = 20)	19 (0.95)	SBA	19.95 ± 0.21
Low imageability-High frequency (*n* = 20)	20 (1.0)	A	19.95 ± 0.29
Low imageability-Low frequency (*n* = 20)	20 (1.0)	A	19.68 ± 0.55
Oral Reading: Grammatical Class (n = 40) (PALPA 32)			
Nouns (n = 20)	19 (0.95)	SBA	19.95 ± 0.21
Adjectives (n = 20)	20 (1.0)	A	19.86 ± 0.34
Verbs (n = 20)	20 (1.0)	A	19.95 ± 0.21
Functional Words (n = 20)	19 (0.95)	A	19.77 ± 0.42
Oral Reading: Grammatical Class x Imag (n = 40) (PALPA 33)			
Nouns (*n* = 20)	19 (0.95)	SBA	19.91 ± 0.29
Functional Words (*n* = 20)	19 (0.95)	SBA	20.00 ± 0.00
Oral Reading: Morphological Endings (PALPA 34)			
Regular Words (*n* = 30)	27 (0.90)	A	29.54 ± 1.30
Irregular Words (*n* = 30)	14 (0.53)	SBA	26.36 ± 5.84
Oral Reading: Non-words (PALPA 36) (n = 24)	22 (0.92)	A	23.22 ± 0,69
Spelling			
Spelling to Dictation: Letter Length (PALPA 39) (n = 24)	24 (1.0)	A	23.8 ± 0.23
Spelling to Dictation: Grammatical Class (PALPA 41)			
Nouns (n = 5)	5	A	4.68 ± 0.55
Adjectives (*n* = 5)	5	A	4.91 ± 0.29
Verbs (*n* = 5)	5	A	4.91 ± 0.29
Functional Words (*n* = 5)	4	A	4.77 ± 0.52
Spelling to Dictation: Grammatical Class x Imag (PALPA 42)	9 (0.90)	A	9.73 ± 0.67
Nouns (*n* = 10)	8 (0.80)	SBA	9.82 ± 0.49
Functional Words (*n* = 10)			
Spelling to Dictation: Non-words (PALPA 45) (n = 24)	24 (1.0)	A	22.54 ± 0.76

All test are from PALPA unless specified; [1]Normative data from Valle and Cuetos (1995). The "performance descriptors" have been obtained by comparison with normative data as follows: A indicates average, SBA slightly below average, and BA below average (see further details in text).

and all of them were lexicalizations (e.g., "cuabro"→ *cuadro* [painting]). Sentence Repetition was also preserved, but Digit Production/Matching Span (PALPA 13) was mildly reduced. Performance on the Spoken Word-Picture Matching (PALPA 47) and the Peabody Picture Vocabulary-III were preserved. Oral reading and spelling to dictation were preserved in most tasks (**Table 3**).

Speech Production

Naming for Nouns and Verbs

Methods

Oral naming was assessed by using black and white pictures from standardized naming batteries. In particular, noun naming was assessed with the standardized set of 260 pictures of the Snodgrass and Vanderwart (1980) battery, whereas verb naming was tested with 100 items from the Action Naming Battery (Druks and Masterson, 2000).

Results

The performance of subject D in noun naming was mildly impaired (214/260 [0.82]) in part due to the inclusion of items not known by subject D (i.e., footballhelmet, sled, spinningwheel). Error analysis mostly disclosed semantic errors (e.g., "envelope"→ *message*) (28 [0.61]) and omissions (14[0.30]), whereas other errors were rarely seen. There were 2 phonological (0.04), 1 formal (0.2) and 1 visual (0.02) errors. His performance in verb naming was preserved (91/100 [0.91]). Error analysis disclosed the production of a noun instead of a verb (e.g., "surf"→ *boat*) (5), and omissions which were always benefited with phonemic cueing (4).

Verbal Fluency

Methods

Phonemic verbal fluency was assessed with the Controlled Oral Word Association Task (F.A.S.) (Borkowski et al., 1967), and semantic fluency was assessed with two categories of living things (animals and fruits) and two categories of artifacts (clothes and transport).

Results

The performance of subject D in phonemic fluency was very poor since he was only able to produce three words in 3 min. In semantic fluency, his performance was also impaired in the four categories (animals: 9; fruits: 7; clothes: 5; transport: 5).

Narrative Production and Communication in Activities of Daily Living

Methods

A sample of picture-generated narrative was used. Subject D was asked to generate a story that corresponds to a novel scene depicting a picnic day with many people along the riverside, enjoying a picnic and performing different activities. The *Picnic Scene* from the Western Aphasia Battery (Kertesz, 1982) was used. Subject D was encouraged to describe the elements depicted in the card (nouns) as well as indicate the actions that the persons were doing (action verbs) during a time limit of 5 minutes. He was also encouraged to describe the scenes using sentences. The description was audio-taped and transcribed. The speech sample was analyzed for percentage of correct information units (%CIU) defined as non-redundant content words that convey correct information about the stimulus (Nicholas and Brookshire, 1993; Marchina et al., 2011; Zipse et al., 2012), using the following formula: number of CIUs/number of words × 100. According to Nicholas and Brookshire (1993) to be classified as CIUs, words should not only be intelligible in context, but also be accurate, relevant and informative with respect to the stimulus. Meaningless utterances, perseverations, paraphasias and other inappropriate information (exclamations) were counted as words, but not classified as CIUs. The duration of the narrative, the total number of words, the number of words per minute and the pauses were counted. Pauses ≥ 3 s were considered abnormal.

Results

The description of the picture was extremely poor. It contained 31 words produced in 53 s. Although the examiner requested subject D to be more explicative in two occasions, he was unable to add further information. Since there were no linguistic errors in the narrative, the number of words and CIUs were the same (31). There were 4 pauses, two of which were long (6.47. and 8.28 s). Subject D produced the following description of the Picnic Scene: *"They are having a snack. . . (2.51 s), a man is speaking, a comet with a dog. . . (6.47 s) there is a man fishing. . . (8.28 s), there are two men on a boat. . . (1.51 s) and there is a child collecting water."*[2]

To examine communication in daily life, the mother of subject D was interviewed using questions of a communication scale developed for adults with aphasia (Communicative Activity Log; Pulvermüller and Berthier, 2008). The mother reported that her son had marked impairment in frequency and quality of communication in questions evaluating making statements or reports about facts, write down short notes, communicate when relaxed or under stressful situations and communicating with foreigners.

Dynamic Dysphasia Testing

To elicit the typical language features of DA, an adaptation of a series of experimental tests developed by Robinson and co-workers to assess ADA (Robinson et al., 1998) was used. The original English version of these experimental tests was slightly modified and adapted to be administered to Spanish speaking individuals (Berthier et al., in preparation). Since these tests are experimental, they were also administered to a group of 10 healthy control adolescent boys matched by age (age range: 10–14; mean age ± SD: 11.87 ± 1.12; Crawford *t*-test, two tailed: $t = 0.111$; $p = 0.914$), handedness (all right handers), and years of schooling (although subject D needed additional classes and training, he did not repeat any academic course). The scores obtained by Subject D in each of these tasks were compared to those obtained by the control group using a two-tailed Crawford's modified *t*-tests. This test allows comparing outcomes from one or more individuals with results derived from small control samples (Crawford and Howell, 1998; Crawford and Garthwaite, 2002; Crawford et al., 2010). Performance on these tests in subject D and healthy controls was analyzed in terms of number of correct responses. The methodology and results of these tests are described below.

[2]This excerpt has been translated from Spanish. Note that the number of words has been counted in Spanish ($n = 31$), so that the number ($n = 33$) does not coincide with the English translation.

Test A

Generation of a single word to complete a sentence

Methods. Two sets of sentences were used. The first included 20 high-constraint sentences with not many usable referent words (e.g., "bicycles have two . . ."") and the second set was composed of 20 low-constraint sentences with numerous usable referent words (e.g., "It is good to be . . ."). One point per item was given if the generated word was appropriate. Sentences were presented in a random order. Results: Subject D completed 17 out of 20 high-constraint sentences correctly (0.85). By contrast, his performance in the low-constraint sentences was poor, completing 5 out of 20 sentences (0.25). Even though there was no time limit for completion of open-ended sentences, all errors were omissions. When asked for the high number of omissions, subject D replied, "I cannot find words" or "no words come to my head." The total score of subject D was low (44/80), whereas the control group scores (78.1 ± 1.91) were significantly better (Crawford *t*-test, two-tailed: $t = -17.02$, $p < 0.001$).

Test B

Generation of a sentence from a single word

Methods. In this task, subject D and controls were asked to produce a whole sentence containing the word spoken by the examiner. Ten common nouns (e.g., "apple") and 10 verbs (e.g., "sleep") were randomly presented. Proper names were not used. Two points per item were given if the generated sentence was complete and grammatically correct and one point if the sentence was correct but not very informative. Results: Subject D produced 18 out of 20 phrases correctly (0.90) and his score was 36/40, whereas the performance of the control group was flawless (40 ± 0.0) (Crawford *t*-test, two tailed: $t = -38.13$, $p < 0.001$).

Test C

Generation of a sentence from a given sentence context

Methods. In this task, subject D was asked to generate a second sentence around the theme of the first. For example, the sentence "Carmen is always smiling" could be followed by the sentence "because she is always very happy." Twenty sentences were presented and one point per item was given if the generated sentence was complete, grammatically correct and thematically related to the first stimulus sentence. Results: The performance of subject D in this task was impaired. He did not generate a novel sentence in 11/20 occasions (0.55). In the remaining sentences, he used some words of the target sentence in the response, usually repeating the verb verbatim or changing the verb tense, indicating echo-answer[3]. The performance in the control group was better than in subject D (25.6 ± 9.2) but the difference did not reach statistical significance (Crawford *t*-test, two-tailed: $t = -0.78$, $p = 0.45$).

[3]Echo-answer refers to the inadvertent repetition of words or sentence fragments of the target stimulus into the response, in general, with the purpose of improving auditory comprehension (Berthier et al., 2017). This was not the case in subject *D* because he had preserved auditory comprehension. It is possible that in this subject, echo-answer resulted from limited linguistic resources to generate novel sentences.

Test D

Generation of a sentence from a single picture

Methods. Subject D and the control group were presented with 10 pictures of common objects (e.g., an iron or an umbrella) and asked to produce a whole sentence incorporating the noun of the picture. One point per item was given if the generated sentence was complete (not to simply name the item), grammatically correct and related to the presented picture. Results: Subject D had a moderately impaired performance in this task as he failed to generate a sentence in 3 out of 10 examples (bicycle, eyeglasses, and rabbit) (0.30). In the remaining items, although the generation of the sentences were correct, responses were very simple (e.g., example: iron; generated sentence: "The iron is used for ironing"). In addition, it was noticeable that the generation of correct sentences was preceded by prolonged latencies (ranging from 3.73 to 24.58 s) in four sentences. The performance in the control group was 10 ± 0.0 (Crawford *t*-test, two-tailed: $t = -57.20$, $p < 0.001$).

Test E

Sentence given a pictorial scene

Methods. Subject D and the control group were asked to produce a sentence to describe simple pictorial scenes selected from the Object and Action Naming Battery (Druks and Masterson, 2000). Twenty pictorial scenes (e.g., a boy playing basketball, a dancing couple) were used. Two points per item was given if the sentence generated was complete, grammatically correct and related to the presented scene. Results: Subject D obtained a score of 28/40 (0.70), whereas controls' performance was flawless (40 ± 0.0) (Crawford *t*-test, two-tailed: $t = -114.41$, $p < 0.001$).

Test F

Generation of sentences from a pictorial scene. what might happen next?

Methods. Subject D and controls were presented with simple pictures selected from the Object and Action Naming Battery (Druks and Masterson, 2000) and asked to generate a sentence describing what might happen next. For instance, a picture showing a man bleeding after being bitten by a dog would be followed by the sentence "he went to the hospital." Twenty pictorial scenes (e.g., a boat sinking, a person tying the laces of his trainers) were presented. Two points per item were given if the generated sentence was complete, grammatically correct and it was not a mere description of the scene, but a prediction of what would follow the corresponding situation. One point was given for an incomplete description. Results: The performance of subject D was significantly worse (5/40, [0.12]) than the one achieved by the control group (39.8 ± 0.42) (Crawford *t*-test, two-tailed: $t = -79$, $p < 0.001$). The qualitative analysis showed that subject D was unable to generate a description in 11 frame pictures (0.55). In the remaining 9 frame pictures there were 2 correct descriptions, 2 incomplete and 5 descriptions of the picture.

Test G

Story generation from a pictorial context

Methods. Subject D and the control group were presented with simple pictures and asked to generate a brief story describing what might happen. Ten pictorial contexts (e.g., a man watering the plants, a woman petting a cat) were presented. One point per item was given if the generated speech consisted of two or more related or connected complete and grammatically correct sentences. Results: As expected from the results obtained by subject D in Test F, he was totally unable to generate any story. Therefore, the test was interrupted after five consecutive failures. The performance of the control group was normal (20 ± 0.0), all of them generated brief meaningful and very illustrative stories.

Neuroimaging

Functional Activations Related to Language and Motor Functions

Methods

(1) MRI data acquisition. MRI data was acquired on a on a 3-T MRI whole-body scanner (Philips 3T Intera, Release 3.2.3.1, with an eight-channel platform) equipped with a six-channel Philips SENSE head coil. Head movements were minimized using head pads and a forehead strap. First, high-resolution T1-weighted structural images of the whole brain were acquired with the following parameters: TR = 10.03 ms, TE = 4.606 ms, slice thickness 0.8 mm, 200 slices, voxel size: 0.75 × 0.75 × 0.8, flip angle = 8°, matrix size 320 × 320 × 200. Then, Diffusion Tensor Imaging (DTI) acquisition was performed using multi-slice single-shot spin-echo echo-planar imaging (EPI) with specific parameters as follows: matrix size 128 × 128 × 65, an acquisition voxel of 1.67 mm × 1.67 mm × 2.00 mm, TE = 91 ms, TR = 11621 ms, b factor = 800, flip angle 90°. After the acquisition of the structural data, four different fMRI were carried out following a block design. Each task involved a functional run consisting on 100 functional images (FFE/EPI sequence with epi factor 35, TR = 3000 ms and TE = 35 ms and flip angle 90°. The image matrix was 64/64 r. 30 axial slices were acquired for each volume, with a 4 mm slice-thickness and no gap. Voxel size was 1.8 mm x 1.8 mm x 4 mm). (2) fMRI experimental design. (2a) To evaluate the brain functional correlates of the language function in subject D, two different fMRI paradigms were used, one to study the functional correlates of phonological fluency and another one of semantic decision. Language production and comprehension may follow a different lateralization pattern (e.g., left hemisphere for production and comprehension, and right hemisphere for comprehension), as it has been shown in healthy subjects (Bernal and Ardila, 2009; Lidzba et al., 2011) and in individuals with developmental brain anomalies (see Berthier et al., 2011). For the Phonological fluency Task, subject D was required to mentally evoke as many words as possible beginning with a specific letter. At the beginning of each active block, the participant heard a letter, and then he was instructed to start producing the words. The letter was different for each block (F, A, S. . .). In the Semantic Decision Task, thirty draws of animals were presented (6 in each block) via MRI compatible goggles and the participant was required to move the right finger if he saw an animal that was a farm animal. Half of the animals were farm animals and the other half were not. (2b) In addition, a finger tapping paradigm was used to evaluate the CMM. Two fMRI runs, one for the left hand and another for the right hand, were carried out. The four functional runs were presented following identical fMRI block designs which consisted of five task blocks interspersed with five blocks of rest in which the participant was just required to stop doing the task and simply wait with the eyes open looking to a fixation point. The fMRI experiment followed a block design in order to measure the sustained brain responses related to the studied language and motor processes. Each block (task and rest blocks) lasted 30 s, therefore the total duration of each run was of 5 min. During the active block, the participant was required to perform a self-paced unimanual finger-tapping task. One run required finger tapping of the right hand (Right finger Tapping Task), and the other required the movement of the left-hand finger (Left Finger Tapping Task). (3) fMRI pre-processing and analysis. Functional imaging data were pre-processed using standard procedures implemented in the Statistical Parametric Mapping software (SPM12)[4]. The same processing steps were performed for each functional run corresponding with each task. Both the high-resolution structural T1 image, and the fMRI runs were AC-PC oriented. Functional images of each run were realigned to the first scan of each series. The functional scans were co-registered to the T1 image. T1 image was segmented into different tissues, and the parameters derived from the segmentation were used for the normalization of the T1-weighted and the functional images. Finally, all functional images were spatially smoothed with an 8-mm FWHM kernel. Then, two conditions were specified for each task/run: Task and Rest. The mean timelines of BOLD signal in white matter and cerebrospinal fluid were included in the model as covariates together with realignment parameters, to remove signal from non-neural sources. The general linear model was applied to find activations of interest using the contrast: Task > Rest. Unless otherwise stated, all statistical results are reported at $p < 0.001$ uncorrected for multiple comparisons at the whole-brain level, with a minimal cluster extent of 20 voxels.

Results

Morphological description of the brain. A visual inspection of the T1-weighted anatomical image of subject D showed several developmental brain anomalies (**Figure 1**). The brain of subject D showed dilated right lateral ventricles, with hypertrophy of bilateral thalamus, caudate head and putamen. In addition, in the left hemisphere, he showed an open frontal operculum, the sylvian fissure was short and it ended in a marked ascending direction compared to a normal brain. Consequently, the left perisylvian area was reduced and the frontal gyri, the posterior temporal gyrus and the inferior parietal cortex were displaced. The right hemisphere seems to be larger than the left one and there was a right occipital petalia, findings already reported in children with specific language impairments (Soriano-Mas et al., 2009).

[4]http://www.fil.ion.ucl.ac.uk/spm/

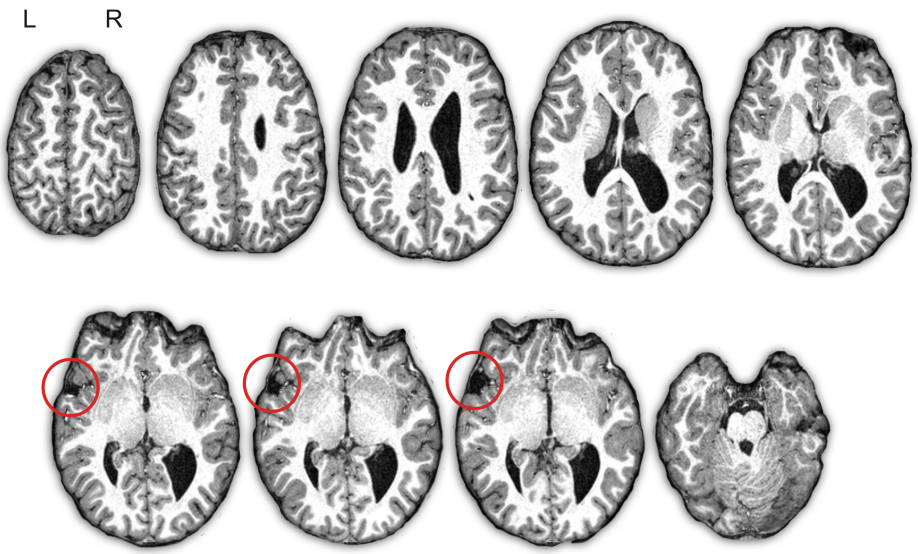

FIGURE 1 | Depiction of subject D's structural T1-weighted images. Axial slices of the brain in native space show the asymmetry of the volume of the lateral ventricles (right > left) with right occipital colpocephaly. There is an "open operculum sign" in the left hemisphere due to arrested development of the inferior frontal gyrus and superior temporal gyrus with exposure of the insular cortex (red circle). L, left; R, right.

Brain activation during phonological fluency task. The activation pattern associated to phonological fluency mainly involved areas of the right frontal lobe, such us the inferior and middle frontal gyri, and the left cerebellum (**Figure 2A** and **Table 4**). Two clusters of increased activation in left hemisphere appeared only with an uncorrected $p < 0.01$ threshold (**Figure 2A**). An overlap of the activation found in subject D in the phonological fluency task vs. rest contrast with a map resulting from a meta-analysis of fMRI studies focused on verbal fluency is reported in the **Supplementary Figure S1A**.

Brain activation during semantic decision task. Semantic decision activated a network comprising the typical ventral language stream bilaterally (see for instance Saur et al., 2008; López-Barroso et al., 2015) (**Figure 2B** and **Table 4**). These areas include bilateral IFG, both pars triangularis and pars opercularis, the anterior temporal lobe, the anterior and posterior superior temporal gyrus and the inferior parietal cortex. An overlap between the activation found in subject D in the semantic decision task vs. rest contrast and a map resulting from a meta-analysis of fMRI studies focused on semantics is reported in the **Supplementary Figure S1B**.

Brain activation during right motor finger tapping task. Subject D showed a bilateral pattern of activation involving the pre- and post- central gyri in both hemispheres as well as bilateral SMA, IFG and cerebellum. Results are reported in **Table 4** and **Figure 2C**.

Brain activation during left motor finger tapping task. Subject D showed a robust activation in the right precentral and postcentral gyri, and small clusters of activation in the right insula and bilateral cerebellum. All significant results are reported in **Table 4** and **Figure 2D**.

Functional Lateralization Indexes for Language and Motor Tasks

Methods

A lateralization index (LI) was calculated considering the activation difference between the left and right sides throughout different regions of interest (ROIs). ROIs were defined using WFU-Pickatlas toolbox[5]; Maldjian et al., 2003). For the four contrasts (Phonological fluency vs. rest, Semantic Decision vs. rest, Left Tapping vs. rest, and Right Tapping vs. rest), a LI was calculated using different ROIs: Hemisphere ROI (the whole right and left hemispheres) was used to calculate the LI in the four contrasts, IFG ROI (i.e., corresponding to Broca's area) was used to explore the LI in the two language contrasts, and the precentral gyrus ROI (i.e., corresponding to primary motor cortex) was used to calculate the LI on the two motor contrasts. The formula used to calculate the LI was: (Right – Left)/(Right + Left)*100, where Left and Right indicated the number of activated voxels in the corresponding left and right ROIs, respectively. The threshold used for the LI was identical as the one used for the contrasts ($p < 0.001$, uncorrected). The lateralization index ranges between -100 (extreme left lateralization) and 100 (extreme right lateralization). Values between −20 and 20 represent bilateral activation, and positive above 20 indicates left lateralization. This cut off to classify the patterns of lateralization was based on previous studies (Binder et al., 1996; Springer et al., 1999).

Results

In subject D, the LI comparing Phonological Fluency vs. rest contrast disclosed that the LI was 100 for both analyses, using the Hemisphere and the IFG ROIs, thus showing an

[5]http://www.nitrc.org/projects/wfu_pickatlas/

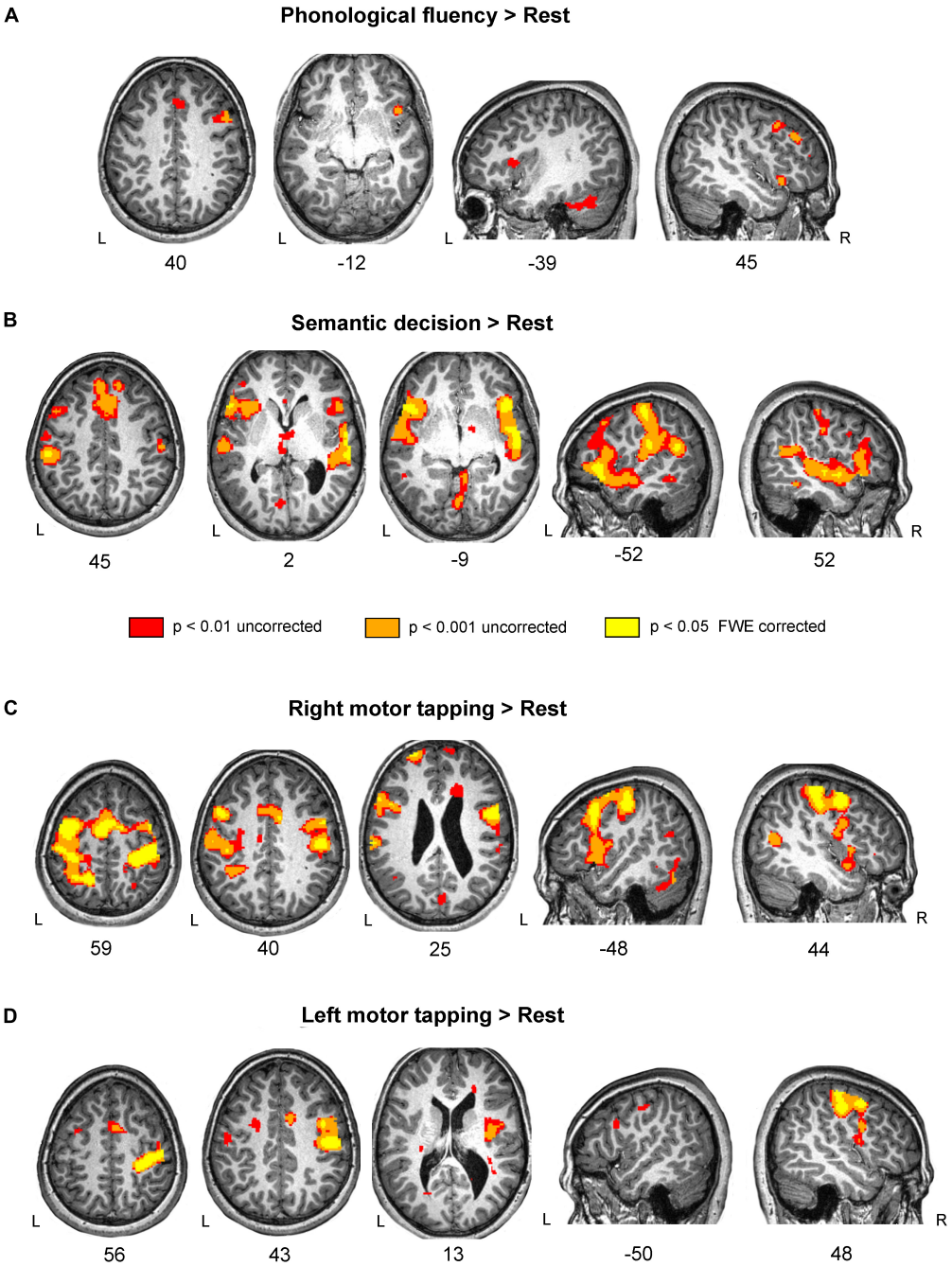

FIGURE 2 | Brain activation during language and motor tasks in subject D. **(A)** Phonological fluency vs. Rest contrast showed a restricted pattern of activation, mainly in the right frontal lobe. Notice that subject D had a marked deficit in fluency tasks, which correspond with the weak activation pattern during the task. **(B)** Enhanced fMRI activity for the Semantic decision vs. Rest contrast was found in a bilateral network involving frontal, temporal and parietal areas. **(C)** Activation in the bilateral pre- and post- central gyri and Supplementary Motor Area (SMA) on the Right motor tapping vs. Rest contrast. **(D)** Left motor tapping vs. Rest contrast revealed increased activity in the right pre-and post-central gyri as well as in the SMA. Results are shown at three different thresholds: $p < 0.05$ corrected; $p < 0.001$ uncorrected; and $p < 0.01$ uncorrected threshold, with 20 voxels cluster extent. Results are shown in standard space over subject D's normalized T1-weighted image. L, left; R, right.

extreme right lateralization in both cases (**Figure 3**). The LI for the activation related to semantic decision revealed that for the hemisphere ROI, the LI was of −13%, and of −10% when using the IFG ROI. Therefore, subject D showed a bilateral pattern of activation during semantic decision (**Figure 3**). The LI for the activation related to right motor tapping was −14% when analyses were restricted to the whole hemispheres, and −7% when they were restricted to the

TABLE 4 | Brain activations during the semantic decision, phonological fluency, left motor tapping and right motor tapping tasks.

Contrast	Cluster	Brain areas	Coordinates (Cluster peak)			Cluster size (no. of voxels)	FWE *p*-value (cluster level)	Unc. *p*-value (peak level)
			x	*y*	*z*			
Phon. fluency vs. Rest	1	R IFG pars triangularis	46	32	30	51	0.646	0.000
	2	L cerebellum Crus 1	−46	−60	−36	49	0.669	0.000
	3	R precental gyrus	28	41	20	48	0.681	0.000
	4	R IFG orbitalis	46	18	−14	37	0.808	0.000
	5	R middle frontal gyrus	30	44	22	45	0.716	0.000
Semantic decision vs. Rest	1	R IFG orbitalis, R superior temporal pole, R superior temporal gyrus	46	24	−14	2994	0.000	0.000
	2	L superior temporal gyrus, L inferior parietal cortex, L middle temporal gyrus	−58	−32	20	2553	0.000	0.000
	3	L superior frontal gyrus	−22	62	20	366	0.000	0.000
	4	L cerebellum (Crus 2 and 1), R cerebellum	−8	−88	−24	2943	0.000	0.000
	5	L IFG triangularis, L superior temporal gyrus	−54	24	−2	2131	0.000	0.000
	6	R SMA, L SMA	10	8	66	463	0.000	0.000
	7	L medial superior frontal gyrus	2	26	42	648	0.000	0.000
	8	R precentral gyrus	137	42	8	36	0.09	0.000
	9	Midbrain	−6	−30	−20	743	0.000	0.000
	10	R middle frontal gyrus,	34	42	24	162	0.054	0.000
	11	R inferior temporal gyrus (occipito-temporal)	50	−46	−20	27	0.97	0.000
	12	R posterior cingulate gyrus, precuneus	18	−44	32	398	0.001	0.000
	13	Cerebellum (vermis)	6	−52	−8	35	0.82	0.000
	14	Midbrain	10	−28	−16	73	0.40	0.000
		R superior frontal gyrus	20	62	28	20	0.95	0.000
	15	R inferior temporal gyrus (occipito-temporal)	−56	−52	−16	21	0.95	0.000
	16	R anterior parahippocampal gyrus	20	−10	−32	20	0.95	0.000
	17	R medial superior frontal gyrus	12	42	44	30	0.87	0.000
	18	R postcentral gyrus	56	−22	50	53	0.6	0.000
		L middle frontal gyrus	−54	18	40	27	0.9	0.000
	19	L anterior cingulum	0	38	22	23	0.93	0.000
Right tapping vs. Rest	1	R cerebellum, L cerebellum	14	−72	−44	338	0.002	0.000
	2	R superior frontal gyrus, R postcentral gyrus, R precentral gyrus	20	−10	72	5477	0.000	0.000
	3	L superior parietal cortex, L precentral gyrus,	−32	−52	64	6322	0.000	0.000
	4	R cerebellum, vermis, L cerebellum	22	−56	−26	2805	0.000	0.000
	5	L superior frontal gyrus	−26	62	22	192	0.025	0.000
	6	R posterior middle temporal gyrus	44	−66	12	87	0.278	0.000
	7	R insula, R rolandic operculum	48	10	0	122	0.121	0.000
	8	L lingual gyrus	−8	−92	−14	68	0.433	0.000
	9	L middle occipital gyrus	−42	−76	18	27	0.9	0.000
	10	L inferior temporal gyrus	−54	−54	−16	51	0.62	0.000
	11	L middle temporal gyrus	−42	−56	18	40	0.76	0.000

(Continued)

TABLE 4 | Continued

Contrast	Cluster	Brain areas	Coordinates (Cluster peak)			Cluster size (no. of voxels)	FWE *p*-value (cluster level)	Unc. *p*-value (peak level)
			x	*y*	*z*			
	12	R calcarine	8	−74	18	189	0.027	0.000
	13	L putamen	−18	−4	−10	36	0.8	0.000
	14	Midbrain	−4	−20	−22	162	0.049	0.000
	15	R lingual gyrus	20	−64	−27	74	0.37	0.000
	16	L cerebellum (Crus 1)	−48	−68	−26	22	0.94	0.000
	17	R insula	42	6	−18	41	0.74	0.000
Left tapping vs. Rest	1	R superior frontal gyrus, R SMA	18	−8	74	432	0.000	0.000
	2	R postcentral gyrus, R precentral gyrus	28	−32	52	2216	0.000	0.000
	3	L cerebellum	−12	−68	−44	27	0.9	0.000
	4	L cerebellum	−6	−48	−14	534	0.000	0.000
	5	R insula, R rolandic operculum	38	−8	12	145	0.06	0.000
	6	R cerebellum	20	−60	−24	104	0.16	0.000
	7	L postcentral gyrus	−40	−20	28	46	0.66	0.000

All results are reported $p < 0.001$, uncorrected for multiple comparisons at the voxel level, with a minimum cluster extent of 20 voxels. Likewise, the results that are also corrected for multiple comparisons (FWE, $p < 0.05$) are also reported. Peak coordinates are reported in MNI coordinates.

precentral gyrus ROIs. Both LIs suggest a symmetrical activation pattern (**Figure 3**) for the right motor tapping task. Finally, the LI for the activation related to left motor tapping was of 100% using both the hemisphere ROIs and the precentral gyrus ROIs, suggesting an extreme right lateralization (**Figure 3**).

Diffusion Tensor Imaging (DTI) Pre-processing

Diffusion data pre-processing started with motion and eddy current correction as using FMRIB's Diffusion Toolbox (FDT) (Smith et al., 2004; Woolrich et al., 2009), and the Brain extraction was performed with the Brain Extraction Tool (BET), both parts of the FMRIB Software Library (FLS)[6]. Diffusion tensor estimation was carried out using Diffusion Toolkit's least-square estimation algorithm for each voxel (Ruopeng Wang and Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital). Whole-brain tractography used an angular threshold of 35° and an FA threshold of 0.15. A fractional anisotropy (FA) map was generated using Diffusion Toolkit.

Deterministic tractography

Methods. Different white matter tracts were selected as tracts of interest due to their implication in language or motor functions, and consequently they were reconstructed and examined. Specifically, as tracts related to language, we selected the three segments of the arcuate fasciculus (AF) (long, anterior, and posterior) and the frontal aslant tract (FAT) as dorsal language pathways; while the inferior fronto-occipital fasciculus (IFOF) and the uncinate fasciculus (UF) were selected as ventral language pathways. Referred to the motor function, we examined the corpus callosum and the corticospinal tracts. Virtual dissections of the tracts were performed using the software TrackVis[7]. Spheres a hand-drawn ROIs were defined over the FA or FA color maps and used to isolate single tracts following previously reported procedures (Catani and Thiebaut de Schotten, 2008; López-Barroso et al., 2013). When required, spurious fibers were removed from the main fiber tracts by using an additional avoidance ROI. All tracts were dissected in native space and in both cerebral hemispheres.

Results. All the tracts were intact (**Figure 4**) and could be virtually reconstructed contrary to what happens when there is a brain injury, however, the morphology of some of these tracts was atypical. In the left hemisphere, among the dorsal tracts the FAT was reconstructed and it showed a normal morphology; the long, the anterior and the posterior segments of the AF were voluminous, especially the long AF segment, but accordingly to the shape of the sylvian fissure in the left hemisphere, both the frontal and the temporal branches were shorter than in a normal brain, while the dorsal terminations of the frontal branches of the anterior and the long segments reached the superior frontal gyrus. The posterior and anterior segments terminated in the inferior parietal cortex, but their atypical shape was a consequence of the displacement of these cortical areas (**Figure 4**). In the right hemisphere, the FAT showed a typical shape, whereas again the three segments of the AF showed an atypical pattern, associated to the atypical morphology of the perysilvian cortex. The ventral tracts were reconstructed in both hemispheres (**Figure 4**). The UF and IFOF of the left hemisphere showed greater volume than in the right hemisphere, following the pattern found for the AF.

The studied motor tracts were also successfully reconstructed (**Figure 4**). With the current methodological resolution, we were not able to find evidence for pyramid decussation at the level of the medulla oblongata. The right corticospinal tract (CST) showed greater volume than the left CST. The corpus callosum that connect the motor areas from both hemispheres was displaced, thus we could not reconstruct direct connections between contralateral frontal motor areas.

[6] www.fmrib.ox.ac.uk/fsl/

[7] www.trackvis.org

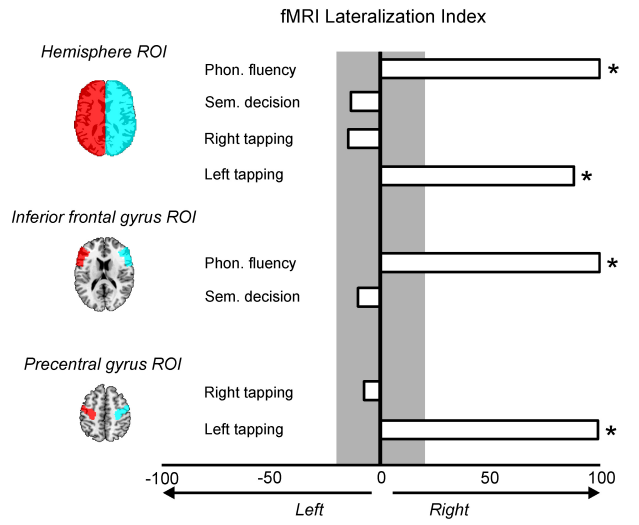

FIGURE 3 | Lateralization indexes (LI) for the four fMRI contrasts and the region of interest (ROI) used. LI values greater than 20% mean right lateralization and are marked with an asterisk; LI values greater than –20% mean left lateralization and no LI was found with this pattern. Values between –20 and 20% (gray color) mean a symmetrical pattern of activation.

Dichotic listening

Methods. Dichotic listening was evaluated with a Spanish version of the three-pair dichotic listening task (DLT) (Strouse and Wilson, 1999; Zenker et al., 2007). Before performing this task, subject D underwent a tonal audiometry which revealed normal hearing bilaterally. Subject D was presented with a series of one to three pairs of numbers. Each pair consists of one number (from one to ten) presented on the left ear and a different number (from one to ten) presented on the right ear. After each number was presented, subject D was required to orally repeat which digits he has heard in each ear. Based on the DLT, Zenker et al. (2007) obtained the LI, which is computed as: LI = [(Right-Left)/(Right + Left)]*100, where Right and Left are computed as the total number of individual digits recognized presented respectively to the right and left ears. In Zenker et al.'s (2007) study, the LI was 17% for the 6–12 age group and 5% for the 13–19 age group.

Results. In the DLT, subject D recognized 30% of the digits presented to the left ear, and only 19% of the digits presented to the right ear. The LI was -55% (i.e., strongly right brain lateralized), clearly below the scores of his age group (i.e., 17%). This means that subject D was less able to detect stimuli processed in the left hemisphere than in the right hemisphere, thus suggesting that his right hemisphere was dominant for auditory processing. These results complemented the findings from fMRI, which showed right hemisphere lateralization for speech production.

Transcranial Magnetic Stimulation

Methods

Motor evoked potentials (MEP) to the four limbs were obtained simultaneously using a transcranial magnetic stimulation (TMS) with a monopulse stimulator (Magstim 100) with a round coil (12 cm). The coil was placed tangentially to the scalp with its center over the vertex for cortical stimulation, and spinal roots were stimulated at C6–C7 and L4–L5 spaces while recording at the same positions bilaterally over the target muscles (1st dorsal interosseous and tibialis anterior muscles) with surface electrodes. Central conduction time (CCT in milliseconds) was measured as the difference between total and peripheral motor conduction time. The amplitude (μv) of the cortical response was measured as the average at least 3 supramaximal responses and as an amplitude ratio with the compound motor action potential (CMAP) electrically elicited (ZAMPR). For identification of cortical silent periods (CSP) the same protocol as for eliciting the MEP (while subject D performed a maximal voluntary contraction) was used. The CSP was quantified as the time elapsed between the onset of the MEP and the time at which the post-stimulus background EMG returned to the pre-stimulus mean amplitude (Poston et al., 2012).

Results

The TMS disclosed cortical bilateral responses with the same latency and amplitude for both 1st dorsal interosseous muscles with unilateral stimulation of hand motor cortical area, with a normal threshold (greater when stimulating the right hemisphere). Stimulation of both hemispheres showed a markedly diminished cortical silent periods (CSP) for both muscles. Values of different parameters (e.g., motor threshold, central conduction time, MEP latency, MEP cortical amplitude) obtained for hands and feet of subject D are presented in **Supplementary Tables S1–S4**.

Genetic Testing

Methods

Genetic testing was performed to detect mutations that disrupt the development of commissural tracts (i.e., Germline DCC mutations) and are associated with CMM (Méneret et al., 2014). The coding and flanking intronic regions of DCC (deleted in colorectal carcinoma [OMIM *120470]), RAD51 (RAD51 recombinase [OMIM *179617]), and DNAL4 (Dynein Axonemal Light Chain 4 [OMIM * 610565]), were amplified by polymerase chain reaction (PCR) and Sanger sequenced on an ABI 3100 automatic sequencer (Applied Biosystems, Foster City, CA, United States). Resulting electropherograms were visually analyzed using Sequencher software (Gene Codes Corp. Ann Arbor, MI, United States). Primer pair sequences and PCR conditions are available under request.

Results

The genetic study did not disclose any pathogenic variant in the three analyzed genes (DCC, RAD51, and DNAL4).

DISCUSSION

We described, for the first time, the case of an adolescent boy who met diagnostic criteria for DLD (DSM-V, code: 315.32 [F80.2]; American Psychiatric Association, 2013) showing a profile of language impairment resembling DA. In all previous

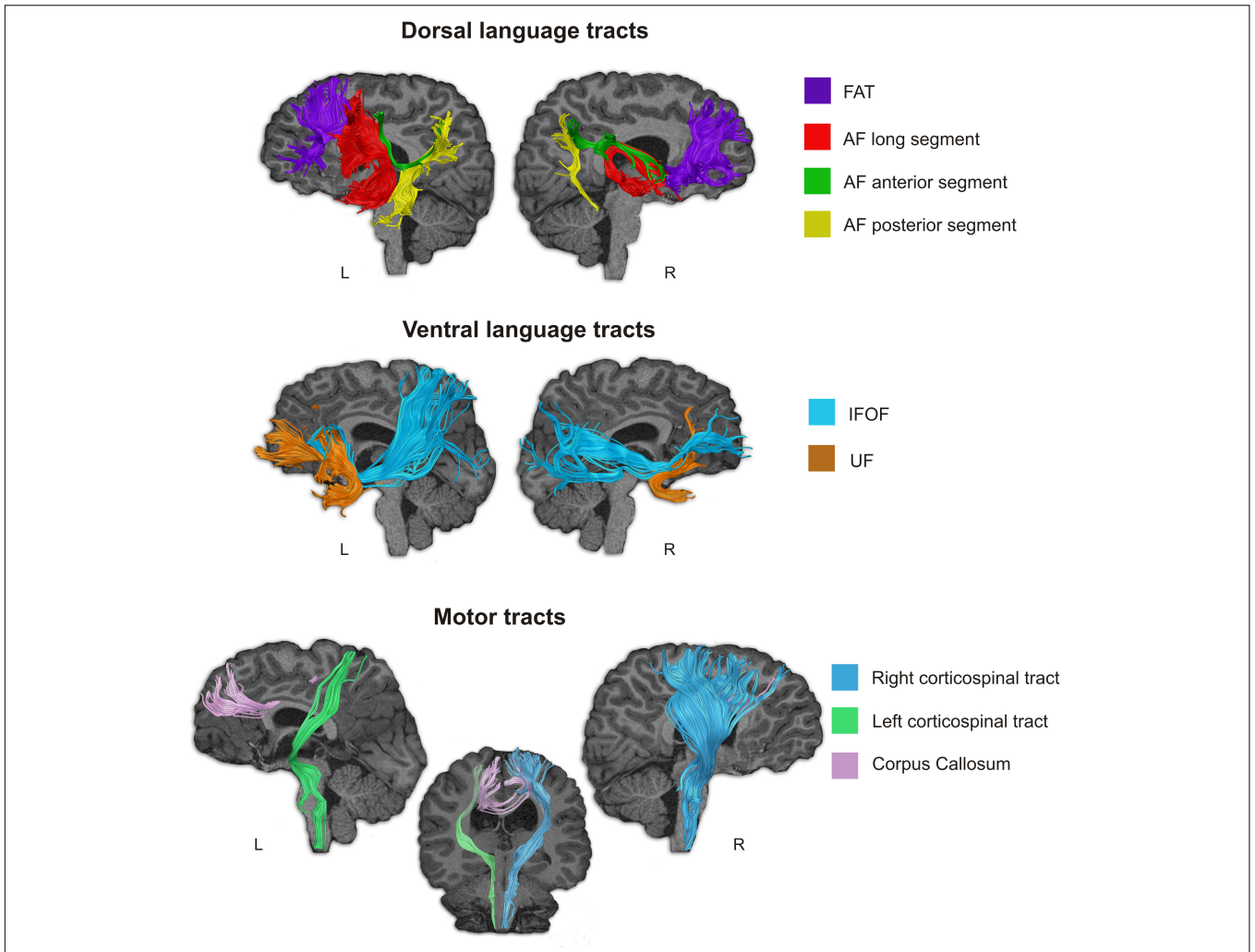

FIGURE 4 | Language-related and motor-related white matter pathways of subject *D* were tracked using deterministic Tractography. Notice that all studied language related pathways (dorsal and ventral) could be reconstructed, however the three segments of the AF showed an atypical distribution. Although they connect frontal, parietal and temporal regions, since these areas were displaced in Subject *D* due to the morphological abnormality in his brain, the shape of these tracts is abnormal. The motor tracts were also reconstructed, but we could not find the pyramid decussation normally found in the caudal part of the medulla oblongata.

reports of ADA it was associated with focal brain lesions (tumors, stroke) and cortical-subcortical atrophy secondary to progressive degenerative disorders mostly involving fronto-subcortical regions. However, in subject D the occurrence of such syndrome coexisted with a malformed brain. Therefore, the neurobiological underpinnings of DDD in this adolescent boy could be considered of developmental origin. In the next section we examine what could be the causal mechanisms that might underlie DDD.

Mechanisms Underpinning Developmental Dynamic Dysphasia

Several competing theoretical interpretations have been advanced to account for ADA (see Robinson et al., 2006). Indeed, cases of ADA have variously linked to impaired verbal planning (Costello and Warrington, 1989; Bormann et al., 2008), impaired selection between competing verbal responses (Robinson et al., 1998, 2005), inadequate semantic strategy formation (Gold et al., 1997) and reduced spontaneous and intentional activation of lexical-semantic representations (Raymer et al., 2002; Cox and Heilman, 2011; Satoer et al., 2014). These disrupted mechanisms may explain the language-specific form of the syndrome (Robinson et al., 1998, 2015). Nevertheless, complementary proposals suggest that reduced speech production may also be related to domain-general deficits resulting from impairment in novel thought generation and deficits in fluent sequencing of novel thoughts (Robinson et al., 2006, 2015a,b; Bormann et al., 2008; Robinson, 2013). Interpretation of ADA within this broader framework coincide with the original formulation by Luria and Tsvetkova (1967), who viewed this syndrome as a condition derived from general executive and attentional impairments related to lesions in the frontal lobes. Therefore, it seems that some cases ADA may result from a hybrid

mechanism that combines failures in domain-general and language-specific functions.

Another candidate mechanism to account for ADA is the impairment of automatic spreading activation of lexical items during production tasks. Luria introduced the term "spreading activation syndrome" for explaining a subtype of ADA (see Lebrun, 1995). In this context, the word "spreading" means that during speech production tasks (e.g., naming) many words are activated simultaneously interfering one each other while the subject is selecting which one should be produced (Dell, 1986; Thompson-Schill et al., 1997; Levelt et al., 1999; Moss et al., 2005; Silkes and Rogers, 2012; Anders et al., 2017; Schnur, 2017). In this connection, we recently studied an adult person with ADA due to a left opercular-insular infarction, who commented on that during language tasks "many words come to my mind, but I cannot decide which one to choose. . ." (Berthier et al., *in preparation*). However, this mechanism seems not to be the one that explain DDD in subject D, who instead reported that no words come to him during speech production tasks. Subject D was capable of carrying out most language tasks dependent upon external stimuli (naming, repetition), but creating and organizing a narrative was challenging for him. It seems that in the case of subject D a marked reduced activation of lexical items prevails as a possible explanation for the impaired ability to generate words and sentences in both real life and testing situations (see Alexander, 2006; Stuss and Alexander, 2007; Cox and Heilman, 2011; Silkes and Rogers, 2012). Moreover, cognitive testing in subject D revealed impaired performance in all tasks tapping executive functions (TMT, HSCT, WCST, ST) unveiling that dysfunctional domain-general mechanisms are also contributing to dDD.

The pattern of performance exhibited by subject D on the two-part sentence completion task (HSCT) and on experimental tasks for DA would further illuminate the putative mechanism of reduced activation of lexical items underlying DDD. The HSCT is thought to assess both initiation speed and response suppression (Burgess and Shallice, 1997); therefore, delays in completing the missing word (Section 1) and failures to inhibit a strongly activated response before generating a new unconnected one (Section 2) are the expected outcomes in persons with frontal lobe involvement (Robinson et al., 2015a, 2016). Analysis of this task in subject D revealed impaired performance in the two sections and errors were omissions. No automatic completions were produced in Section 2 and, instead, subject D produced no responses. Failure to generate a completion word has been associated with left frontal lesions (Robinson et al., 2015b, 2016) and represents a typical pattern of performance in individuals with ADA (Robinson et al., 2005). In the same vein, he performed significantly worse than healthy controls in experimental tests of DA (Robinson et al., 1998), particularly in the more demanding ones. One constant characteristic of subject D while performing these tasks was that he frequently remained silent when asked to produce a sentence or to generate a brief story. When he was asked why he did not produce the requested information, he said "I have no words. . .. Words don't come to me." Moreover, his performance on the picture-generated narrative and phonological and semantic fluency tasks were also extremely poor. Nevertheless, other language functions (i.e., semantic comprehension, repetition of words, non-words and sentences, noun and verb naming, oral reading and spelling) were slightly below average or average. This dissociation, characteristic of ADA (Robinson et al., 1998, 2006; Berthier, 1999), may also characterize DDD. Defective semantic strategy formation has been considered implicated in some case of ADA (Gold et al., 1997), but subject D was fully capable of activating semantic knowledge when given an external stimulus as demonstrated by his preserved ability to name nouns and verbs. This pattern of performance (failure in initiating and sustaining a response in the absence of external cues) in subject D may be indicative of failure to spontaneously active lexical semantic representations (Cox and Heilman, 2011) perhaps due to impaired attentional processes (energization) (Stuss and Alexander, 2007; Stuss, 2011; Barker et al., 2018).

Pitfalls of Establishing Brain-Behavior Relationships in a Malformed Brain

The syndrome of ADA is uncommon (Robinson et al., 1998; Berthier, 1999; Alexander, 2006) and we envisage that a DDD, as the one found in subject D, may be even rarer because it coexisted with bilateral brain malformations that distorted the architecture and connectivity of networks mediating expressive language and communication. Nevertheless, piecemeal analysis of the different malformations may illuminate the mechanisms underlying DDD in the present case. In first place, we analyze the role of gyral abnormalities in the left operculum on speech production deficits. The structural MRI showed a short sylvian fissure with arrested development of the left fronto-temporal operculum and exposure of a hypoplastic insular cortex (open operculum) indicative of a cortical dysplasia (Tatum et al., 1989; Piven et al., 1990; Van Bogaert et al., 1998). Detailed visual analysis of thin slices in high-resolution MRI also revealed that the configuration of the right Sylvian fissure was also atypical. Functional imaging also showed atypical results. While healthy subjects activate the left IFG in fluency tasks, as revealed by the Neurosynth meta-analysis for the term "verbal fluency" (**Supplementary Figure S1A**), the fMRI acquired during a phonological fluency task in subject D revealed that increased activation in the left inferior frontal gyrus resulted only when using an uncorrected $p < 0.01$ statistical threshold during this language task compared to rest. Small foci of activation were found in the homologous contralateral gyrus at a lower statistical threshold $p < 0.001$ uncorrected). Although the fMRI experiment and the structure of the fluency task applied in this study did not allow to separate right from bad trials (i.e., sustained brain response was measured during the whole block in which the subject was instructed to mentally evoke as many words as possible), the atypical pattern of functional activation together with the fact that subject D showed a poor performance in fluency task, suggest that contralateral functional plasticity in this case has been maladaptive. These results suggest that in the presence of a dysfunctional left frontal cortex, the right anterior perisylvian area was not fully competent to subserve efficient communication. Thus, it seems that this cross-hemispheric plasticity (left → right) could compensate basic language operations (i.e., object and verb naming, repetition), but was not sufficient to guarantee more

elaborated language and communication skills required for the generation of fluent discourse.

Early left hemisphere injury may result in functional reorganization that, although permits sparing of language and motor skills, may distort the development of right hemisphere functions (Sandson et al., 1994; Satz et al., 1994). Moreover, individuals with unilateral, bilateral or diffuse gyral abnormalities in the frontotemporal operculum, like the ones found in subject D, have language delay (Guerreiro et al., 2002) which may persist into adulthood (Graff-Radford et al., 1986; Guerreiro et al., 2000). In such cases, positron emission tomography shows altered (decreased, increased or both) metabolic activity in both cerebral hemispheres (Van Bogaert et al., 1998; Luat et al., 2006). In the same line, children with specific language impairments (developmental dysphasia) show lack of fMRI activation during category fluency, responsive naming and picture naming tasks in left perisylvian language areas with hyperactivation in the right inferior frontal gyrus, insula and caudate nucleus (de Guibert et al., 2011). Note that the compensation of language deficits by the right hemisphere in left brain-damaged children is variable and depends on the residual capacity of the left hemisphere to maintain some language function (see references in Reilly et al., 2013). Nevertheless, another influential factor for the expected bias of transferring language functions to the right hemisphere in cases with left hemisphere damage (developmental or acquired) would be the functional status of the right hemisphere. We suggest that DDD in subject D may have resulted from the left perisylvian dysgenesis and also for the limited capacity of the unfit right hemisphere to ensure the development and evolution of more elaborated aspects of oral expression (i.e., conversation, narrative discourse) (Berthier et al., 2012; Catani and Bambini, 2014; Lomlomdjian et al., 2017). In other words, impaired language generation (verbal adynamia) in subject D may have resulted from inefficient neural plasticity in both hemispheres. By contrast, auditory comprehension in subject D ranged from preserved to mildly impaired performance in most tasks and the fMRI showed that activation during a semantic decision task occurred in canonical areas mostly linked by the ventral stream (Saur et al., 2008; López-Barroso et al., 2015). These areas include bilateral IFG, both pars triangularis and opercularis, the anterior temporal lobe, the anterior and posterior superior temporal gyrus and the inferior parietal cortex. **Supplementary Results** revealed that although there was a substantial overlap between the meta-analysis fMRI results in healthy subjects for the term "semantic" and the results from the contrast Semantic Decision vs. rest in subject D (**Supplementary Figure S1B**), the pattern found in subject D was more bilateral. This higher overlap compared to the one observed for the fluency task is in line with the fact that subject D's performance in comprehension and semantic tasks was acceptable, and in addition it would show some evidence that at least in some functions, the atypical brain configuration observed in this case can be functional. Nevertheless, since results from the supplementary Neurosynth fMRI meta-analysis come from heterogeneous studies (e.g., different population, different tasks), these results should be taken cautiously and interpreted as a whole with the rest of the image results and clinical characteristics reported.

In second place, we examine the putative role of the dysmorphic white matter tracts in DDD. Previous studies have shown a strong relationship between the failure to identify the left AF and language dysfunction in cases with developmental cortical gyral abnormalities (Andrade et al., 2015; Paldino et al., 2015, 2016). Poor development of the left FAT has been related to profound expressive language impairmentin a child with a sex-linked chromosomopathy (karyotype 49, XXXXY) syndrome (Dhakar et al., 2016) and therapeutic interventions improving speech production and everyday verbal communication in post-stroke aphasia correlated with structural plasticity of the FAT and direct segment of the AF (Berthier et al., 2017). While there is marked individual variability in the configuration of left and right white matter tracts in healthy subjects (Gharabaghi et al., 2009; Berthier et al., 2012), the spatial arrangement of most white matter bundles in subject D was atypical. We could retrieve all long-distance white matter tracts in both cerebral hemispheres, but their configuration was distorted adopting an architecture that markedly deviated from the normal pattern. The cumbersome arrangements of most retrieved white matter tracts in both cerebral hemispheres were probably the result of the non-canonical configuration of the cortical mantle. DTI-tractography also disclosed abnormal decussation of the CSTs, a finding that correlated in subject D with the CMM.

The study of neurophysiological correlates of CMM with TMS study showed that unilateral stimulation of hand motor cortical area disclosed cortical bilateral responses. There are some limitations of our TMS study. First, TMS was not guided by a neuronavigation software module. Therefore, we cannot confidently determine the position of the current with respect to the brain sulcus and surface of subject D. Second, the use of a round coil in our TMS study cannot rule out the simultaneous stimulation of the motor cortex in both hemispheres because of the coil structure. Third, we also found that stimulation of both cerebral hemispheres showed diminished cortical silent periods (CSP) for both muscles. CSP are indexes of corticospinal inhibition during a tonic muscular contraction probably representing a GABAb-mediated inhibitory neurotransmission (Tergau et al., 1999). Therefore, shortened CSP after unilateral TMS in subject D may reflect the output from the non-stimulated M1 so that both the activity of motor cortices (M1) was released with intended uni-manual movements (Cincotta et al., 2002). These bilateral responses were absent when studying the cortical stimulations for leg muscles. Genetic testing to identify mutations associated to altered development of commissural tracts (i.e., Germline DCC mutations) (Méneret et al., 2014) were negative.

Is the Diagnosis of Developmental Dynamic Dysphasia Reliable?

There is a caveat about reliability of diagnosis when one describes a well-known yet rare syndrome occurring for the first time in association with a new pathological condition (abnormal brain development). Analysis of more cases is clearly needed to confirm or reject the accuracy of the diagnosis. Note, however, that original cases of ADA were invariably associated

to focal lesions (tumors, stroke, trauma) (i.e., Costello and Warrington, 1989; Robinson et al., 1998) but several years later similar cases have been related to different neurodegenerative conditions (i.e., Parkinson's dementia, progressive supranuclear palsy, corticobasal degeneration, prion diseases) (Kartsounis et al., 1991; Esmonde et al., 1996; Warren et al., 2003; Caine et al., 2018; Magdalinou et al., 2018). The syndrome of ADA is a variant of TCMA (Berthier, 1999) and cases of this syndrome of developmental origin have not been reported so far. However, developmental conduction aphasia has recently been reported in a group study showing that specific and long-lasting problems with speech repetition were similar to the syndrome reported in adults (Northam et al., 2018). Similarly, the foreign accent syndrome previously described associated to focal lesions (Moreno-Torres et al., 2016) and neurodegenerative disorders (Luzzi et al., 2008) has recently been reported as a developmental disorder (Mariën et al., 2009; Berthier et al., 2016; Keulen et al., 2016). The second point is that subject D had non-language cognitive and motor disorders that may cast doubts on the reliability of the diagnosis of DDD. The contribution of impaired performance on tasks tapping executive functions to DDD is in agreement with reports of ADA, which attributed such deficits to impaired domain-general mechanisms (Robinson et al., 2006). Nevertheless, we consider the presence of CMM and low intellectual function unrelated to DDD. In support of this argument, most cases of CMM are discrete and not disabling coursing without concomitant cognitive deficits (Méneret et al., 2014, 2015) and low IQ is a constant feature of patients with ADA of different etiologies (Robinson et al., 1998, 2006, 2015).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Research Committee Provincial of Malaga, Spain. The participants provided their written informed consent to participate in the study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. MB, GD, MT-P, and DL-B were involved in conception and design, acquisition of data, or analysis and interpretation of data. LE, LM-C, DM-S, and PZ were involved in cognitive and language testing. JC and OD-I performed genetic testing. IM-T, VF, and MP performed the neurophysiological studies. MB and DL-B interpreted the neuroimaging data. MB, GD, and DL-B drafted the manuscript and revised it critically for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2020.00073/full#supplementary-material

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Pharmacotherapy of Traumatic Childhood Aphasia: Beneficial Effects of Donepezil Alone and Combined With Intensive Naming Therapy

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At present, language therapy is the only available treatment for childhood aphasia (CA). Studying new interventions to augment and hasten the benefits provided by language therapy in children is strongly needed. CA frequently emerges as a consequence of traumatic brain injury and, as in the case of adults, it may be associated with dysfunctional activity of neurotransmitter systems. The use of cognitive-enhancing drugs, alone or combined with aphasia therapy, promotes improvement of language deficits in aphasic adults. In this study we report the case of a 9-year-old right-handed girl, subject P, who had chronic anomic aphasia associated with traumatic lesions in the left temporal-parietal cortex. We performed a single-subject, open-label study encompassing administration of the cholinergic agent donepezil (DP) alone during 12 weeks, followed by a combination of DP and intensive naming therapy (INT) for 2 weeks and thereafter by a continued treatment of DP alone during 12 weeks, a 4-week washout period, and another 2 weeks of INT. Four comprehensive language and neuropsychological evaluations were performed at different timepoints along the study, and multiple naming evaluations were performed after each INT in order to assess performance in treated and untreated words. Structural magnetic resonance imaging (MRI) was performed at baseline. MRI revealed two focal lesions in the left hemisphere, one large involving the posterior inferior and middle temporal gyri and another comprising the angular gyrus. Overall, baseline evaluation disclosed marked impairment in naming with mild-to-moderate compromise of spontaneous speech, repetition, and auditory comprehension. Executive and attention functions were also affected, but memory, visuoconstructive, and visuoperceptive functions were preserved. Treatment with DP alone significantly improved spontaneous speech, auditory comprehension, repetition, and picture naming, in addition to processing speed, selective, and sustained attention. Combined DP-INT further improved naming. After washout of both interventions, most of these beneficial changes remained. Importantly, DP produced no side effects and subject P attained the necessary level of language competence

to return to regular schooling. In conclusion, the use of DP alone and in combination with INT improved language function and related cognitive posttraumatic deficits in a child with acquired aphasia. Further studies in larger samples are warranted.

Keywords: language, childhood aphasia, anomia, traumatic brain injury, donepezil, pharmacological treatment, intensive naming therapy

INTRODUCTION

Childhood aphasia (CA) is defined as a language impairment that affects previously acquired linguistic abilities, which cannot be explained by other cognitive or physical disorders (Aram, 1998). Since the diagnosis of CA requires a minimum development of linguistic skills prior to the brain injury, the age of 2 years is the established cut-off to differentiate CA from language developmental disorders (Woods and Teuber, 1978; Aram et al., 1985; Van Hout, 1997; Van Hout, 2003; Avila et al., 2010).

CA exhibits some singularities that distinguishes it from adult aphasia and raises the need for developing specific lines of research that take into account the characteristics of this population. Among these differences is the fact that brain damage during childhood may not only affect previously acquired language functions but also interfere with the ongoing brain maturation and language development. A further relevant differential feature is related to the etiology, thus while stroke is the leading cause of adult aphasia, the main cause of cognitive disability and aphasia in children and adolescents is traumatic brain injury (TBI) (Rothenberger, 1986; Jennett, 1996; Sergui-Gomez and MacKenzie, 2003; Babikian and Asarnow, 2009). Relevantly, one third of children that suffer a severe TBI, as measured by the Glasgow Coma Scale (Teasdale and Jennett, 1976), exhibit residual cognitive and language deficits (Anderson et al., 2001; Anderson et al., 2005; Anderson and Catroppa, 2006; Anderson et al., 2009) that may persist in the long term. Language disorders such as aphasia have a tremendous impact in the cognitive, social, and emotional development in children and adolescents, often resulting in reduced social integration, poor academic achievement, and behavioral problems (Beitchman et al., 2001; Johnson et al., 2010), as well as an increased risk of developing anxiety and social isolation during adulthood (Brownlie et al., 2016).

TBI usually results in focal and diffuse brain damage causing a wide range of linguistic deficits that may be contingent on several variables such as age at the time of injury, lesion size and location, severity of the injury, as well as premorbid language functioning (Sullivan and Riccio, 2010). Axonal injury derived from diffuse damage emerges as a result of the sudden acceleration and deceleration forces together with the simultaneous rotation of the freely moving brain mass (Levin, 2003; Vik et al., 2006). Importantly, diffuse axonal injury frequently affects white matter bundles connecting frontal and temporal cortical areas (Levin, 2003; Vik et al., 2006) that support linguistic and executive functions, including attentional capacity and processing speed. Accordingly, linguistic deficits in CA are frequently associated with weakened executive functions, such as deficits in lexical access as observed in naming tasks (Coelho, 2007; Slomine and Locascio, 2009). In fact, word finding difficulties (i.e. anomia) in spontaneous speech, naming and fluency tasks (Laine and Martin, 2006) are common deficits in the medium and long term after TBI and may persist even when other domains have been recovered (Van Hout et al., 1985; Narbona and Crespo-Eguilaz, 2012). However, despite its high frequency (Ewing-Cobbs and Barnes, 2002), reported cases of CA resulting from TBI are scarce, probably because in many cases linguistic deficits are hidden behind general cognitive impairments (e.g., attention).

At brain level, language and executive functions depend on the activity of distributed networks involving bilateral dorsal and ventral structures. Current models suggest that language functions are supported by two functionally and anatomically segregated processing streams: dorsal and ventral (Hickok and Poeppel, 2000). On the one hand, the dorsal stream is involved in verbal production and repetition (Saur et al., 2008) required, for instance, for phonological word learning (López-Barroso et al., 2013). This stream is supported by the arcuate fasciculus (AF) system connecting frontal, postero-temporal, and infero-parietal areas (Hickok and Poeppel, 2007). On the other hand, the ventral stream projects from the superior temporal gyrus to the middle and inferior temporal cortices to support semantic and comprehension processes (see Hickok and Poeppel, 2007). This ventral interaction occurs mainly through the inferior fronto-occipital fasciculus (IFOF), the inferior longitudinal fasciculus (ILF) and the uncinate fasciculus (UF) (Catani and Thiebaut de Schotten, 2008). Despite the above-mentioned functional division of labour, the language system is flexible enough to recruit additional areas during high-demanding language situations (Lopez-Barroso et al., 2011; Torres-Prioris et al., 2020) or during development, when some pathways are not fully mature (Brauer et al., 2011). For instance, studies of children with brain injury have shown that early damage to the AF may be succesfully compensated through recruitment of ipsilateral and contralateral brain areas and tracts, resulting in an average performance on multiple language tasks (Rauschecker et al., 2009; Asaridou et al., 2020), although some deficits may persist (Yeatman and Feldman, 2013). In this line, after early brain damage, functional and structural rightward lateralization of the dorsal pathway is associated with better language outcomes (Northam et al., 2018; François et al., 2019). Despite this evidence, spontaneous readjustment of the language system after brain lesion seems to be limited as evidenced by the frequent persistence of language deficits (Tavano et al., 2009; Turkstra et al., 2015; François et al., 2016). Therefore, research aimed at developing effective interventions to potentiate language recovery in CA is highly needed.

Despite the increasing efforts to advance in the development of effective therapeutic strategies for the cognitive and language after-

effects of childhood TBI, studies targeting modern treatment approaches (cognitive/language therapy, pharmacotherapy, non-invasive brain stimulation) in CA are still scarce (for a review on rehabilitation programs for children with acquired brain injury not focused on language, see Laatsch et al., 2007; Slomine and Locasio, 2009). The fact that there are so few studies on this topic is probably because interventions for CA are frequently tailored to individual cases and carried out in instructional settings (Bowen, 2005; Duff and Stuck, 2015) with no sound methodological designs. The few existing intervention studies mainly focused on exploring the efficacy of behavioral strategies, as well as on identifying compensatory behaviors (Sullivan and Riccio, 2010; Turkstra et al., 2015). Overall, these interventions have proven beneficial effect for intensive training (6 to 8 weeks) of different language skills (lexical retrieval, verbal comprehension, fluency, communication pragmatic) and cognitive functions (attention, executive functions) commonly affected in TBI (Thomas-Stonell et al., 1994; Wiseman-Hakes et al., 1998; Chapman et al., 2005). Yet, the results from these studies are variable and, despite the growing number of published reports on cognitive and behavioral deficits after childhood TBI, rehabilitation recommendations are still insufficient.

The well-established strategy of using cognitive-enhancing drugs alone or in combination with speech-language therapy in adults with post-stroke aphasia (see Berthier and Pulvermuller, 2011; Berthier et al., 2011) has not been explored in CA. In adult post-stroke aphasia, several clinical trials have shown that a combined intervention with the cholinesterase inhibitor donepezil (DP) and speech-language therapy significantly improves language skills and communication (see Berthier et al., 2011; Zhang et al., 2018). The rationale for using cholinergic compounds to treat aphasia arises from the fact that brain lesions disrupt the cholinergic transmission from the basal forebrain and brainstem nuclei to the thalamus, basal ganglia, subcortical white matter, and cerebral cortex, including the left perisylvian language core (Simić et al., 1999; Mesulam, 2004; Mena-Segovia and Bolam, 2017; Markello et al., 2018). The resulting cholinergic depletion negatively influences learning, declarative memory, language, and attention by reducing experience-dependent neural plasticity to relevant stimuli during training (Kleim and Jones, 2008; Rokem and Silver, 2010; Gielow and Zaborsky, 2017). Although experimental TBI studies have shown that cholinergic neurotransmission is chronically depleted after TBI (Dixon et al., 1996; Dixon et al., 1997; Ciallella et al., 1998), the role of the cholinesterase inhibitor DP in adult TBI is controversial (Walker et al., 2004; Warden et al., 2006; Shaw et al., 2013) unless when used in combination with environmental enrichment therapies (*see* De la Tremblaye et al., 2019).

Accumulating evidence suggests that anticholinesterasic agents improve executive functions (Castellino et al., 2012; Castellino et al., 2014), sustained attention (Spiridigliozzi et al., 2007), learning, memory (Spiridigliozzi et al., 2007; Castellino et al., 2012), and language functions (Heller et al., 2004) in children. Importantly, the safety of these drugs in the pediatric population has been widely demonstrated (Biederman and Spencer, 2000; Hardan and Handen, 2002; Heller et al., 2004; Spiridigliozzi et al., 2007; Kishnani et al., 2010; Handen et al., 2011; Castellino et al., 2012; Sahu et al., 2013; Thornton et al., 2016). Over the last twenty years, the anticholinesterasic compound DP has been variously used to counteract impaired cognitive functions resulting from oncologic treatment of pediatric brain tumors (Castellino et al., 2012; Castellino et al., 2014; Lassaletta et al., 2015); to improve the core symptoms of attention-deficit/hyperactivity disorder (Biederman and Spencer, 2000; Popper, 2000; Wilens et al., 2000; Banaschewski et al., 2004; Pityaratstian, 2005) and of inattention-hyperactivity and communication abnormalities in autism spectrum disorders (Doyle et al., 2006; Hazell, 2007; Tamasaki et al., 2016). However, up to now there are no intervention studies aimed to explore the efficacy of cognitive-enhancing drugs, such as DP, to ameliorate language and cognitive deficits in CA.

The main aim of the present study was to evaluate the effects of pharmacotherapy with DP alone and combined with intensive naming therapy (INT) on CA recovery. Our secondary objective was to examine the effects of both interventions on naming, reading, and other linguistic and cognitive functions (executive functions, attention, memory), which were expected to change due to the interventions. Finally, the impact of TBI on the brain structure was explored at baseline to describe the possible brain-behavior relationship in light of the current knowledge. To do that, we studied the case of a 9-year old girl (subject P) with posttraumatic chronic anomic aphasia who was evaluated and treated following a single-subject, open-label design with DP alone and in combination with INT. DP was selected because it has repeatedly been shown to be effective in reducing aphasia severity, but also in boosting performance on lexical retrieval tasks (picture naming) in post-stroke aphasic adults (Berthier et al., 2003; Berthier et al., 2006). In addition, it is well known that the effect of cholinergic stimulation is more powerful when it is combined with behavioral training to promote experience-dependent plasticity (Berthier et al., 2014; Berthier et al., 2017). INT was selected because previous works have demonstrated that short-term intensive language therapies are more effective than distributed therapies (Pulvermuller et al., 2001; Kurland et al., 2010; Berthier et al., 2014). Considering previous evidence, it was expected that DP alone would induce significant improvements in attentional and executive functions and, as a result, language functions would be enhanced. Further gains were expected in language, attentional, and executive functions with the synergistic action of combined treatment with DP and INT. Since we also envisioned that gains in naming would be maintained after INT, several post-therapy evaluations were performed. To our knowledge, this is the first study evaluating the effects of DP and INT on language recovery in CA after TBI.

MATERIALS AND METHODS

Case Description

Subject P was a 9-year-old right-handed girl [+ 100 on the Edinburgh Handedness Inventory (Oldfield, 1971)] who suffered

a severe closed TBI after being hit by a car on a pedestrian crossing. At the time she was admitted to the emergency room of a local Pediatric University Hospital, she was in profound state of coma, with bilateral otorrhagia, and a right hemiparesis. An emergency computerized tomography scan of the brain revealed diffuse bilateral brain edema, peribrainstem subarachnoid hemorrhage, and a focus of contusion in the left temporal-parietal region. A structural brain magnetic resonance imaging (MRI) 4 days later (acute stage) revealed marked communicating hydrocephalus and left temporo-parietal and parahippocampal non-hemorrhagic contusions (**Figure 1**). The hydrocephalus was uneventfully resolved with a ventriculo-peritoneal shunt. In the following days, subject P presented a gradual recovery of consciousness that uncovered a pronounced language impairment. Bedside language testing revealed that she was mute with null comprehension but had severe automatic echolalia, a profile compatible with mixed transcortical aphasia (Berthier, 1999). The aphasia and the right hemiparesis improved and subject P was referred to our Unit for evaluation of residual language deficits 6 months after the TBI. Her parents contacted the research team after reading about our work on combined treatments by using cognitive-enhancing drugs and aphasia therapy to treat acquired language disorders. Subject P was of Chinese origin, being adopted at the age of 4 by a Spanish couple living in Malaga, Spain. Her medical records from China indicated that she had no medical problems and showed typical motor, cognitive, and language developmental milestones. At the time of adoption, subject P only spoke Chinese, but she rapidly learned Spanish and started using it both at school and at home. At the time she suffered the TBI, she had normal language development and schooling records. She attended the third grade of elementary school, which was the academic course corresponding to her age.

Study Design

A single-subject, open-label design was used. **Figure 2** depicts the study design. At the beginning of the trial (week 0), DP was started at a very low dose (2.5 mg/day) and titrated up to 5 mg/day one month after initiating the treatment (week 4). This DP dose was maintained and administered alone for 8 weeks (weeks 4 to 12) and then it was combined with INT (INT1) for 2 weeks (weeks 12 to 14). Thereafter, subject P continued treatment with DP alone (5 mg/day) for 12 weeks (weeks 14 to 26) and thereupon it was gradually tapered off over 4 weeks (weeks 26 to 30). This intervention phase was followed by a washout period of 4 weeks (weeks 30 to 34) and then by 2 weeks of INT alone (INT2) (weeks 34 to 36)[1]. Language and neuropsychological evaluations (LNE) were performed at different timepoints (LNE1, LNE2, LNE3, LNE4; as illustrated in **Figure 2**) in order to track the language and cognitive impact of the different interventions. In addition, to evaluate the duration of the potential gains achieved with each INT, six post-therapy naming evaluations (NE) were performed after each INT phase in which naming performance for treated and untreated control words was assessed. A baseline NE (NE0), including all treated and untreated words, was performed before INT1. Evaluations and language therapies were performed by the first author (GD), a neuropsychologist with experience in aphasia testing and treatment.

[1] Intensive Naming Therapy 2 (INT2) was planned at the starting point of the trial. However, it was not intended to make direct comparisons between treatment with DP alone and DP-INT combined against INT alone. In fact, this new course of INT after the washout period was requested by the Ethical Committee and the parents of subject P. Thus, INT2 served the purpose of maintaining the benefits of the interventions on word retrieval deficits to further support the patient needs.

Drug Treatment

The cholinergic agent DP was used according to the statement of ethical principles for medical research involving human subjects of the Declaration of Helsinki (section 37: Unproven Interventions in Clinical Practice). The protocol of this study was approved by the local Ethical Research Committee (Provincial of Malaga, Spain). DP has been used in several developmental and acquired cognitive and behavioral disorders involving children and adolescents (Biederman and Spencer, 2000; Popper, 2000; Wilens et al., 2000; Hardan and Handen, 2002; Spencer and Biederman, 2002; Heller et al., 2004; Pityaratstian, 2005; Doyle et al., 2006; Hazell, 2007; Spiridigliozzi et al., 2007; Cubo et al., 2008; Kishnani et al., 2010; Buckley et al., 2011; Handen et al., 2011; Srivastava et al., 2011; Castellino et al., 2012; Sahu et al., 2013; Castellino et al., 2014; Lassaletta et al., 2015; Tamasaki et al., 2016; Thornton et al., 2016). Treatment with DP in this population has proven to be safe (Biederman and Spencer, 2000; Hardan and Handen, 2002; Heller et al., 2004; Spiridigliozzi et al., 2007; Kishnani et al., 2010; Handen et al., 2011; Castellino et al., 2012; Sahu et al., 2013; Thornton et al., 2016), demonstrating good efficacy profile (Biederman and Spencer, 2000; Popper, 2000; Wilens et al., 2000; Hardan and Handen, 2002; Spencer and Biederman, 2002; Heller et al., 2004; Pityaratstian, 2005; Doyle et al., 2006; Hazell, 2007; Spiridigliozzi et al., 2007; Cubo et al., 2008; Buckley et al., 2011; Srivastava et al., 2011; Castellino et al., 2012; Castellino et al., 2014; Lassaletta et al., 2015). Therefore, we considered that the prescription of this agent for an unapproved use was appropriate for this particular case of CA. The dose of DP was chosen based on the prescription used in previous studies of DP in pediatric population (Kishnani et al., 2010; Srivastava et al., 2011; Sahu et al., 2013), on the child's weight (Hardan and Handen, 2002; Kishnani et al., 2004; Castellino et al., 2012), and on the proven tolerability of this agent (Heller et al., 2004; Spiridigliozzi et al., 2007). Subject P's parents were provided with the package leaflet of DP, and they were also fully informed about the pharmacological characteristics, the potential benefits, and adverse events of the drug. Written informed consent was obtained from subject P and her parents. During both the titration phase and the drug treatment, they were contacted regularly to detect potential adverse events and to track the adherence to the drug treatment.

Intensive Naming Therapy (INT)

INT based on hierarchical cueing was administered 1.5 h per day, 7 days per week, first during 2 weeks combined with DP (INT1, **Figure 2**) and, after, during 2 more weeks administered alone in the DP washout phase (INT2, **Figure 2**), resulting in a total duration of 4 weeks (~ 42 h). Stimuli in each INT session were black and white pictures representing Spanish nouns presented on a computer screen. Naming therapy based on cueing

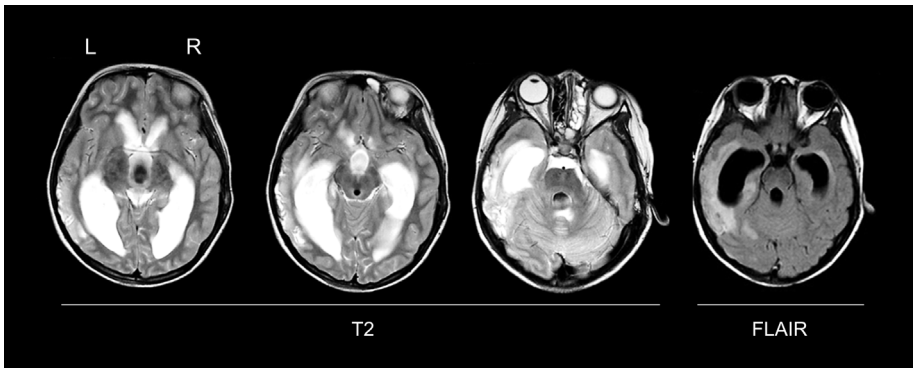

FIGURE 1 | Structural magnetic resonance imaging (MRI) in the acute stage. A MRI (T2-weighted, and FLAIR sequences) was performed 4 days after traumatic brain injury, showing a marked communicating hydrocephalus with transependymal edema and a large area of contusion in the left lateral temporal lobe extending into the parahippocampal gyrus. Axial slices in native space are shown. L, left; R, right.

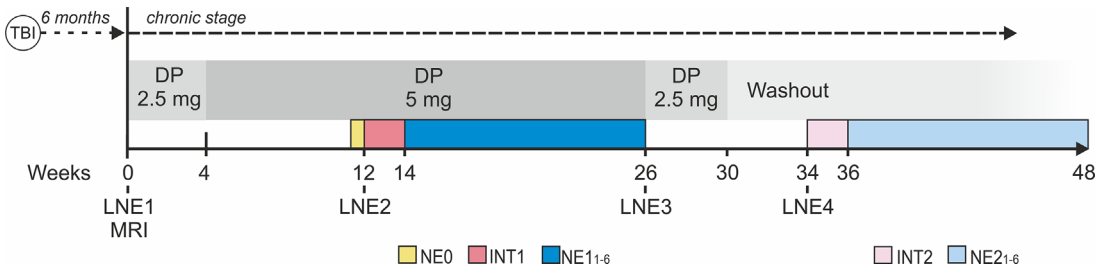

FIGURE 2 | Study design. A single-subject, open-label longitudinal design with drug and language interventions was used. DP, donepezil; TBI, traumatic brain injury; INT, intensive naming therapy; LNE, language and neuropsychological evaluation (1-4); NE0, baseline naming evaluation in which naming performance for the full set of treated and untreated words used in INT1 and INT2 was evaluated; NE, naming evaluations (1-6) performed after each INT; MRI, magnetic resonance imaging.

hierarchy has been shown to be effective in the treatment of naming deficits (Fridriksson et al., 2005; Green-Heredia et al., 2009; Best et al., 2013; Suárez-González et al., 2015). After each picture was presented, subject P was required to name the depicted stimulus. If she could not name the target picture in 20 s, a written phonological cue (i.e., the first syllable of the stimulus name) was then presented beneath the picture, and the word stem was read aloud by the therapist. In those circumstances in which subject P was still unable to name the target word, the full written name was presented underneath the picture and was read aloud by the therapist. After hearing it, subject P was asked to repeat the word aloud.

A set of 153 pictures consisting of white line drawings of living beings and non-living things was selected, all of them represented nouns. Half of these stimuli were trained in the two INTs (INT1 and INT2), and the other half were used as control items. The selection of these pictures was based on two criteria: (i) pictures that subject P consistently failed to name in the naming tests included in LNEs prior to INT1 (LNE1 and LNE2); and (ii) pictures selected from her natural science textbook, subject in which her parents reported marked naming difficulties. Specifically, 117 items were selected from the following naming tests: the object naming subtest of the Western Aphasia Battery-Revised ([WAB-R], Kertesz, 2007), the Snodgrass and Vanderwart Object Pictorial Set ([SVPS], Snodgrass and Vanderwart, 1980), the Boston Naming Test ([BNT], Kaplan et al., 1983), the Nombela 2.0 Semantic Battery ([NSB], Moreno-Martínez and Rodríguez-Rojo, 2015), and two naming subtests of the Psycholinguistic Assessments of Language Processing in Aphasia ([PALPA 53 and PALPA 54], Kay et al., 1992; Valle and Cuetos, 1995). The pictures from her natural science book (36 items) were selected by the therapist.

The 153 stimuli were divided into two sets, one containing 77 pictures and the other one 76 pictures, which were used as the to-be-trained and control items, respectively, for the INT1 and INT2. Specifically, 37/77 pictures were trained (hereinafter *treated words*) in the INT1 phase and 40/77 pictures corresponded to the treated words in the INT2 phase. The remaining pictures (36/76 and 40/76) were used as control items (hereinafter *untreated words*) in the six NEs performed after INT1 and INT2, respectively. The sets of

treated and untreated words were matched by frequency (INT1: t(71) = -0.233, p = 0.816; INT2: t(78) = -1.58, p = 0.119), number of phonemes (INT1: t(71) = -0.394, p = 0.694; INT2: t(78) = -0.477, p = 0.635), syllables (INT1: t(71) = 0.089, p = 0.930; INT2: t(78) = -0.648, p = 0.519) and semantic category. In each INT session, the full set of treated words assigned to each INT was presented twice. To avoid associative learning between items, the presentation order of the words was randomized. For this, 10 lists were created containing all the items assigned to each INT but with different presentation order. Two lists were used in each daily session.

Language and Neuropsychological Evaluations

In order to assess treatment-induced changes, a set of primary and secondary outcome measures comprising language, executive functions, attention and memory functions were selected. In addition, visuoconstructive and visuospatial functions were measured only at baseline. Note that the same outcome measures were used for both interventions (DP alone and combined treatment of DP and INT), in line with the expected changes.

Outcome Measures

The primary outcome measures consisted on different measures of the WAB-R (Kertesz, 2007). Specifically, these were the aphasia quotient (WAB-R AQ) and the WAB-R subtests scores: information content and fluency in spontaneous speech, comprehension, repetition, and naming. Despite contributing to the WAB-R AQ, the different WAB-R subtests were also included individually as primary outcome measures in that they are sensitive to detect treatment-induced changes and may show a differentiated evolution pattern (Berthier et al., 2003; Berthier et al., 2006).

The secondary outcome measures included a set of tests selected to assess relevant aspects of language and other cognitive functions, especially attentional and executive functions. As for the primary outcome measures, the functions targeted by these tests were expected to improve with the treatments. The selected language tests were: (a) the SVOPS, BNT, and NSB to evaluate naming; (b) the Peabody: Picture Vocabulary Test (PPVT-III), Dunn et al. (2006) to evaluate comprehension *via* word-picture matching; (c) the PALPA (Kay et al., 1992; Valle and Cuetos, 1995) to evaluate repetition, naming, comprehension, and reading; (d) the Token Test- short version ([TT-sv], De Renzi and Vignolo, 1962) to evaluate comprehension of syntax and spatial relationships; (e) and the Controlled Oral Word Association Task ([COWAT], Borkowski et al., 1967) to assess phonological verbal fluency (see **Table 2**). These tests as well as the ones included as primary outcome measures were administered in each LNE. The selected memory and executive functions tests were: Memory and Learning Test ([TOMAL], Reynolds and Bigler, 1996) (LNE1 and LNE2), Digit Span ([WISC-V] of the Wechsler Intelligence Scales for Children-V, Wechsler, 2014) (LNE1, LNE2, LNE3); attention: d2 Attention Test ([d2 Test], Brickenkamp and Cubero, 2002) (all LNEs); Neuropsychological Evaluation of Executive Functions in Children ([ENFEN], Portellano et al., 2009) (LNE1, LNE2, LNE3), Stroop (Stroop, 1935) (LNE1, LNE2, LNE3), and Five-Digit Test ([FDT]Sedó, 2004) (all LNEs).

Furthermore, although they were not expected to change due to treatment and, therefore, were not considered primary or secondary outcome measures, visuoconstructive and visuoperceptive functions were also assessed at baseline to estimate premorbid cognitive functioning. For this purpose, the two following tests were used: Rey–Osterrieth Complex Figure ([ROCF], Osterrieth, 1944), Benton Laboratory of Neuropsychology Tests ([BLNT], Benton et al., 1994) (see **Table 2**). As some of the employed tests in the LNEs are widely used in the Spanish population but may not be familiar to the English speaking countries, a brief description of these tests is provided in the **Supplementary Material**.

Naming Evaluations (NE)

First, a baseline naming assessment (NE0) comprising the full set of 153 words was performed after treatment with DP alone and before INT1 (**Figure 2**). Then, in order to track the maintenance of gains in naming performance for treated words and the potential generalization to untreated ones, multiple NEs were performed after each INT. Specifically, after INT1 and INT2, six NEs were performed: 20 min after the end of each INT ($NE1_1$ and $NE2_1$), and at days 2 ($NE1_2$ and $NE2_2$), 7 ($NE1_3$ and $NE2_3$), 21 ($NE1_4$ and $NE2_4$), 49 ($NE1_5$ and $NE2_5$), and 84 ($NE1_6$ and $NE2_6$) (**Figure 2**). In each NE, treated and untreated words were evaluated. The presentation order of the words in each NE was randomized. No feedback was provided to subject P during the NEs.

Control Group

Since there are no normative data for most of the language tests used in the evaluation of subject P, a control group of healthy children (classmates and relatives of subject P) was recruited in order to obtain reference scores for these tests. The group was composed of 7 children (4 boys and 3 girls) matched with subject P for age (8.9 ± 0.69 years; range: 8-10 years; Crawford's t, two-tailed = 0.136; p = 0.896), general intelligence (verbal IQ: subject P = 95; control group = 112.43 ± 20.02 [Crawford's t, two-tailed = -0.814; p = 0.446]; non-verbal IQ: subject P = 103; control group = 115.57 ± 15.43; [Crawford's t, two-tailed = -0.762; p = 0.475]) and sociocultural background. Control children were administered the WAB-R and other tests (SVOPS, NSB, PALPA, and COWAT). Healthy adults tend to show a ceiling effect on the WAB-R AQ (AQ ≥ 93.8/100), and subjects with scores below this cut-off are considered to have aphasia. Regarding WAB-R use in children, it was reasoned that healthy children with ages between 8 and 10 years and high verbal intelligence quotient (IQ) (≥ 110) would have a good performance in the WAB-R.

The parents of the control children were informed about the aim of the study and written informed consent was obtained.

Structural Neuroimaging

Image Acquisition

The MRI acquisition was performed at baseline (6 months after TBI) on a 3-T MRI scanner (Philips Gyroscan Intera, Best, The Netherlands) equipped with an eight-channel Philips SENSE

head coil. Head movements were minimized using head pads and a forehead strap. Three-dimensional magnetization prepared rapid acquisition gradient echo (3D MPRAGE) was performed with the following parameters: acquisition matrix, 268/265; field of view, 224 mm; repetition time (TR), 9.2 ms; echo time (TE), 4.2 ms; flip angle, 8o; turbo field echo (TFE) factor, 200; reconstruction voxel size, 0.68 mm x 0.68 mm x 0.8 mm. Two hundred ten contiguous slices were acquired, with a 0 mm slice gap, the total acquisition time of the sequence was about 2 min and 50 s.

Lesion-Based Approach to Mapping Disconnection

Two different methods were used to gain knowledge about the direct and remote structural effects of the brain lesion. Tractotron and Disconnectome Maps, included in the BCB Toolkit (http://toolkit.bcblab.com/; Foulon et al., 2018).

In order to apply these methods, subject P's lesion was manually delineated over the T_1-weighted image in native space using MRIcron software (Rorden and Brett, 2000). Then, both the T_1-weighted image and the binarized lesion mask were normalized to the MNI space using Statistical Parametric Mapping 12 (SPM 12, www.fil.ion.ucl.ac.uk/spm/). The normalized lesion was mapped onto tractography reconstructions of white matter pathways obtained from a group of 10 healthy controls (Rojkova et al., 2016). The analyses were focused on different language-related dorsal and ventral tracts, being these white matter pathways commonly affected in individuals with aphasia (Ivanova et al., 2016). Three ventral tracts were studied: (1) the IFOF connecting fronto-temporal regions, crossing from one lobe to the other through the extreme capsule; (2) the ILF that connects the posterior inferior, middle, and superior temporal gyri with the temporal pole; and (3) the UF which links the temporal pole with frontal areas (Catani and Thiebaut de Schotten, 2008). Three dorsal tracts were also explored, corresponding with the three segments of the AF: (1) the long segment that connects the frontal (including Broca's area and the premotor cortex) and the temporal cortices (including Wernicke's area and the middle and inferior temporal gyri); (2) the anterior segment that connects the same frontal areas with the angular and supramarginal gyri in the inferior parietal cortex; and (3) the posterior segment which connects the same parietal areas with the inferior and middle temporal gyri (Catani et al., 2005). Different measures were explored for each of the studied tracts. First, *Tractotron* provided the *probability* of a given tract to be affected by the brain lesion (≥ 50% was considered pathological) and the *percentage* of damage of each tract. Second, *Disconnectome maps* software provides a spatial map representing the probability of remote areas to be indirectly affected by the lesion. These indexes allowed to explore the remote impact of the focal brain lesions in the brain circuitry. Thus, the normalized lesion of subject P was used as seed point to identify which tracts passed through the lesion. Subject P's disconnectome map was thresholded at a value of $p > 0.9$. A detailed description of these methods and software is reported in Foulon et al. (2018).

Statistical Analyses

First, in order to evaluate longitudinal changes due to treatment effects, performance of subject P in each test included in the LNEs was either compared to the performance of the matched control group or to normative data. Specifically, for those tests that do not provide normative data for the age range of subject P, her performance was compared to the achievement of the control group on these tests. Notice that this served the purpose of the main aim of the study, that is to establish the effect of the different treatments on aphasia recovery, seeking for the return of subject P to an average performance in primary and secondary outcome measures. Statistical comparisons were performed using one-tailed Crawford's modified *t*-tests (Crawford et al., 2010), as done in previous studies (François et al., 2016; Birba et al., 2017; Cervetto et al., 2018). This statistic allows the comparison between a single subject and a control group. It has proven to be robust for non-normal distributions, and it has low rates of type-I error. Effect sizes for all results are reported as point estimates (Z_{CC}) (Crawford et al., 2010) (see **Table S1**). In all analyses, the alpha level was set at $p < 0.05$. For those tests reporting normative data, raw scores derived from subject P's performance were standardized (percentile or decatype) (for details see **Tables 1** and **2**), unless specified otherwise.

Second, results derived from each NE were analyzed in three different ways: i) in order to explore naming gains promoted by each INT, McNemar tests (two-tailed) were used to compare performance in the first NE after each INT against naming performance for those same words in NE0; ii) to track the evolution patterns of the potential gains found in $NE1_1$ and $NE2_1$, performance in each of the subsequent NEs (2-6) was compared to the performance in the first evaluation after INT ($NE1_1$ and $NE2_1$). The analyses i) and ii) were performed independently for the treated and untreated words; iii) performance in treated and untreated words in each NE was compared *via* Chi-squared tests (with Yate's correction).

RESULTS

Findings From Language and Neuropsychological Evaluation 1 (LNE1): Baseline

In relation to the primary outcome measures, subject P obtained a WAB-R AQ score of 78.4, which is significantly lower than the cut-off score for adults (≤ 93.8) and the mean of the age-matched control group (95.13 ± 2.73; Crawford's t, one-tailed = -5.73; $p \leq 0.001$). Her language deficits were characterized by impoverished information content with fluent yet anomic speech production. Specifically, significant lower scores were found in the subtests of the WAB-R targeting information content and fluency in spontaneous speech, and naming (see **Tables 1** and **S1**), whereas performance in comprehension and repetition did not differ from that of the control group. According to the WAB taxonomic criteria, this profile was compatible with an anomic aphasia (Kertesz, 1982). The mean WAB-R AQ of the control group (95.13) was above the cut-off score (93.8) for the clinical diagnosis of aphasia in adults (Kertesz, 1982). However, 3/7 control children obtained AQ scores slightly below the cut-off (92.4, 92.5, and 93.3). These children, being the youngest ones (8

TABLE 1 | Language Assessment.

	Subject P				Reference value [a]	
	LNE1	**LNE2**	**LNE3**	**LNE4**	**Mean**	**SD**
Primary Outcome Measures						
Aphasia Quotient- Western Aphasia Battery Revised (WAB-R AQ)	78.4*	92.6	95.8	94.2	95.13	2.73
Information Content	8*	10	10	10	10	0
Fluency	8*	10	10	10	10	0
Comprehension	8.5	9.7	9.9	10	9.01	0.78
Repetition	8	9	9.2	9	9.31	0.91
Naming	6.7*	7.6*	8.8	8.1	9.24	0.72
Secondary Outcome Measures						
Snodgrass and Vanderwart Object Pictorial Set (SVOPS)	138*	167*	220	211*	232.86	10.48
Nombela 2.0 Semantic Battery (NSB)						
Picture Naming	23*	39	51	53	44.29	9.64
Semantic Fluency	56*	79	102	79	136.71	35.4
Word-Picture Matching	29*	32	35	34	36.67	2.73
Boston Naming Test (BNT)[1]	23*	31*	52	40	46.41[b]	4.4[b]
Peabody: Picture Vocabulary Test III (PPVT-III)[2]	2	42	63	39	Standard scores[†]	
Token Test (Shortened version) (TT-sv)[3]	<5	95	50	70	Standard scores[†]	
Psycholinguistic Assessments of Language Processing in Aphasia (PALPA)						
Repetition: Nonwords (PALPA-8)	16*	22	24	23	23.42	0.79
Repetition: Imageability x Frequency (PALPA-9)	147*	160	–	–	160	0.00
Repetition: Sentences (PALPA-12)	26*	23*	28*	–	35.14	0.69
Reading: Visual Lexical Decision (PALPA-25)	138*	142*	138*	–	151.43	3.03
Reading: Grammatical Class (PALPA-32)	76*	75*	72*	–	80	0
Reading: Nonwords (PALPA-36)	20*	19*	19*	–	23.86	0.38
Reading: Sentences (PALPA-37)	33*	24*	32*	–	36	0
Semantics: Spoken Word-Picture Matching (PALPA-47)	36*	37	39	–	38.14	0.69
Semantics: Written Word-Picture Matching (PALPA-48)	35*	40*	38	–	38.28	0.76
Semantics: Spoken Word-Written Word Match (PALPA-52)	33*	32*	34	–	36.80	1.64
Semantics: Picture Naming (PALPA-53)	29*	34*	36	38	38.20	1.30
Semantics: Picture Naming x Frequency (PALPA-54)	53*	55*	55*	–	58.85	1.07
Spoken Sentence-Picture Matching (PALPA-55)	48*	52	53	53	56.28	2.69
Written Sentence-Picture Matching (PALPA-56)	46*	48*	53	52	55.14	2.54
Controlled Oral Word Association Test (COWAT)	9	23	15	17	24.14	7.97

Asterisks (*) indicate significant differences at $p < 0.05$. Statistical comparisons were performed using one-tailed Crawford's t-tests in all cases except for tests marked with†. No statistical comparisons were needed for these tests since standardized scores provide a framework for comparing subject P's performance against normative data. [a]Reference values represent the mean scores and standard deviations (SD) of the control group, except for [b], that represents the normative mean scores and SDs provided by the test, and †, that refers to normative data. †The numbers in each evaluation are the percentiles corresponding to the raw score obtained by subject P. Underlined scores are bellow two SD of the normative mean. Normative data were obtained from: [1]Halperin et al. (1989), [2]Dunn et al. (2006), and [3]Olabarrieta-Landa et al. (2017).

years), committed a few failures in comprehension of reversible sentences in the sequential commands subtest of the WAB-R. Despite this age-dependent limitation, the WAB-R was considered appropriate for being administered to subject P.

Regarding secondary outcome measures, subject P's scores were significantly lower than those of the control group in all selected naming measures (SVOPS, BNT, picture naming and semantic fluency [NSB], PALPA-53, and PALPA-54), auditory comprehension of nouns (word-picture matching [NSB], PALPA-47, and PALPA-52), auditory comprehension of sentences (PALPA-55), word repetition (PALPA-9), nonwords repetition (PALPA-8), sentence repetition (PALPA 12), and reading (PALPA-25, PALPA-32, PALPA-36, PALPA-37, PALPA-48, and PALPA-56). Also, performance in auditory word comprehension (PPVT-III) and of sentences (TT-sv) was lower than the normative data for her age. Lastly, performance of subject P in the verbal fluency test (COWAT) was not different from controls, although a trend toward significance was found (see **Tables 1** and **S1**).

In relation to other cognitive functions, compared to normative data subject P showed poor performance on most of the executive function tests (see **Table 2**), reflecting slow processing speed (word reading [STROOP]; number reading [FDT]), limited cognitive flexibility (color trails [ENFEN]; alternation and flexibility [FDT]) and low selective and sustained attention levels (concentration [d2 Test]). Yet, executive function impairments were not generalized, since subject P showed high scores in tests measuring inhibition of a prominent response (inhibition [FDT]). Furthermore, subject P's performance on most of verbal and nonverbal memory tests was within the normal range of normative data (see **Table 2**) except for the reduced auditory-verbal short-term memory (Digit Span). The scores obtained by subject P in tests assessing visuoconstructive and visuoperceptive functions, which are mostly related to the

TABLE 2 | Neuropsychological Assessment.

	Subject P				Reference value
	LNE1	LNE2	LNE3	LNE4	
Executive Functions and Attention Tests					
Neuropsychological Evaluation of Executive Functions in Children (ENFEN)[1]					
Grey trail	6	6	4	–	standard scores[†]
Color trail	3	4	4	–	(scale 1 to 10)
Interference	6	6	6	–	
Stroop Test[2]					
Word reading	< 5	< 5	< 5	–	standard scores[‡]
Colors naming	< 5	10	15	–	(scale 1 to 99)
Five-Digit Test (FDT)[3]					
Reading numbers	1	2	1	1	standard scores[†]
Counting	1	1	3	3	(scale 1 to 10)
Alternate	1	1	2	3	
Inhibition	8	9	9	10	
Flexibility	1	1	5	7	
d2 Attention Test (d2 TESTS)[4]					
Concentration	25	95	95	98	standard scores[‡]
Fluctuation	55	60	40	10	(scale 1 to 99)
Items processed	70	95	99	95	
Number of successes	25	96	99	98	
Omission errors	1	40	80	85	
Commission errors	25	35	60	85	
Memory Tests					
Test of Memory and Learning (TOMAL)[5]					
Verbal memory	75	99	–	–	standard scores[‡]
Non-verbal memory	95	99.6	–	–	(scale 1 to 99)
Composite memory	84	99.6	–	–	
Verbal delayed recall	37	91	–	–	
Attention and concentration	9	16	–	–	
Sequential memory	25	37	–	–	
Free recall	50	75	–	–	
Associative recall	2	37	–	–	
Learning	9	63	–	–	
Digit Span[6]					
Direct	10	10	10	–	standard scores[‡]
Inverse	50	50	50	–	(scale 1 to 99)
Visuoconstructive and Visuoperceptive Functions					
Rey-Osterreith Complex Figure Test (ROCF)[7]					
Copy	50	–	–	–	standard scores[‡]
Immediate recall	80	–	–	–	(scale 1 to 99)
Benton Laboratory of Neuropsychology Tests (BLNT)[8]					
Finger localization	49	–	–	–	53[§]
Visual form discrimination	41	–	–	–	23[§]
Judgment of line orientation	26	–	–	–	17[§]
Right-left orientation	18	–	–	–	16[§]

Reference data were obtained from either the test's manual or published normative data as indicated by the reference of the superscript numerals located by each test's name. [1]Portellano et al. (2009). [2]Rivera et al. (2017). [3]Sedó (2007). [4]Brickenkamp and Cubero (2002). [5]Reynolds and Bigler (1996). [6]Gardner (1981). [7]Arango-Lasprilla et al. (2017). [8]Rey et al. (1999). There are no children's normative data for BLNT; reference values used are based on an adult sample. [†]Standard scores ranging from 1 to 10 (decatypes) have, by definition, a mean of 5.5 and a standard deviation of 2. [‡]Percentiles (standard score 1 to 99) have a median of 50. Underlined scores are bellow two standard deviations of the normative mean. [§]Test cut-off value; scores greater than the cut-off are considered within a normal range.

undamaged right hemispheric functioning, were within the normal range (**Table 2**).

Findings From Language and Neuropsychological Evaluation 2 (LNE2): DP Alone

Regarding primary outcome measures, the WAB-R AQ of subject P significantly improved after 12 weeks of DP treatment alone (see LNE2 column in **Table 1**). The AQ score increased 14.2 points (from 78.4 to 92.6) indicating that she could be considered a "good responder" to the pharmacological intervention (Berthier et al., 2009; Cherney et al., 2010). In fact, in the LNE2, the scores obtained in information content and fluency in spontaneous speech improved and they were comparable to the performance of the control group. Statistically significant lower scores were only found in the naming subtest of the WAB-R, which remained moderately impaired (**Tables 1** and **S1**).

In relation to secondary outcome measures, subject P showed improved naming abilities in both noun retrieval (picture naming and semantic fluency [NSB]), and auditory word (word-picture

matching [NSB], PPVT-III, PALPA-47) and sentence (TT-sv, PALPA-55) comprehension. Likewise, improvements promoted by DP alone were found in words and nonwords repetition (PALPA-9 and PALPA-8). Performance in these tests was comparable to controls, and, in the case of the PPVT-III, fell within the normal range of the normative data. Comprehension improved slightly for written words (PALPA-48) and written sentences (PALPA 56), yet remained significantly lower than the performance of the control group. Conversely, sentences repetition (PALPA-12) showed a mild decrement (**Table 1**). As regard other cognitive functions (**Table 2**), high scores in selective and sustained attention were obtained (d2 Test) in comparison to normative data. Although an increase in processing speed was observed in some tests (word reading [STROOP], and in the number items of processed [d2 Test]), other measures of this domain remained low (e.g., reading numbers [FDT]). Further, slight improvements in cognitive flexibility were also found (color trails [ENFEN]), but this finding was not substantiated by other tests (alternate and flexibility [FDT]). Likewise, Digit Span remained low (**Table 2**).

Findings From Language and Neuropsychological Evaluation 3 (LNE3): DP-INT1

This evaluation assessed gains in language after two weeks (weeks 12–14) of DP-INT1 and another 12 weeks of DP treatment. Concerning primary outcome measures, there were no statistically significant differences between subject P and the control group neither in the WAB-R AQ nor in the WAB-R subtests, meaning that subject P achieved an average performance on all language domains. This was the first evaluation in which she showed a naming score comparable to the controls (naming subtest of the WAB-R) (see **Table 1**).

Regarding secondary outcome measures, all improvements observed after DP treatment alone (LNE2) remained in LNE3 (as revealed by comparison of subject P's performance with the control group's). Besides, at this endpoint, further improvements were observed in almost all language-related secondary outcome measures: (a) noun retrieval test (SVOPS, BNT, picture naming, and semantic fluency [NSB], and PALPA-53); (b) all auditory word comprehension tests (word-picture matching [NSB], PPVT-III, PALPA-47, and PALPA-52); (c) auditory sentence comprehension (PALPA-55; but not in TT-sv); (d) nonword repetition (PALPA-8); (e) written-recognition of spoken words (PALPA-52) and comprehension of written sentences (PALPA-56). However, in the picture naming x frequency subtest (PALPA-54), subject P's performance remained significantly lower than that of the control group, as well as sentence repetition and most of the reading measures. In relation to other cognitive functions, no relevant changes in measures of executive, attention or memory functions were observed at LNE3.

Findings From Language and Neuropsychological Evaluation 4 (LNE4): Washout

In week 26, the dose of DP was gradually tapered off and suspended at week 30. As regards primary outcome measures, in LNE4 (week 34) it was observed that the improvements found in the primary outcome measures (WAB-R AQ and subtests) were maintained four weeks after withdrawal of DP (see **Table 1**). Thus, no statistically significant differences were found between subject P and the control group in any of the primary outcome measures at this point.

Concerning secondary outcome measures, the benefits observed in comprehension of auditory sentences (PALPA-55),

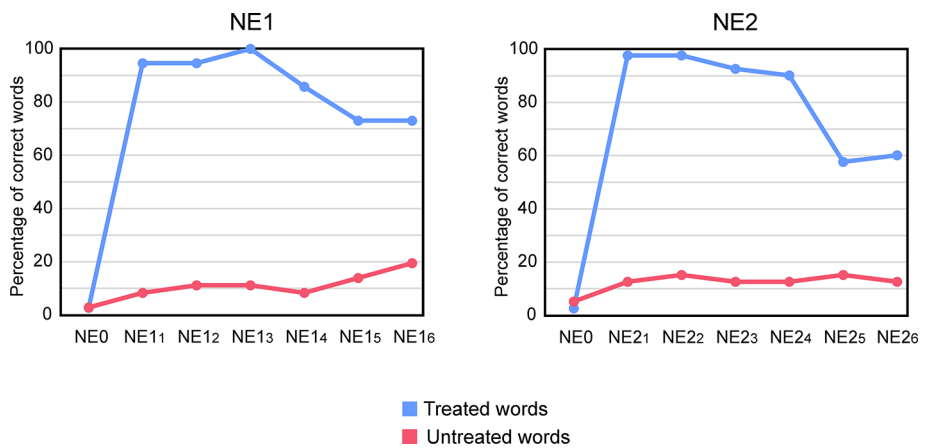

FIGURE 3 | Performance of subject P in the multiple naming evaluations (NE). Percentage of correct words in each evaluation is shown. NE0 indicates the performance in the baseline NE performed before INT1. NE0 at the left of $NE1_{1\text{-}6}$ indicates pre-treatment performance for the treated and untreated words used in INT1 and $NE1_{1\text{-}6}$. NE0 at the left of $NE2_{1\text{-}6}$ indicates pre-treatment performance for the treated and untreated words used in INT2 and $NE2_{1\text{-}6}$. Six NEs were performed after INT1 ($NE1_{1\text{-}6}$) and after INT2 ($NE2_{1\text{-}6}$). $NE1_{1\text{-}6}$ and $NE2_{1\text{-}6}$ were performed: 20 min after the end of each INT ($NE1_1$ and $NE2_1$), and at days 2 ($NE1_2$ and $NE2_2$), 7 ($NE1_3$ and $NE2_3$), 21 ($NE1_4$ and $NE2_4$), 49 ($NE1_5$ and $NE2_5$), and 84 ($NE1_6$ and $NE2_6$) after the end of each INT.

nonword repetition (PALPA-8), and comprehension of written sentences (PALPA-56) remained unchanged. Performance in some naming tests dropped down (naming subtest of the WAB-R, BNT, and SVOPS), although only the SVOPS score was significantly lower than the control group. A slight decline in semantic fluency (NSB) and word comprehension (word-picture matching [NSB], and PPVT-III) was also observed, although performance did not differ from that of the control group (NSB) or was within the normal range (PPVT-III). In relation to other cognitive functions, compared to normative data, subject P maintained a within-average level of selective and sustained attention (d2 Test), cognitive flexibility (FDT) and attentional fluctuation (d2 Test) after drug withdrawal. Processing speed was within normal range when measured with the d2 Test, but was impaired when measured with the FDT.

Naming Findings 1 (NE1)

Figure 3 (left panel) depicts performance of subject P in NE0 (before INT1) and in the six NEs performed after INT1. Performance in NE0 was very low, with subject P naming correctly only 1/37 (2.70% correct) of the treated words and 1/36 (2.77% correct) of the untreated words.

At $NE1_1$ subject P correctly named 35/37 of the treated words (95% correct). At this point, she produced two semantic paraphasias ("spinach" → *artichoke*; "rocking chair → *buck*) that were self-corrected immediately. Thus, naming performance was significantly higher in $NE1_1$ compared to NE0 (McNemar, $p \leq 0.001$). In $NE1_2$, naming performance for treated words remained stable (35/37 [95% correct; McNemar, p = 1]) compared to $NE1_1$. In this evaluation, errors consisted of an omission that was finally corrected with phonemic cueing, and a semantic paraphasia ("rocking chair" → *comfortable*), which was self-corrected. In $NE1_3$ (7 days after the end of INT1), she correctly named 100% of treated words (37/37), being this not significantly different from the performance in $NE1_1$ (McNemar, $p = 0.500$). At $NE1_4$ (21 days after the completion of the INT1), there was a non-significant decrease in performance compared to $NE1_1$ (30/37 [81% correct]; McNemar, $p = 0.063$). The decrease was due to 7 omissions. At $NE1_5$ (after 49 day of the end of INT1), a significant decrease compared to $NE1_1$ was observed (27/37 [73% correct]; McNemar, $p = 0.008$). Errors included 8 omissions and 2 semantic paraphasias ("asparagus" → *spinach*; "vertebra" → *pelvis*). Finally, at $NE1_6$ (84 days after the end of the INT_1), subject P showed the same level of performance than in $NE1_5$ (27/37 [73% correct]) which was significantly lower than the performance in $NE1_1$ (McNemar, $p = 0.008$). Thus, treatment-induced improvements in naming performance of treated words remained stable for 21 days ($NE1_4$) while a significant decrement was detected in the evaluations performed after 49 days ($NE1_5$ and $NE1_6$). Nevertheless naming performance for treated words in all post-treatment evaluations ($NE_{1\text{-}6}$) was significantly higher compared to baseline (NE0) (McNemar, $p \leq 0.001$).

In relation to untreated words, performance in $NE1_1$ did not significantly differ from performance in NE0 (McNemar, $p = 0.500$). Accordingly, naming performance in $NE1_{2\text{-}6}$ was comparable to that on $NE1_1$ ($NE1_2$: McNemar, $p = 1$; $NE1_3$: McNemar, $p = 1$; $NE1_4$: McNemar, $p = 1$; $NE1_5$: McNemar, $p = 0.500$; $NE1_6$: McNemar, $p = 0.125$).

Finally, naming performance for treated and untreated words was comparable at baseline (NE0; $\chi^2(1) = 0.44$ p = 0.508) but higher for treated than for untreated words in all post-treatment NEs, revealing no generalization from treated to untreated words just after INT. Differences were statistically significant for: $NE1_1$ ($\chi^2(1) = 51.00$, $p \leq 0.001$), $NE1_2$ ($\chi 2(1) = 48.79$, $p \leq 0.001$), $NE1_3$ ($\chi 2(1) = 55.00$, $p \leq 0.001$), $NE1_4$ ($\chi 2(1) = 36.10$, $p \leq 0.001$), $NE1_5$ ($\chi 2(1) = 23.53$, $p \leq 0.001$), $NE1_6$ ($\chi 2(1) = 18.92$, $p \leq 0.001$).

Naming Findings 2 (NE2)

Figure 3 (right panel) depicts performance of subject P in NE0 and in the six NEs performed after INT2. Baseline (NE0) naming performance was 1/40 (2.5% correct) for treated words and of 2/40 (5% correct) for untreated words.

At $NE2_1$ subject P produced 39/40 correct responses (97% correct) in treated words, committing a phonemic paraphasia. Thus, compared to NE0, naming performance for treated words significantly increased after treatment (McNemar, $p \leq 0.001$). These results remained stable at $NE2_2$ (treated words: 39/40 [97% correct; McNemar, $p = 1$], wherein she committed just an omission. At $NE2_3$, she correctly named 37/40 [92% correct] of the treated words, which was not significantly different from the performance in $NE2_1$ (McNemar, $p = 0.500$). At this timepoint, subject P produced one omission and two phonemic paraphasias. At $NE2_4$ the number of correct responses in treated words was of 36/40 [90% correct] (4 omissions), comparable to the performance observed in $NE2_1$ (McNemar, $p = 0.250$). At $NE2_5$, a decrease in correct responses for treated words was observed (23/40 [57% correct]; 16 omissions and 1 semantic paraphasia) compared to $NE2_1$ (McNemar, $p \leq 0.001$). Finally, performance at $NE2_6$ remained stable compared to $NE2_5$ (23/40 [57% correct]; 15 omissions and 2 semantic paraphasias), which was significantly lower than the performance in $NE2_1$ (McNemar, $p \leq 0.001$). Thus, like in INT1, treatment-induced gains in naming remained stable for 21 days ($NE2_4$), but a significant decrease was detected in the evaluations performed after 49 days ($NE2_5$ and $NE2_6$).

In relation to untreated words, performance in $NE2_1$ did not significantly differ from performance in NE0 (McNemar, $p = 0.250$). Naming performance in $NE2_{2\text{-}6}$ was comparable to that on $NE2_1$ (for all comparisons: McNemar, $p = 1$).

Finally, naming performance was significantly higher for treated words than for untreated ones in all NEs, but N0, revealing no generalization from treated to untreated words: NE0 ($\chi^2(1) = 0.35$, p = 1), $NE2_1$ ($\chi^2(1) = 55.00$, $p \leq 0.001$), $NE2_2$ ($\chi^2(1) = 52.01$, $p \leq 0.001$), $NE2_3$ ($\chi^2(1) = 48.17$, $p \leq 0.001$), $NE2_4$ ($\chi^2(1) = 45.03$, $p \leq 0.001$), $NE2_5$ ($\chi^2(1) = 13.85$, $p \leq 0.001$), $NE2_6$ ($\chi^2(1) = 15.88$, $p \leq 0.001$).

Neuroimaging Findings

Lesion Location

MRI performed 6 months after the TBI showed left cortical tissue damage, mostly involving the inferior temporal gyrus (Brodmann area [BA] 37) and to a lesser extent the middle temporal gyrus (BA21) and the angular gyrus (BA39) (**Figure 4A**).

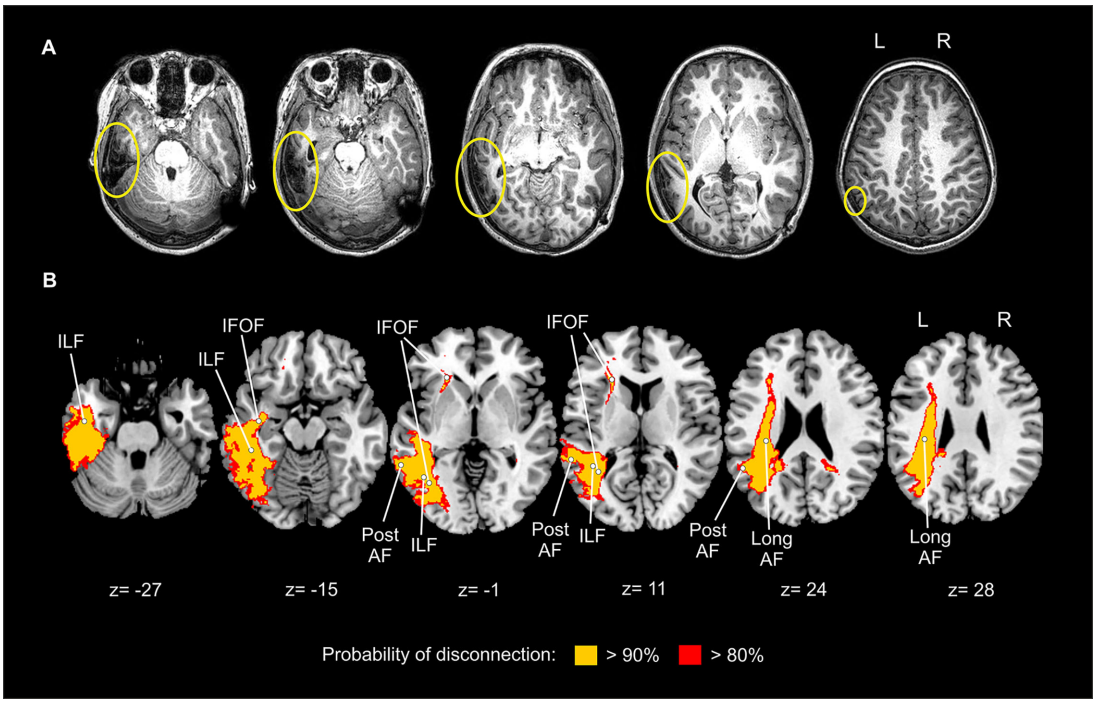

FIGURE 4 | Depiction of the brain lesion and disconnection pattern. **(A)** MRI T_1-weighted image showing the lesion in the left temporo-parietal cortex in native space. Yellow circles indicate brain lesions. **(B)** Probability of disconnection of brain areas not directly affected by the lesion as revealed by the *Disconnectome map* software. Two different probability thresholds are presented. The disconnection map is overimposed on a brain template in standard MNI space. L, left; R, right; ILF, inferior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; post AF, arcuate fasciculus posterior segment; long AF, arcuate fasciculus long segment.

There was also a focal cortical atrophy and gliosis in the subcortical white matter, causing a discrete retraction of the temporal horn of the left lateral ventricle. The ventricular-peritoneal shunt was correctly placed in the occipital horn of the right lateral ventricle.

Mapping Disconnection: Tractotron and Disconnectome Maps

Tractotron revealed that in the left hemisphere, the AF anterior segment showed a probability of 48% to be directly affected by the lesion; and the AF long and posterior segments showed a probability of 98%. Ventrally, the ILF showed a 100% probability of involvement; the IFOF showed a probability of 92%, while the UF was unlikely to be affected (probability of 0%). In the right hemisphere, none of these tracts were damaged (all probabilities were equal to 0%). The high probability of affectation found for the AF posterior and long segments, the ILF and the IFOF are in line with the cortical damage observed in subject P, which affected the inferior and middle temporal gyri and the angular gyrus, regions connected by these tracts (Catani and Thiebaut de Schotten, 2008).

Yet, the probability of a given tract to be affected does not inform on the amount of damage. To obtain this measure, the proportion of damage was extracted. The proportions of each tract to be affected by the lesion were: AF anterior segment: 0%; AF long segment: 29%; AF posterior segment: 32%; ILF: 13%; IFOF: 4%; UF: 0%. Finally, note that those distant cortical areas that showed a high probability of disconnection (> 80%) due to the TBI are in fact the ones connected by the affected white matter pathways as revealed by Tractotron (**Figure 4B**).

DISCUSSION

In the present intervention study, we described the case of subject P, a girl with chronic anomic aphasia secondary to a TBI in the left temporo-parietal region. She received three successive treatments: (1) DP alone; (2) a combination of DP and INT; and (3) INT alone. Multiple language and other cognitive domains evaluations were performed at baseline and at different time-points (**Figure 2**) in order to track changes promoted by these interventions. Results obtained from these evaluations were compared to a socio-demographically matched control group.

Several important findings of our study should be highlighted. First, at baseline, subject P showed significantly lower scores than the control group in the primary and secondary outcome measures targeting language, attentional, and executive functions. Second, treatment with DP alone (week 0 to week 12) induced improvements in primary outcome measures (see LNE2 results). Aphasia severity and scores in different language domains (fluency and information content during spontaneous speech and naming) improved, and at this point subject P performance was comparable to the control group's in all primary outcome measures (WAB-R AQ and WAB's subtests),

except for naming. Third, combined treatment with DP-INT1 (week 12 to week 26, see LNE3 results) further increased the WAB-R AQ, placing the language deficits of subject P in the non-aphasic range. Fourth, the combined intervention provided further gains in picture naming, the most affected language function at baseline (LNE1). Fifth, secondary outcome measures improved with DP alone (LNE2), denoting the beneficial effect of the drug, and most of the differences to the controls observed at baseline disappeared with combined treatment (DP-INT1; LNE3). Lastly, most gains provided by DP intervention were stable 4 weeks after withdrawal. It is noteworthy that at washout evaluation, the WAB-R AQ remained within the normal range as compared to the control group.

Language disorders in childhood often have important implications in everyday life and represent a risk factor of developing anxiety and social problems in adulthood (Brownlie et al., 2016; Ryan et al., 2018). Currently, the only available treatment for CA is speech-language therapy, and although it often promotes recovery of linguistic and other cognitive functions, restoration is far for being complete. However, research aimed at finding new therapeutic strategies to improve outcomes in CA is still underdeveloped. Overlooking the investigation of new therapeutic approaches to improve CA may have negative consequences such as preventing the development of language and communication skills during childhood and adolescence. There is now encouraging evidence derived from model-based interventions indicating that adult aphasia outcomes can be improved with intensive aphasia therapy and other therapeutic approaches (pharmacotherapy, non-invasive brain stimulation) (Pulvermüller and Berthier, 2008; Berthier and Pulvermüller, 2011; Breitenstein et al., 2017; Fridriksson et al., 2018). Taking advantage from data on these new interventions in adults with aphasia, in the present case study we used a similar therapeutic approach demonstrating, for the first time that DP is safe and well tolerated in CA and can be used alone and in combination with a tailor-made aphasia therapy (e.g., INT) to boost recovery of language and cognitive deficits.

Pre-Treatment Behavioral Profile and Brain-Behavior Relationships

Baseline testing (LNE1) with the WAB-R classified the language disorder in subject P as anomic aphasia (Kertesz, 1982), yet she also displayed deficits in phonology and semantic processing. On the WAB-R, the deficits were mainly observed in spontaneous speech (information content and fluency), and naming. Furthermore, subject P showed significantly lower scores in most of the secondary outcome measures than the control group (auditory and visual-verbal comprehension, repetition, noun naming, and reading). Subject P also showed low performance in tests measuring executive functions, attention, and auditory verbal short-term memory, manifested by slow processing speed, limited cognitive flexibility, low selective and sustained attention levels, and reduced verbal span. Impairments in executive and attentional functions are common after TBI due to diffuse cerebral damage that frequently affects the white matter bundles in frontal and temporal lobes (Levin, 2003; Vik et al., 2006). Although memory dysfunction is usually associated to oral language deficits in children with TBI (Conde-Guzón et al., 2009), the performance of subject P on the different memory subscales revealed that this function was preserved, except for a reduced digit span. In addition, performance in visuoconstructive and visuoperceptive tests was preserved.

Structural MRI in the chronic stage showed a large contusion in the left temporo-parietal cortex together with focal cortical atrophy and gliosis in the subcortical white matter. Our lesion-based approach suggests that the tract with major proportion of damage was the AF posterior segment, which connects regions that were specifically damaged in subject P (i.e., inferior parietal cortex and ventral posterior temporal cortex). This segment is part of the indirect connection of the AF system implicated in verbal repetition (Forkel et al., 2020) and reading (Thiebaut de Schotten et al., 2014). Notice that at baseline evaluation (LNE1, **Table 1**), both nonword (PALPA-8) and sentence (PALPA-12) repetition, as well as reading (PALPA-25, PALPA-32, PALPA-36, PALPA-37) were impaired. Ventrally, the ILF was the tract with the major proportion of damage. This tract runs in parallel from posterior to anterior parts of the temporal lobe and is implicated in lexical access (Herbet et al., 2019). This is consistent with the fact that naming was the main deficit of subject P. Thus, the high probability of affectation of these tracts together with the observed cortical involvement of temporo-parietal areas (BA21, BA37, and BA39) may explain the prominent naming difficulties found in subject P, as well as the pattern of committed errors (semantic paraphasias). For instance, axonal degeneration of the ILF is related to naming deficits and the production of semantic paraphasias in post-stroke aphasia (McKinnon et al., 2018) and in patients with brain tumors (Sierpowska et al., 2019). In addition, the ILF has been systematically implicated in semantic processing, lexical access (Nugiel et al., 2016; Herbet et al., 2019) and word learning involving lexical-semantic association in healthy subjects (Ripollés et al., 2017). In this line, BA37, which is damaged in subject P, is an important cortical hub for two distinct networks implicated in visual recognition (perception) and semantic functions (Ardila et al., 2015), and its damage is associated with fluency, comprehension, repetition, and naming impairments after stroke (Gleichgerrcht et al., 2015). The subtle involvement of BA21 in the posterior middle temporal cortex may have altered semantic control for comprehension (Noonan et al., 2013). Finally, despite the small size of the parietal cortical damage, the angular as well as the supramarginal gyri may be disconnected due to the affectation of the AF posterior segment, as revealed by the lesion analyses. Therefore, although it seems that the lesion sizes were not large enough to induce major disconnections, they were strategically placed to interrupt intrinsic connections within the left perisylvian language area. Unfortunately, since we only were able to perform a MRI study at baseline[2], we could not compare pre- and post-

[2]Multimodal MRI studies at baseline and repeated scanning at different time points were not performed because exposing patients with ventricular shunts to prolonged 3-Tesla MRI procedures poses a significant risk of unintentional changes in shunt settings. Therefore, subject P only underwent a single, rapid acquisition of structural MRI. Despite this, reprogramming of the shunt was needed after the study.

treatment MRIs to explore the brain correlates of the observed improvements in naming.

Drug Treatment Alone Improves Language and Cognitive Deficits

Although the beneficial action of the cholinesterase inhibitor DP is controversial in adult TBI, with studies showing both positive effects and lack of benefits (Walker et al., 2004; Warden et al., 2006; Shaw et al., 2013), our findings clearly show that CA may be improved with cholinergic potentiation. After 12 weeks of DP treatment (LNE2), a decrease in aphasia severity was found in subject P, as revealed by increased scores on both the WAB-R AQ and its subtests, except for naming. In fact, improvements were found for some naming tests (NSB subscale), but not for others (SVOPS, BNT, EPLA-53, EPLA-54). The treatment with DP alone also induced significant improvements in measures of verbal fluency (semantic and phonological), auditory-verbal comprehension (words and sentences), and word and nonword repetition. These linguistic improvements may be associated with enhancement of selective and sustained attention which eventually favored phonological and lexical processing for these stimuli. This is consistent with the role of anticholinesterase drugs, like DP, in improving sustained attention (Spiridigliozzi et al., 2007) and language function (Heller et al., 2004) in children. The bulk of the lesion in subject P was in the left temporal cortex, and this lobe contains more choline acetyltransferase than its homologous counterpart (Amaducci et al., 1981; Hutsler and Gazzaniga, 1996). Therefore, a neurobiological explanation for this finding would be that the language improvements could be accounted for cholinergic-induced neural plasticity in left perilesional temporal cortical areas and white matter tracts (ILF and IFOF), though the contribution of remote right cortical regions cannot be dismissed.

The gains produced by DP in selective and sustained attention were not associated with improvement in other frontal executive functions, which most likely resulted from diffuse axonal injury and the pressure effects of acute hydrocephalus on frontal tissue. Although an increase in processing speed was observed in d2 Tests, the performance on other tests evaluating this domain remained low. Likewise, there were slight improvements in cognitive flexibility (ENFEN), but this finding was not substantiated by other tests. Repetition and written comprehension of sentences, reading functions, and auditory-verbal short-term memory (Digit Span) also remained altered. This is in accord with Martin and Ayala's findings (2004) who have reported significant correlations between the severity of language impairment (in both phonological and lexical-semantic measures) and the size of digit and word span in individuals with aphasia.

Reading problems persisted in subject P. The fact that associative visual areas in the left inferior occipito-temporal cortex, such as the visual word form area (VWFA), were damaged, might be the simplest explanation of the reading deficits in subject P. The VWFA is a region specifically devoted to the recognition of the written words in literate persons (Cohen et al., 2000; López-Barroso et al., 2020) and its damage causes alexia. Although compensation by recruitment of the VWFA homolog in the right hemisphere can take place (Cohen et al., 2003), this plastic shift may require intensive training.

Combined Therapy Increases Gains Obtained With Drug Monotherapy

Treatment with DP alone improved language deficits in subject P. Nevertheless, recent evidence suggests that cholinergic stimulation in adults with TBI is useful when combined with environmental enrichment (De la Tremblaye et al., 2019). The current findings further support the importance of augmenting the effect of DP on brain tissue with INT. Almost all scores obtained under treatment with DP alone showed further improvements after two weeks of combination therapy (LNE3). Moreover, in comparison with baseline (LNE1) and the evaluation after DP alone (LNE2), the highest gains after combination therapy (LNE3) were in several measures of naming production (see **Table 1**). Naming evaluations post-INT1 (NE1) under ongoing DP treatment (weeks 14-26) showed significantly better performance for treated items than for untreated ones. During this time period, gains in treated items were maintained, whereas low scores in untreated items remained unchanged.

Since then, DP was gradually tapered off (weeks 26-30) and followed by a washout period (weeks 30-34) and a new phase of INT (INT2). Post-washout evaluation (LNE4) showed that improvements observed in the WAB-R AQ decreased slightly but remained comparable to the scores of the control sample and well above subject P's baseline score. At this point, the score on the naming subtest of the WAB-R presented a slight decrease, but decrements were more evident in other naming tasks (SVOPS, semantic fluency, BNT). By contrast, the benefits observed in other language tasks (fluency, word and nonword repetition, auditory sentence comprehension, sentence reading comprehension, and phonological and semantic fluency) were stable. Likewise, washout testing revealed that subject P maintained an above-average level in several attentional and cognitive flexibility measures. Naming evaluations post-INT2 alone (NE2) showed a similar tendency to the outcomes of naming evaluation in NE1 except for the more pronounced decline in the two last NE2s.

Two of these results were unexpected. First, although beneficial effects of DP-INT1 were generalized to several language and cognitive domains, it was surprising that untreated items showed no improvement. The lack of generalization did not result from differences in selection of treated and untreated words, because both sets of words were closely matched controlling key linguistic variables. Although this negative evidence deserves further research, our results suggest that the effect of the DP on untreated nouns was not as powerful as when the drug was combined with intensive noun training, aimed to strengthen experience-dependent plasticity. Similarly, combined dexamphetamine with naming therapy in two subjects with

chronic adult post-stroke aphasia improved treated nouns but not untreated ones, nor a control nonword reading task (Whiting et al., 2007). The second unexpected finding was that the results of post-INT2 (NE2) evaluations (without pharmacotherapy) were similar to those obtained in post-INT1 evaluations (NE1) while subject P was still under DP treatment. A likely explanation could be that the previous prolonged treatment with DP (duration: 26 weeks) induced long-lasting brain changes that were then profitable seized by the application of INT2 after a short washout period (4 weeks). Thus, a lesson to be learned from this finding would be that once the brain has been primed with a combined intervention (DP-INT1), it would be similarly responsive to a single modality of intervention (INT2 or a drug) applied at a later stage (see Berthier et al., 2009; Berthier, 2020).

Finally, the results of the present study should be interpreted considering some limitations. First, this is an open-label study performed in a single subject. Thus, randomized controlled trials in larger samples are strongly needed. Second, we initiated the drug treatment before aphasia therapy, so that the effect of the naming training alone could only be evaluated after previous treatment with DP. Therefore, other designs should be evaluated in the future. Lastly, it is not possible to rule out that some beneficial changes in subject P may have resulted from the continued maturation and evolution of cognitive and language processes that may be partially blended with the beneficial effects of the two therapeutic interventions. Yet, this is unlikely, at least for naming ability, since no improvements were seen for untreated items which served as control. A further strategy to reduce the confounding factor of language and cognitive development and maturation in outcomes of an intervention trial in CA is performing multiple baseline assessments. Multiple baseline assessments were not used in this study. Notice that we performed a very comprehensive language and cognitive evaluation that took several days to be completed. This may preclude the utilization of multiple baseline testing. Indeed, longer and repetitive evaluations are very tiring, particularly for children, and may reduce motivation, putting at risk adherence to evaluation and treatment. The rationale to use such a large test battery in subject P was to examine, for the first time, the effect of DP and INT not only in language functions but also in several other cognitive domains, which are commonly affected after TBI and may influence outcomes. To overcome this limitation, future studies may perform multiple baseline assessments in the most affected language domain(s) (e.g., naming in subject P) or in the domain(s) targeted for the intervention.

In summary, subject P, who presented an acquired aphasia after suffering a TBI involving the left temporo-parietal region, significantly improved anomia and related cognitive deficits through the use of a cholinergic agent (DP) alone and in combination with INT.

DATA AVAILABILITY STATEMENT

The dataset that support the findings of this study will be available upon request from the corresponding author.

ETHICS STATEMENT

The Ethics Research Committee *Provincial de Málaga* approved this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version. GD, MM, MT-P, MB, LE, and DL-B were involved in conception and design, acquisition of data, or analysis and interpretation of data. GD, MM, MT-P, LM-C, LE, and DL-B were involved in cognitive and language assessment. GD, MT-P, MB, and DL-B interpreted neuroimaging data. GD, MT-P, MB, and DL-B drafted the article and revised it critically for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.01144/full#supplementary-material

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Parent Language Input Prior to School Forecasts Change in Children's Language-Related Cortical Structures During Mid-Adolescence

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Children differ widely in their early language development, and this variability has important implications for later life outcomes. Parent language input is a strong experiential factor predicting the variability in children's early language skills. However, little is known about the brain or cognitive mechanisms that underlie the relationship. In addressing this gap, we used longitudinal data spanning 15 years to examine the role of early parental language input that children receive during preschool years in the development of brain structures that support language processing during school years. Using naturalistic parent–child interactions, we measured parental language input (amount and complexity) to children between the ages of 18 and 42 months (n = 23). We then assessed longitudinal *changes* in children's cortical thickness measured at five time points between 9 and 16 years of age. We focused on specific regions of interest (ROIs) that have been shown to play a role in language processing. Our results support the view that, even after accounting for important covariates such as parental intelligence quotient (IQ) and education, the amount and complexity of language input to a young child prior to school forecasts the rate of change in cortical thickness during the 7-year period from 5½ to 12½ years later. Examining the proximal correlates of change in brain and cognitive differences has the potential to inform targets for effective prevention and intervention strategies.

Keywords: MRI, language acquisition, brain structure, parental language input, language development, cortical thickness

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INTRODUCTION

Language skills are fundamental for children's later life outcomes (e.g., Duncan et al., 2007; Marchman and Fernald, 2008; Bleses et al., 2016). Variability in children's language skills early in life has been linked to variability in children's home environments. Indeed, one of the best-established findings in the developmental literature is that variability in children's early language

skill is influenced by the quantity and quality of language input they receive from their parents (e.g., Huttenlocher et al., 1991, 2002; Hart and Risley, 1995; Weizman and Snow, 2001; Hoff, 2003; Rowe and Goldin-Meadow, 2009; Rowe et al., 2009; Cartmill et al., 2013). Variability in early child language skills have also been shown to predict variability in later structural brain differences in language areas. For example, vocabulary growth measured at age 14–58 months predicts cortical thickness in the left supramarginal gyrus (SMG) at age 8 to 10 years old (Asaridou et al., 2017). However, less is known about the relation between children's experiential factors early in life and *change* in later brain structures. Here, we attempt to bridge this gap using a unique longitudinal data set spanning 15 years. We ask whether parental language input during preschool years predicts *changes* in later (mid-adolescent) cortical structures that subserve language processing, over and above possible covariates such as parental socioeconomic status (SES) or intelligence quotient (IQ).

PARENTAL LANGUAGE INPUT AND CHILD LANGUAGE DEVELOPMENT

Previous behavioral work highlights the role of parental cognitive stimulation, and the role of parental language input more specifically, in shaping children's cognitive outcomes. One of the most frequently reported findings in the developmental literature is the association between early parental language input and language development (e.g., Huttenlocher et al., 1991, 2002; Hart and Risley, 1995; Weizman and Snow, 2001; Hoff, 2003; Rowe and Goldin-Meadow, 2009; Rowe et al., 2009). Language input more strongly predicts child language outcomes than SES or a variety of other characteristics of parent–child interactions, such as parental affect. Measures of language input often focus on its quantity, such as the number of word tokens parents produce (Huttenlocher et al., 1991; Hart and Risley, 1995; Weizman and Snow, 2001; Rowe, 2008, 2012; Barnes, 2011; Weisleder and Fernald, 2013; Demir-Lira et al., 2019; Rowe and Snow, 2020). More recent research has also highlighted the complexity of language input, such as parental use of rare words or talk about abstract topics, as a predictor (e.g., Demir et al., 2015; Rowe and Snow, 2020; see also Cartmill et al., 2013). In the current paper, to gain a comprehensive view of children's input, we consider both the quantity and complexity of early parental input in predicting later child brain structure.

BRAIN AREAS ASSOCIATED WITH LANGUAGE DEVELOPMENT

A wide set of networks in the brain supports language development. One network, particularly specialized for language, includes (among other regions) the superior temporal gyrus (STG), superior temporal sulcus (STS), middle temporal gyrus (MTG), SMG, and inferior frontal gyrus (IFG; pars opercularis and pars triangularis) (Wilke et al., 2009; Friederici and Gierhan, 2013). Among other roles, STG is thought to be involved in speech perception (Hickok and Poeppel, 2007), MTG in semantic processing (Price, 2012), the SMG in phonological processing (Rodríguez-Fornells et al., 2009), and the IFG in speech processing and lexical competition (Davis and Gaskell, 2009; Rodríguez-Fornells et al., 2009; Price, 2010, 2012; Fedorenko and Thompson-Schill, 2014; Li et al., 2014). Brain structure in these regions of interest (ROIs) is related to children's language skills. For example, left IFG, MTG and STG volumes differentiate typically-developing children from children with language disorders (e.g., Badcock et al., 2012; Lee et al., 2020).

The focus of the current paper is on brain structure, specifically, cortical thickness, because underlying cellular components of cortical thickness are amenable to *change* as a result of postnatal experience and learning (Diamond et al., 1964; Black et al., 1990; Anderson et al., 1994; Kleim et al., 1996). Cortical thickness is measured by the distance between the boundary of white and cortical gray matter, and gray matter and the pia mater. Cortical thickness varies roughly between 2 and 4 mm, with frontal and occipital poles being thinnest and temporal and insular cortices being thickest (Ribeiro et al., 2013). Although, as a general trend, cortical thickness decreases over childhood and early adolescence, ultimately plateauing in early- to mid-adulthood, development varies across cortical regions. Some regions, such as temporal areas, exhibit less linear and more quadratic patterns of development than other areas (Sowell et al., 2003; Raznahan et al., 2011; Mutlu et al., 2013; Mills et al., 2016).

PARENTAL LANGUAGE INPUT AND BRAIN AREAS ASSOCIATED WITH LANGUAGE DEVELOPMENT

Discussions of the role that parental input plays in language development rarely include the underlying neural basis of this development. When experiential factors have been considered in relation to the neurobiological basis of language processing, parental SES (typically measured by family income, parental educational attainment, and/or parental occupational prestige) has been the focus (Duncan and Magnuson, 2012). For example, SES disadvantage has been associated with reduced volume (e.g., Jednoróg et al., 2012; Hair et al., 2015), thickness (Mackey et al., 2015), and surface area (Noble et al., 2015) in cortical regions underlying language comprehension, including perisylvian areas (e.g., STG) and ventrolateral prefrontal areas (e.g., IFG; Noble et al., 2012; Piccolo et al., 2016). SES-related differences are also observed in white matter structures, and in functional brain systems, involved in language processing (Raizada et al., 2008; Gullick et al., 2016; Younger et al., 2019). However, parental SES is a complex construct of many components (e.g., parental income, education, and neighborhood characteristics). Any one of these components of SES could be influencing children's academic outcomes via more day-to-day interactions, such as parental language input.

A few recent studies have begun to examine the associations between parental language input and brain structure and function for language processing. Avants et al. (2015) found associations between HOME, an observational measure of the home environment, and later cortical thickness in areas central

to language processing. Using naturalistic recordings of parent–child conversations in the home, Romeo et al. (2018a) showed that, in 4 to 6-year-old children, the number of conversational turns with adults in the home environment (a measure of input complexity), predicts left IFG activation during a story-listening task completed at the same age, and that number of turns mediates the relation between SES and children's language skill, as well as white matter connectivity in left arcuate and superior longitudinal fasciculi, also at the same age (Romeo et al., 2018b). Building on this work, Merz et al. (2020) found that the greater the input quantity (number of adult words) and complexity (number of conversational turns) in 5- to 9-year-old children, the greater left perisylvian cortical surface area in these children at the same age. The input quantity and complexity measures were highly correlated and revealed similar associations.

We add to this small but growing literature in several ways. First, previous investigations examined *concurrent* relations between parental input and child brain structure. However, to explore predictive relations, we need to examine parental input early in development, and child brain structure later in development in the same children – the focus of this paper. Second, previous studies measured brain structure at a single time point, but parental input might have different effects on child measures if those measures are taken longitudinally (e.g., Rowe et al., 2012, with respect to behavioral measures; Piccolo et al., 2016, with respect to brain measures). Here, we assess *changes* in brain structure over time during development. Third, existing studies rely on recording devices (e.g., LENA devices) that provide automatized measures, but do not produce transcription of audio recordings. Past studies leveraged conversational turns as a measure of input complexity, which is automatically calculated by LENA. However, conversational turns do not reveal the specific linguistic features that are predicting later outcomes. Here, we consider measures not only of input quantity, but also of input complexity, which requires hand-coding. Fourth, the youngest children included in previous studies of parent language input–child brain structure relations were 4 years old; however, by 4, children already vary greatly in their language skills (Fenson et al., 1994). Recent work shows that early parental input may predict later child outcomes better than input in later preschool years (Rowe et al., 2012). Here, we focus on parental input beginning at child age 18 months. Finally, we examine the relation of this early parental input to child brain structure in mid-adolescence, a much later age than has typically been studied.

CURRENT STUDY

Ours is the first study to examine predictive, longitudinal relations between early parental language input and *changes* in child brain structure over time. We examine the relation between two measures of early parental input – quantity and complexity – between child age 18 and 42 months, and changes in child cortical thickness between 9 and 16 years of age. To do so, we gathered a range of input measures collected directly from naturalistic interactions in the home at child age 18–42 months, when children already show great variability in language development. We then assessed children's brain structure at five different time points between 9 and 16 years of age. We focus on brain regions that have been shown to play a particularly strong role in language processing. We also focus on cortical thickness as our measures of brain structure. Cortical thickness is tied to the number of neurons in a cortical column, the amount of glial and capillary support, and dendritic branching (Rakic, 1988, 2009), all of which are amenable to change as a result of postnatal experience and learning and thus deem cortical thickness as particularly sensitive to environmental experiences (Black et al., 1990; Anderson et al., 1994; Kleim et al., 1996). Our main research question is how parental language input during preschool years relates to changes during mid-adolescence in child brain structures involved in language processing. Based on prior behavioral and neuroimaging literature, we hypothesize that parental language input will positively predict both average cortical thickness and *changes* in cortical thickness, controlling for parent background variables, such as parent income, education and IQ.

MATERIALS AND METHODS

Participants

Twenty-three children (12 female) participated in the study. All were native speakers of American English and were studied over a 15-year period. The children were drawn from a sample of 64 children participating in a larger, longitudinal study of children's language development in the greater Chicago area (see Goldin-Meadow et al., 2014). Participants were recruited from the Chicago area via mailings to families in targeted zip codes and via an advertisement in a free parent magazine. A subset of the 64 children from the original sample agreed to participate in the neuroimaging component of the larger study (n = 23); these are the families described in this study. Each parent gave written informed consent following the guidelines of the Institutional Review Boards for the Division of Biological Sciences at The University of Chicago, and the Office of Research at the University of California, Irvine, which approved the study. Children gave verbal assent. All participants reported normal hearing and normal or corrected-to-normal vision. No parent reported any history of neurological or developmental disorders in their child. Handedness was assessed using the Edinburgh handedness inventory (Oldfield, 1971).

Parent language input measures were collected at the 18, 30, and 42 month behavioral visits (see procedure below). A total of 30 participants were tested in the Magnetic resonance imaging (MRI) component over the 5 years between 9 and 16 years of age. Seven participants were excluded from the analyses because they did not have the early parental input data, resulting in a final sample of 23 families. As described below, children were scanned a maximum of five times – a number of individual MRI sessions were excluded because the child failed to complete the session or moved excessively (more than 10% of the total number of volumes).

According to parent report, 19 children were White, 2 were African–American, and 2 were of mixed race. In terms of

ethnicity, 3 of the children were reported to be Hispanic and 20 were non-Hispanic. Parent education (in years) was coded on a categorical scale (10 = less than high school degree, 12 = high school degree, 14 = some college or associate degree, 16 = college degree, 18 = more than college). In this sample of 23 children, average parent education was 15.6 years (SD = 2.4, range = 10–18) and average family income was $59,456 (SD = $30,738, range = $7500–$100,000). For 22 children, mother was the primary caregiver; for 1 child, father was the primary caregiver. All but 3 of the families reported the education level of a secondary caregiver as well. For these 20 families, education levels for the primary and secondary caregivers were highly correlated, $r = 0.57$, $p = 0.008$. Because family income and caregiver education were highly correlated, the two were combined using a principal components analysis (PCA), which returned a single composite measure for SES. Correlation between SES composite and education is $\rho = 0.86$, and correlation between SES composite and income is $\rho = 0.69$. SES captured 47% of the variability between education and income.

Behavioral Procedure

The parental language input included in this study was collected as part of the larger longitudinal study described previously (see Goldin-Meadow et al., 2014). We coded videotapes of parents interacting with their children for approximately 90 min during home visits that occurred every 4 months between child ages 14–58 months. Parents were not given any specific instructions and were asked to engage in their normal daily activities. Typical activities included toy play, book reading, and eating meals and snacks. In the current study, three visits were chosen (visits at child age 18, 30, and 42 months). We focused on these three time points for multiple reasons: (1) previous research using data from the larger sample showed significant relations between input provided at these three time points and later child outcomes, highlighting the role of children's early experiences (Rowe et al., 2012); (2) the earlier the ages, the lower the possibility of children directing the input parents provide to them, (3) recent work has shown that parents tend to be stable in their input in these early years (Silvey et al., 2021); and finally, (4) input in earlier preschool years, compared to the entire preschool period up to 58 months, reveals similar relations to later outcomes (Rowe et al., 2012).

Behavioral Measures

Parent Language Input Measures

All parent and child speech in the videotaped sessions were transcribed. Only speech directed to the child was used in the current analyses based on previous work suggesting that language directed to the child might be more strongly related to child language development than overheard speech (Shneidman et al., 2013; Weisleder and Fernald, 2013). The unit of transcription was the utterance. An utterance was defined as any sequence of words that was preceded and followed by a pause, a change in conversational turn, or a change in intonational pattern. Transcription reliability was established by having a second individual transcribe 20% of the videotapes with a reliability criterion of 95% agreement on utterance transcription. Our measures of input consisted of three different components: (1) the number of word tokens, (2) number of rare words, and (3) decontextualized utterances parents produced at child age 18, 30 and 42 months during the 90-min visits. Word tokens were the total number of words parents produced. Rare words were identified using the method described by Beals and Tabors (1995) (see also Weizman and Snow, 2001). We removed all non-dictionary words from the corpus of spoken parent words and the most common words (and all their inflected forms) known by fourth graders, as judged by teachers, and compiled in the Dale-Chall word list (Dale and Chall, 1948; Chall and Dale, 1995). The remaining words in the parent input corpus were considered rare words. Decontextualized language utterances produced by parents and children were identified and coded as in Rowe (2012). Categories of decontextualized language included narrative, pretend, and explanation (see Rowe, 2012; Demir et al., 2015; for detailed definitions of each category). All utterances marked as narrative, pretend or explanation were considered decontextualized. Since effectiveness of specific input features varies by child age, we focused on features of the input that have been shown to predict child language outcomes during the period observed (Rowe and Snow, 2020; Silvey et al., 2021). We also excluded interactional aspects of the input, such as conversational turns, that might reflect broader characteristics of the parent–child interactions, such as parent sensitivity or parent–child synchrony.

Parent IQ

Parent verbal IQ was measured using Wechsler Abbreviated Scale of Intelligence (WASI-II, Wechsler, 2011) when children were in 5th grade. Average parent IQ was 113.5 (SD = 18.4, range = 80–149).

Child Peabody Picture Vocabulary Test

To examine the impact of early parent language input on later child brain imaging, above and beyond the child's language skill at the time of imaging, we included a measure of children's language skill (Peabody Picture Vocabulary Test, PPVT III; Dunn and Dunn, 1997), administered at 4th grade during the period when the imaging was done. The PPVT is a widely used measure of vocabulary comprehension with published norms. Average PPVT score was 113.61.

Neuroimaging Procedure

Children were scanned in five waves from 9 to 16 years of age. As in other large-scale studies focusing on brain development during childhood, this age span was selected to capture a rapid period of brain development during late childhood and adolescence when high individual variability is observed (e.g., Sowell et al., 2001, 2002; Casey et al., 2018). For a detailed summary of the number of children that participated in each year and their age, see **Table 1**. Not all children participated in all scanning sessions and each child contributed 1–5 scans. Six children were scanned once, 3 children were scanned twice, 4 three times, 2 four times, and 8 five times. On average children were scanned 2.9 times, and we had a total of 83 scans. Although the sample size is modest ($n = 23$), it is important to highlight that, according to a recent review on neuroimaging studies on structural brain development, only 16

TABLE 1 | Descriptive statistics for child age at MRI scanning session.

	Age		
	***M* (SD)**	**Range**	***n***
Year 1	9.31 (0.54)	8.66–10.29	16
Year 2	10.47 (0.60)	9.71–11.32	11
Year 3	11.44 (0.50)	10.79–12.19	13
Year 4	13.94 (0.59)	13.21–15.29	19
Year 5	15.97 (0.28)	15.48–16.40	14

Descriptive statistics include mean age (M), standard deviation (SD), and sample size per year with valid measurements (n).

prior studies had on average more than 2 scans per participant, and only 3 prior studies had included three or more scans on average per participant (Vijayakumar et al., 2018).

MRI Acquisition

The first to third waves of imaging data were acquired on a 3T Siemens Trio scanner with a 32-channel head-coil at Northwestern University's Center for Translational Imaging in Chicago. A T1-weighted structural scan was acquired for each participant (1 mm × 1 mm × 1 mm resolution; sagittal acquisition). T1-weighted 3D spoiled gradient echo (MP-RAGE) sequences were obtained with TR = 2,300 ms, TE = 2.91 ms, flip angle = 9°, inversion time = 900 ms, and 256 contiguous slices (slice thickness = 1 mm, voxel size = 1 mm × 1 mm × 1 mm, matrix size = 256 × 256). The fourth to fifth waves of imaging data were acquired on a 3T Siemens Prisma Scanner with a 32-channel head-coil, also at the Northwestern University Center for Translational Imaging. A T1-weighted structural scan was acquired with a magnetization-prepared rapid gradient echo (MP-RAGE) sequence (TR = 2300 ms, TE = 1.86 ms, flip angle = 7°, Inversion Time = 1180 ms, 208 contiguous sagittal slices, slice thickness = 0.8 mm, voxel size = 0.8 mm × 0.8 mm × 0.8 mm, matrix size = 320 × 320). Head motion was minimized using foam padding around the head, and scanner noise was minimized with earplugs.

Freesurfer Processing: Cortical Parcelation

Cortical reconstruction of white and pial surface models was performed using Freesurfer version 5.3.0[1] (see Dale et al., 1999; Fischl et al., 1999). The cortical surface models were manually reviewed and edited for technical accuracy. We also performed quality assurance using the Freesurfer QA Toolbox v1.2. Sulcal and gyral structures were identified automatically (Fischl, 2004) and parcellated using the Destrieux cortical atlas for anatomical labeling (Destrieux et al., 2010). This parcelation scheme results in 148 cortical regions (74 per hemisphere). Cortical thickness was estimated as the average distance between the white and the pial surface reconstructions (Fischl and Dale, 2000).

[1]See http://surfer.nmr.mgh.harvard.edu/ for details on the Freesurfer surface-based pipeline.

Given our overall modest sample size, we focused on six ROIs that have been shown to play a particularly important role in language processing. Based on the previous literature on neurobiological basis of language development and our own work, which has found a relation between children's own early language skills and their later cortical thickness in the children observed in this study (Asaridou et al., 2017), we examined cortical thickness in six ROIs in each hemisphere (12 regions in total): STG, STS, MTG, SMG, IFG (pars opercularis and pars triangularis) in each of the hemispheres (e.g., Price, 2010; Li et al., 2014).

Statistical Analysis Plan

To address our research question, we built two sets of models. For the first set of models, we ran traditional, frequentist analysis of the data using linear mixed models. Given the sample size, we also performed the model fitting process under a Bayesian paradigm to complement the frequentist analyses (McNeish and Stapleton, 2016). The second set of analyses can be found in **Supplementary Tables 1, 2** and **Supplementary Figure 1**. The direction of effects for parameters of interest was consistent across the frequentist and Bayesian models. For the frequentist approach, linear mixed models were built in R using the lmer package (R Core Team, 2017). The dependent variable was cortical thickness. We started with a parsimonious model of fixed effects including variables which, on theoretical grounds, we wanted to control for independent of effect size. These variables included a measure for parent SES composite, maternal IQ, sex, age, and an indicator for the fMRI scanner used (which changed after the 3rd scan). As measures for body size were unavailable, a mean thickness from 5 occipital regions of the brain (middle occipital gyrus, superior occipital, occipital pole, occipital sulcus, and parieto-occipital sulcus), typically not associated with auditory language processing, were used to control for brain size (Price, 2010). As we were interested in change in thickness over time, the minimum age value was subtracted from all ages, thus centering age at the beginning of the first scan. Similar to other longitudinal studies, this was done so that the zero-time point (the beginning of first scan) was included in the range of the model, and so that age-related coefficients could be interpreted as one-year increases in age from the onset of the scans. Further, by doing so, we can interpret the intercept term as cortical thickness at the beginning of the study. Additionally, exploratory analyses suggested that the largest difference in mean thickness between high and low language input groups (partitioned by the sign of the first principal component) occurred at younger ages. Setting the adjusted age to start at zero allowed this time to serve as a baseline for model covariates. Model covariates for IQ, language input composite, SES composite, mean occipital thickness were all centered and scaled.

Previous studies (e.g., Vijayakumar et al., 2016) indicate that change in brain thickness during the 9–16 year period, especially in the areas we focus on, could follow a quadratic pattern. Since our null hypothesis was that linguistic input does not have relate to brain thickness over time, we included a quadratic interaction between age and model covariates. Specifically, in addition to the hypothesized quadratic change in thickness over age, we

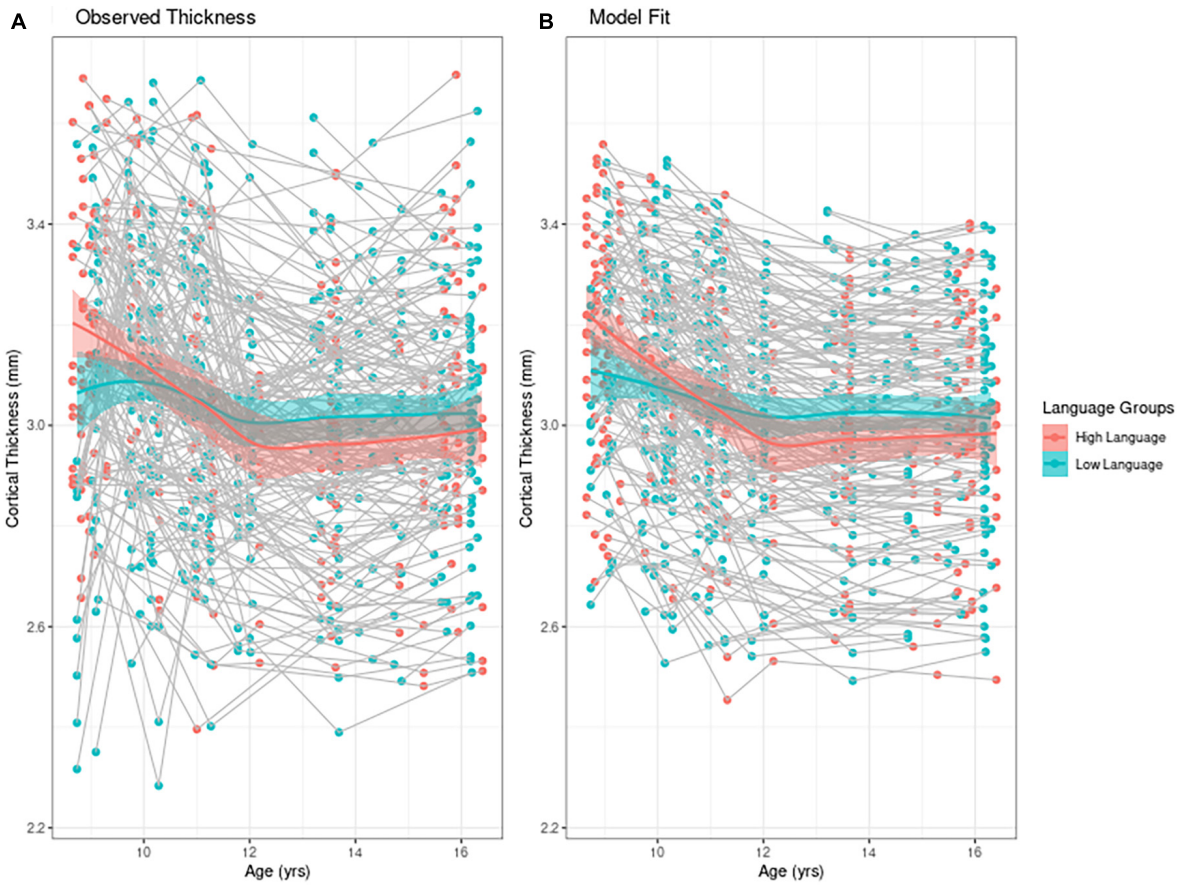

FIGURE 1 | Individual trajectories of cortical thickness **(A)** mean observed cortical thickness by group and **(B)** model fit by group. For visualization purposes only, high and low language groups are separated by median language input PCA value. In both figures the solid line represents the Loess curve fit on the observation. The six children who participated in only one MRI session are represented with a single point in the figure.

attempted to account for the fact that linguistic input itself (as well as other covariates) may have a quadratic effect on cortical thickness. Inclusion of input for language, as well as quadratic interactions of all variables with age, were determined by Akaike information criterion (AIC). Random effects for the model were used to account for correlation between observations, and were selected based on the restricted maximum likelihood (REML) criterion. Random effects selected include random intercepts for subject, brain region, and laterality. A residuals analysis was performed on the final models to verify the assumption of normality for the model error. Reported *p*-values were computed with Satterthwaite approximation in the R package lmerTest (Kuznetsova et al., 2016).

RESULTS

Descriptive Analyses

Parents showed variability in the quantity and complexity of language input at 18, 30, and 42 months (see **Table 2**). For example, some parents produced no decontextualized utterances at all; others produced over 600 during their 90-min visits. We included in this study only those children who took part in the MRI study. The numbers for the subsample who were included in the study were representative of the results based on the full sample discussed in other publications (e.g., Rowe, 2012). Parent input measures on our subsample at different time points were significantly correlated with each other, with correlations ranging from 0.19 to 0.74, and an average correlation of 0.48 – consistent with our work with the full sample showing that parents are relatively stable in their input over time (Silvey et al., 2021). See the **Supplementary Materials** for correlations between different time points separately (**Supplementary Table 3**).

Because the primary goal of the current study was to gather an overall view of children's early language input, we used PCA to create a single composite measure of language input. The decision to focus on a composite input measure was further justified by the high degree of collinearity between the different measures. Measures of parental input were significantly correlated with each other (mean word tokens and decontextualized utterances, $r = 0.81$, $p < 0.001$; mean word tokens and rare words, $r = 0.59$, $p < 0.001$; mean decontextualized utterances and rare words, $r = 0.45$, $p < 0.001$). However, including rare words in the PCA decreased the variance explained by the first principal component

TABLE 2 | Descriptive statistics for parental input measures including mean (*M*), standard deviation (SD), and min–max range (n = 23).

	18 months	30 months	42 months
		M (SD) Range	
Word tokens	3.435 (2.176) 360–9.227	3.603 (1.825) 1.096–7.673	3.634 (1.923) 488–9.087
Decontextualized utterances	18.87 (22.23) 0–73	62.3 (67.01) 0–301	84.13 (133.09) 0–628
Rare words	25.57 (19.52) 1–83	30.09 (15.59) 10–76	37.35 (22.72) 6–100

to 32%, a net loss even after considering the addition of three measures (one for each time point), suggesting that including rare words increased noise that may, or may not, be related to our outcome of interest. We conducted analyses by combining mean word tokens and decontextualized utterances from the three time points into a single composite input score. The first principal component was highly correlated with each of these input measures and accounted for 62% of the total variance in linguistic input. Consequently, we focused on the principal component including word tokens and decontextualized utterances. We replicated the analysis with models using a principal component that also included rare word types. These models revealed similar results, though with a higher AIC, i.e., a worse fit. The results using the measure of parental input that also included rare words are included in the **Supplementary Table 4**.

Linear Mixed Model Approach

To find the best fitting model for cortical thickness, we first present an empirical plot of children's cortical thickness between 9 and 16 years. **Figure 1A** is a plot of the observed individual trajectories of cortical thickness for each participant. Please note that language input was measured continuously for the statistical analyses. For visualization purposes only, we divided the observations into high/low language input groups separated by the median language input PCA value. Superimposed on both of these plots is a solid line for each group representing the Loess curves fit to the values. Children who participated in only one MRI session (n = 6) are represented with a single point in the figure. We see that children with higher language input had higher values for cortical thickness than their lower language input peers, while also exhibiting steeper *change* within the time period observed. **Figure 1B** represents the model fit which we describe next.

To formally test the patterns observed, we ran linear mixed model analyses. Results are shown in **Table 3**. Considering our covariates first, we saw a non-linear effect with age on cortical thickness. Mean occipital thickness, as expected, was a significant predictor of thickness in our ROIs. Higher SES was associated with greater thickness overall, and SES moderated the relations of age to cortical thickness, where higher SES children had larger decreases in cortical thickness, compared to lower SES children. Female sex was both positively related to overall cortical thickness and negatively associated with change over time. Female sex was also positively related to the quadratic term. Mother IQ and scanner type did not predict cortical thickness when accounting for other factors in the model.

Particularly relevant to our main question, we saw that language input interacted quadratically with age. Specifically, the covariates indicate a concave upward parabola for children with greater language input during the early years than for children with less language input. This trend suggests that children with high language input had overall higher cortical thickness at the beginning of the observed time period, i.e., around 9 years of age. The signs and effect sizes of the linear and quadratic terms suggest that children with higher language input experienced larger decreases in cortical thickness in the 9–16 age range, compared to children with lower language input, who exhibited a more attenuated change. Although our sample size is modest, the direction of effects for parameters of interest is consistent across the frequentist and Bayesian models (see **Supplementary Table 5**). Further, the directions of effects for parameters for age are also consistent with prior studies (Vijayakumar et al., 2016, 2018). Importantly, the results remained unchanged when analyses were repeated on the subsample of 17 children who had at least two or more scans and we could directly assess change over time (see **Supplementary Materials 5**). Since SES and language input composite are both centered and scaled, it is possible to compare the effect of the two factors in the model. The estimates suggest that the effect size of language

TABLE 3 | Results of a linear mixed model analysis for the relationship between parental language input PCA (word tokens and decontextualized utterances) and cortical thickness.

	Estimate	Std. Error	95% L	95% U	*p*-value
Intercept	3.1692	0.1615	2.8527	3.4857	< 0.001*
Age	−0.0293	0.0188	−0.0662	0.0077	0.1208
Age^2	0.0018	0.0024	−0.0029	0.0064	0.4593
Mean occipital thickness	0.0872	0.008	0.0716	0.1029	<0.001*
Scanner	0.0195	0.0283	−0.036	0.075	0.492
Mother IQ	−0.0009	0.0022	−0.0052	0.0033	0.6694
SES composite	0.0205	0.0271	−0.0327	0.0737	0.4572
SES composite × Age	−0.0061	0.0025	−0.011	−0.0012	0.0148*
Sex	0.1569	0.0667	0.0261	0.2877	0.0216*
Sex Age	−0.0762	0.0315	−0.1379	−0.0144	0.016*
Sex Age2	0.0072	0.0039	−0.0004	0.0148	0.0653
Language input PCA	0.068	0.0369	−0.0044	0.1404	0.069
Language input PCA × Age	−0.0378	0.0156	−0.0685	−0.0072	0.0158*
Language input PCA × Age^2	0.0042	0.0019	0.0005	0.0079	0.0274*

We controlled for the following covariates: child age, mean occipital thickness, sex, scanner type, mother IQ, and family SES. Inferential statistics include estimate, standard error, 95% CI upper and lower limit, and p-value.
**p < 0.05.*

input and age on cortical thickness is comparable to (slightly larger) than the effect size of SES on cortical thickness. Finally, to examine the specificity of the relations of later input to later child cortical thickness, we included children's PPVT scores as a covariate in our model; the results were unchanged (see **Supplementary Table 6**).

Region-Specific Relations

Given our modest sample size, we refrain from making strong conclusions about region-specific effects. For completeness, we report exploratory analyses including intercept, linear, and quadratic terms for each ROI as fixed factors. The values for non-region relevant covariates, such as age, SES, and sex matched the previous main models. Previous analyses did not reveal strong laterality differences and thus cortical thickness for the left and right were averaged per region. IFG pars opercularis showed the strongest relation to language input and STG and STS revealed non-significant trending associations. No significant relations were observed in other regions such as IFG pars triangularis or SMG. For these former three regions, as in the main model, language input was positively related to thickness at baseline, negative to slope and positive to quadratic term. In other words, children with greater early input had a higher intercept (indicating higher cortical thickness at the beginning of the study), and a steeper change over the observed time period than children with less early input. The tentative conclusion that language input might have a particular impact on IFG, STG, and STS is supported by previous evidence (e.g., Romeo et al., 2018a). See **Supplementary Materials** for region-specific linear mixed-model analysis (**Supplementary Table 7**), region-specific cortical thickness change trajectories (**Supplementary Figure 2**), and region-specific Bayesian analysis (**Supplementary Table 2**).

DISCUSSION

Our results reveal, for the first time, that early parental language input prior to school predicts *changes* in children's language-related cortical structures during the school years in mid-adolescence. Cortical thickness decreases during childhood, particularly from mid-childhood to adolescence (Mills et al., 2014; Wierenga et al., 2014; Vijayakumar et al., 2016; Tamnes et al., 2017). Even though there is a general decline in thickness, the trajectory of change displays substantial individual variability, and the trajectories vary by region. Vijayakumar et al. (2016) reported a negative quadratic pattern of cortical thickness change in temporal areas, which is similar to the pattern observed here. Individual variability is largest in temporal and frontal regions across the lifespan (Frangou et al., 2020). These structural variations can be linked to a wide range of child internal factors. For example, Asaridou et al. (2017) showed, in the sample studied here, that differences in children's early language development predict differences in later brain structure. The structural variations can also be linked to a wide range of experiential factors. For example, SES and parental cognitive stimulation predict variability in child brain regions supporting language processing (e.g., Luby et al., 2013; Merz et al., 2020). To the extent that previous studies explore the relations between parental language input and child brain structure, they focused on *concurrent* relations between input and brain structure. In contrast, we examined *predictive* relations between early parental language input and later child brain structure. The strength of our approach is that we modeled *change* in later brain structure using longitudinal data with multiple observations.

We found unique relations between early parental input and *change* in later child cortical thickness, which were stronger than relations between early parental input and the average level of later child cortical thickness. Finding stronger relations between parent input and change over time in child brain structure than to values at a single time-point dovetails with previous work showing that the *trajectory* of cortical thickness, rather than its value at a given time point, is a good index of individual variability in performance (Sowell et al., 2001). We found that the greater the early parental language input, the steeper the change in child cortical thickness years later. In other words, change was slower for children at the lower end of the parent input continuum. Our findings are also consistent with studies showing extended growth trajectories in children from higher SES families (Hanson et al., 2013), continued cortical thinning in children from higher SES families throughout late adolescence, and early plateauing in children from lower SES families (e.g., Piccolo et al., 2016), which is considered a sign of accelerated development in children from lower SES families (LeWinn et al., 2017). With respect to cortical thickness, children from higher SES backgrounds show steady age-related decreases, particularly in regions related to language processing (e.g., left STG); in contrast, children from lower SES backgrounds begin to plateau during late adolescence (Piccolo et al., 2016; McDermott et al., 2019). We extend previous work by identifying, for the first time, a direct measure – early parental language input – that predicts later change in child cortical thickness, over and above SES.

Why might children who have been exposed to a higher quantity and complexity of language input early in development exhibit continued change in cortical thickness, whereas low input children plateau? Certain enriching experiences might keep the window for structural brain development open, allowing for additional cortical thinning. In contrast, developmental thinning might be sped up for individuals who are not as frequently exposed to enriching experiences, resulting in an earlier-closing window and less thinning overall. Literature on severe environmental adversity, such as traumatic childhood experiences, supports the notion that damaging early life experiences can derail brain development, specifically leading to accelerated maturation and narrower windows of plasticity (Gur et al., 2019; Miskolczki et al., 2019). Here, we focused on only the role of enriching experiences and variability within the normative range. However, within the normative range, our results suggest a comparable profile of extended change for children exposed to richer experiences, and of restricted change for children with more impoverished input. Future work is needed to explore whether negative and positive experiences are part of the same continuum with respect to brain development. Another possible explanation for the differences we find between children coming from homes that provide high versus low

levels of cognitive enrichment is that children exposed to more language input might have resources to spare, as evidenced by their overall greater cortical thickness early in development, which might lead to continued thinning. In other words, more parental input might lead to thicker cortex to begin with, which then supports more protracted thinning. Overall, the computational properties of a network might be better revealed by considering its developmental origins *and* change over time together (Dündar-Coecke and Thomas, 2019).

Three developmental theories have been proposed to explain apparent cortical thinning in the age range examined: pruning, myelination and cortical morphology, but not to neuron generation or loss (Vandekar et al., 2015; Vijayakumar et al., 2016). Synapse elimination, pruning and myelination continues well into adulthood (Huttenlocher, 2009). Important underlying cellular changes include changes in the number of neurons in a cortical column, the amount of glial and capillary support, and dendritic branching (Rakic, 1988, 2009). More recent evidence supports the hypothesis that the cortical thinning during childhood is primarily due to increased myelination. The observed thinning is considered to be due to increased myelination altering the contrast between gray and white matter in MRI images, which in turn affects the apparent cortical boundary (Natu et al., 2019). Experiential factors have been shown to predict myelination (e.g., Hensch, 2004; Knudsen, 2004). Myelination is also important for concluding of periods of plasticity (Hensch, 2004; Hensch and Bilimoria, 2012). Taken together, reduced environmental stimulation might be associated with early narrowing of plasticity associated with overall lower myelination which might then result in smaller subsequent changes in cortical thickness, whereas higher input might keep windows of plasticity longer and thus might be associated with larger subsequent changes (Tooley et al., 2021).

The behavioral mechanisms by which early parental input relates to later child brain development remains an open question. One possibility is that simply being exposed to rich language input influences efficiency of language processing (e.g., Fernald et al., 2013), which, in turn, is associated with changes at the neural level. Another possibility is that, when parents produce rich language, children engage in rich conversations and it is *children* producing language that is associated with differences in brain structure (Romeo et al., 2018a). The two possibilities are not mutually exclusive, and it is also possible that the relation between early parental input and later child behavioral and neurological development varies depending on the specific brain region considered. We did not have early measures of children's general cognitive development, such as their memory or attention. Measures of general cognitive development would be needed to establish the specificity of the relation between early parental language input and later child neurological development, and to explore whether parental input might relate to later child outcomes via broader aspects of cognitive development. Although we emphasize the role of parental input, children are active participants in this interaction and might drive the input in different ways. Our recent work presents novel statistical models that account for the contribution of the child in eliciting parental input (Silvey et al., 2021), which we are currently applying to neuroimaging data. Finally, whether it is early parental input that predicts later change in child brain structures (which would be consistent with sensitive period hypotheses, Newport et al., 2001), or whether parents must continue to provide rich input to their children to trigger later change needs to be examined in future studies.

A number of limitations should be considered when interpreting our results. First, our findings are correlational. Although we accounted for important covariates, such as parental education and IQ, we cannot make claims about causation. Second, we have a modest sample size, which limits our ability to derive strong conclusions. We also observed multicollinearity between some covariates. For example, children with greater language input were more likely to be male and from higher SES homes, giving us few observations with which to isolate either of these covariates. Despite the uncertainty in our models (frequentist and Bayesian), the parameter fits from the observed data largely match the background literature and support our hypotheses. Further, we focused on a single factor, parental language input, following previous work emphasizing the role of early parental input in predicting later child behavioral outcomes, and also its role in predicting structural differences in brain areas subserving language processing at the same age. One could argue that language input might be correlated with other factors that predict brain structure – some of these include general cognitive stimulation, toxins, sleep differences, and even stress and glucocorticoids during pregnancy (Kaufman and Charney, 2001; Davis et al., 2013). We attempted to account for other general differences in children's environments by controlling for overall parental SES, as well as parental IQ. However, we cannot rule out the possibility that there were unique but related factors that contributed to differences in later child brain structure. Future work is needed to compare and contrast the role of other experiential factors on later changes in child cortical structure. Finally, although our study might be underpowered and recent reports suggest that replicable brain-behavior correlations with fMRI may require larger sample sizes (Yarkoni and Braver, 2010; Marek et al., 2020) than the one used here, our results are valuable in that they generate hypotheses to be tested with larger samples.

In sum, our study leverages a unique longitudinal dataset combining naturalistic observations of parent–child interactions and structural neuroimaging measures during a period spanning 15 years. For the first time, we show that early parental language input prior to school predicts changes in child cortical structure in mid-adolescence, over and above the contributions of SES or parental IQ. Our results are consistent with previous work examining SES-related differences in brain structure, and move the literature forward by contributing to our understanding of the mechanisms underlying individual differences in brain development. Pinpointing specific experiential factors that predict brain structure has the potential to inform prevention and intervention strategies designed to draw upon and integrate early home support.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Chicago BSD/UCMC Institutional Review Boards and the Office of Research at the University of California, Irvine. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SS and SG-M conceived the longitudinal project. ÖD-L and SA were involved in the neuroimaging data collection and analysis. ÖD-L was involved in parental language input coding and drafted the manuscript. ÖD-L and CN analyzed the data for the current manuscript in consultation with SA, SS, and SG-M. All authors critically edited, extensively contributed to the project, and approved the final submitted version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.650152/full#supplementary-material

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