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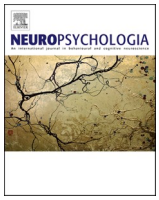

Distinctive neural correlates of phonological and reading impairment in fetal alcohol-exposed adolescents with and without facial dysmorphology

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ABSTRACT

Prenatal alcohol exposure (PAE) has been linked to atypical brain and cognitive development, including poor academic performance in reading. This study utilized functional magnetic resonance imaging and diffusion tensor imaging to characterize functional and structural mechanisms mediating reading deficits in 26 adolescents with PAE-related facial dysmorphology (fetal alcohol syndrome (FAS)/partial FAS (PFAS)), 29 heavily-exposed (HE) non-syndromal adolescents, in comparison with 19 typically developing controls. The FAS/PFAS and HE groups were balanced in terms of levels of PAE and reading (dis)ability. While neural alterations in the posterior association cortices were evident in both PAE groups, distinctive neural correlates of reading (dis)abilities were observed between adolescents with and without facial dysmorphology. Specifically, compared to the HE and control groups, the syndromal adolescents showed greater activation in the right precentral gyrus during phonological processing and rightward lateralization in an important reading-related tract (inferior longitudinal fasciculus, ILF), suggesting an atypical reliance on the right hemisphere. By contrast, in the HE, better reading skills were positively correlated with neural activation in the left angular gyrus and white matter organization of the left ILF, although the brain function-behavior relation was weaker than among the controls, suggesting less efficient function of the typical reading network. Our findings provide converging evidence at both the neural functional and structural levels for distinctive brain mechanisms underlying atypical reading and phonological processing in PAE adolescents with and without facial dysmorphology.

1. Introduction

Fetal alcohol spectrum disorders (FASD) refer to a wide range of physical, cognitive and behavioral impairments resulting from prenatal alcohol exposure (PAE; Glass et al., 2017; J. L. Jacobson et al., 2011; S. W. Jacobson et al., 2004; Mattson et al., 2019). Although these disorders frequently go undiagnosed due to social stigma, diagnostic complexity and referral bias (McLennan, 2015), FASD affect an estimated 1.1%–5% of the U.S. and European populations (May et al., 2018; Wozniak et al., 2019) and can range as high as 30.6% in some communities in South Africa (May et al., 2021). The most severe cases, who are diagnosed with fetal alcohol syndrome (FAS; Hoyme et al., 2005), show distinctive craniofacial dysmorphology, growth restriction, and small head circumference. A diagnosis of partial FAS (PFAS) is given to individuals who exhibit some but not all of the facial dysmorphology and growth restriction seen in FAS. Nevertheless, regardless of the presence of

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dysmorphology, cognitive and behavioral impairments are seen in all children with FASD, including heavily exposed (HE) individuals who lack the characteristic facial anomalies (e.g., S. W. Jacobson et al., 2008).

Children with FASD often show poorer academic performance in both reading and arithmetic tasks, compared to their peers (Hoyme et al., 2016; Sampson et al., 1989; Streissguth et al., 1990). Behavioral studies have reported mathematical deficits in both number estimation (Kopera-Frye et al., 1996) and calculation (J. L. Jacobson et al., 2011) in individuals with FASD (Burden et al., 2005; Coles et al., 1991; Streissguth et al., 1990), even after controlling for IQ (Goldschmidt et al., 1996; Kerns et al., 1997). Utilizing imaging methodologies, such as event-related potentials (ERP) and functional magnetic resonance imaging (fMRI), neural alterations associated with arithmetic deficits have been identified in affected populations (e.g., Meintjes et al., 2010; Santhanam et al., 2009; Ben-Shachar et al., 2020), as early as infancy (Berger et al., 2019). Although reading has been less extensively investigated, children and adolescents with PAE have shown poorer performance on standardized word reading and spelling tests, when compared to controls (Glass et al., 2015, 2017; Howell et al., 2006; Lindinger et al., 2018; Sowell et al., 2008), and were more likely to fail to attain reading "benchmarks" in school in a large population sample ($N = 4056$, O'Leary et al., 2013).

While previous studies have examined cognitive mechanisms underlying reading deficits associated with PAE, application of neuroimaging techniques has the potential to unravel the neural underpinnings of these impairments. For example, impairment in phonological processing, a foundational literacy skill referring to the ability to recognize and manipulate the sound structure of words, has been observed in children with FASD (Adnams et al., 2007; Korkman et al., 2003; Streissguth et al., 1994). Moreover, these deficits have been shown to account for their poorer reading and spelling abilities compared to controls (Glass et al., 2015), suggesting that one of the potential cognitive etiologies of the PAE-associated reading impairments may lie in deficient phonological skills. At the neural level, typical reading development relies primarily on a left-lateralized network (Richlan et al., 2009, 2011, 2013) that comprises the temporoparietal region responsible for speech perception and phonological processing (e.g., Cattinelli et al., 2013; Pugh et al., 2001; Schlaggar and McCandliss, 2007), the temporooccipital cortex underlying orthographic representation (e.g., Cohen et al., 2000; Vinckier et al., 2007), as well as the anterior frontal associated with syntactic and semantic processing and domain-general functions, such as executive function and working memory (e.g., Bonhage et al., 2015; Fiez et al., 1996; Malins et al., 2016; Pugh et al., 2001; Rimrodt et al., 2009; Rodd et al., 2015). Individuals with FASD, however, exhibit atypical structural morphometries in the left posterior temporoparietal cortex, including brain volumes reductions, cortical gyrification alterations (De Guio et al., 2014; Sowell et al., 2001, 2002), as well as disrupted developmental trajectories (Lebel et al., 2012), aligning with the atypical phonological skills frequently reported in individuals with FASD. Moreover, white matter tracts underlying the typical reading network (McCandliss and Noble, 2003; Ozernov-Palchik and Gaab, 2016; Pugh et al., 2000) have been shown to be altered in FASD (Donald et al., 2015a,b; Fan et al., 2016; Lebel et al., 2008; Sowell et al., 2008), and the atypical development of these tracts could be further associated with the reading development among children with FASD, suggesting functional significances of the implicated tracts in reading acquisition (Treit et al., 2013). In addition, PAE-associated changes in the structural asymmetries of the temporal lobes have also been reported (Sowell et al., 2002). These findings suggest that structural brain characteristics important for reading and its sub-components may be particularly susceptible to alcohol teratogenesis. However, empirical evidence is lacking as to whether and how the functional alterations observed in children with FASD are associated with their deficits in reading and its sub-components, such as phonological skills.

Another important question is whether distinctive neural characteristics of atypical cognitive function, reading and foundational literacy skills in this case, might emerge in FASD subtypes that differ in presentation of facial morphology (Moore et al., 2014). Significant correlations have been observed between PAE-related facial morphologies and brain volumes (Lebel et al., 2012; Roussotte et al., 2011), suggesting a link between brain structure and facial dysmorphology. Moreover, differences in PAE-associated brain alterations between children with FAS and PFAS and those who are heavily exposed but nonsyndromal have recently been reported (Cheng et al., 2017; Diwadkar et al., 2013; Li et al., 2009; Robertson et al., 2015; Sullivan et al., 2020). However, degree of PAE and severity of cognitive impairment were often not controlled in these previous studies, which could have contributed to the observed neural differences. It is important to evaluate the brain-behavioral relations between participants with FAS or PFAS and those seen in nonsyndromal HE children independently of these confounding factors.

To address these issues, the current study examined the neural mechanisms associated with atypical reading skills in two groups of adolescents (FAS/PFAS vs. HE) with similar levels of PAE and reading proficiency, in comparison with typically developing controls. Given the critical role of phonological skills in reading acquisition (Melby-Lervåg et al., 2012; Wagner and Torgesen, 1987) and the wide range of reading skills observed in adolescents with FASD, neural responses during phonological processing were examined in an fMRI study. In addition, diffusion tensor imaging (DTI) data were acquired and analyzed to characterize the structural mechanisms underlying (atypical) reading development in participants with FASD. Based on the previous findings of the PAE-associated reading deficits and brain alterations, we predicted that, compared to controls, individuals with FASD would show atypical functional responses during phonological processing and white matter disruptions in reading-related tracts. Given the previously identified associations between PAE-related facial dysmorphologies and brain structure, we expected that syndromal participants, i.e., those with FAS and PFAS, would differ in neural correlates of reading performance, compared with nonsyndromal adolescents with HE.

2. Methods

2.1. Participants

The sample consisted of 75 adolescents from the Cape Coloured (mixed ancestry) community in Cape Town, South Africa. One participant was removed due to incidental findings identified during the imaging session, resulting in 74 adolescents included in the current analyses. Among them, 58 were from the Cape Town Longitudinal Cohort (S. W. Jacobson et al., 2008), whose mothers were initially recruited during pregnancy. To increase the sample size, 16 adolescents were recruited from classrooms from the same public schools attended by the adolescents in the original cohort. 26 of the 75 participants were diagnosed with FAS ($n = 10$) or PFAS ($n = 16$) following a standard protocol (Hoyme et al., 2005; S. W. Jacobson et al., 2021). 29 adolescents whose mothers reported heavy drinking during pregnancy but did not meet criteria for FAS or PFAS were classified as non-syndromal heavily exposed (HE). 19 participants were controls with reading proficiency in the normal range (defined below), whose mothers had abstained from alcohol use during pregnancy. The three groups were balanced by age and sex (Table 1). Moreover, the ratios of the longitudinally-recruited (23 FAS/PFAS, 20 HE and 15 controls) and retrospectively-recruited (3 FAS/PFAS, 9 HE and 4 controls) adolescents were comparable across the three groups ($X^2 = 3.1$, $p = 0.21$). Finally, all participants were right-handed, except for 4 left-handed (3 HE and 1 control) and 4 ambidextrous (1 FAS/PFAS, 1 HE and 2 controls). Approval for human research was obtained from the Wayne State University Institutional Review Board, which has reliance agreements at Boston Children's Hospital, and the University of Cape Town Faculty of

Table 1
Sample characteristics.

	FAS/PFAS	HE	Control	Group effect
Number	26	29	19	–
Sex (Female/Male)	10/16	9/20	7/12	$X_2 = 0.36$
Age (years)	16.8 ± 0.7	16.4 ± 1.2	16.3 ± 1.1	$F_{2,71} = 1.5$
Family socio-economic status	16.7 ± 6.6[a]	19.4 ± 6.8[a]	24.6 ± 7.6[b]	$F_{2,71} = 7.3$**
ADHD comorbidity (Yes/No)	11/15	13/16	8/11	$X_2 = 0.05$
Language (English/Afrikaans)	8/18[a]	16/13[a]	17/2[b]	$X_2 = 15.3$***
Alcohol consumption, smoking and drug use during pregnancy				
Absolute alcohol (oz)/day	1.2 ± 1.4[a]	0.9 ± 1.1[a]	0 ± 0[b]	$F_{2,71} = 7.2$**
Absolute alcohol (oz)/drinking day	4.1 ± 1.7[a]	3.8 ± 1.9[a]	0 ± 0[b]	$F_{2,71} = 43.5$***
Frequency of drinking (days/week)	1.8 ± 1.2[a]	1.5 ± 1.1[a]	0 ± 0[b]	$F_{2,71} = 19.7$***
Cigarettes (#/day)	7.9 ± 6.3[a]	8.1 ± 6.9[a]	1.8 ± 2.9[b]	$F_{2,71} = 7.8$**
Marijuana (days/week)	0.2 ± 0.62[ab]	0.8 ± 1.8[a]	0 ± 0[b]	$F_{2,71} = 3.6$*
Psychometric assessment				
TOWRE: Phonetic Decoding Efficiency	74.2 ± 16.0[a]	81.9 ± 19.2[a]	95.2 ± 10.3[b]	$F_{2,68} = 8.8$***
TOWRE: Sight Word Efficiency	72.3 ± 12.1[a]	77.8 ± 12.7[a]	92.8 ± 6.9[b]	$F_{2,70} = 18.7$***
WASI IQ	68.7 ± 9.9[a]	80.7 ± 13.1[b]	86.2 ± 15.4[b]	$F_{2,71} = 11.5$***
fMRI task performance				
Accuracy (% correct)	93.2% ± 0.08	92.3% ± 0.11	96.1% ± 0.04	$F_{2,69} = 1.14$

Note. Values are mean (± standard deviation) for continuous measures and frequencies for dichotomous measures. Groups with the same superscripts did not differ from each other on post hoc tests.
FAS: fetal alcohol syndrome; PFAS: partial fetal alcohol syndrome; HE: non-syndromal heavily exposed; TOWRE: Test of Word Reading Efficiency; WASI: Wechsler Abbreviated Scale of Intelligence.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Health Sciences Research Ethics Committee. Written informed consent was obtained from the adolescent's parent or guardian; written assent, from the adolescent.

2.2. Assessment of prenatal alcohol exposure and drug use

The Cape Town Longitudinal Cohort was recruited during pregnancy between 1999 and 2002 (S. W. Jacobson et al., 2008) from a local antenatal clinic that serves an economically disadvantaged mixed ancestry population in which heavy drinking during pregnancy is highly prevalent (Croxford and Viljoen, 1999; May et al., 2013). Mothers were interviewed at recruitment, mid-pregnancy and 1-month postpartum about their drinking behavior on a day-by-day basis using a timeline follow-back approach (S. W. Jacobson et al., 2002a,b). Volume was recorded for each type of alcoholic beverage consumed each day and converted to ounces (oz) of absolute alcohol (AA) using multipliers proposed by Bowman et al., 1975 (liquor = 0.4, wine = 0.12, beer = 0.05, cider = 0.06). Three summary measures were constructed: average oz AA/day, oz AA/drinking occasion, and days/week of alcohol consumption. Heavy drinking was defined as ≥14 standard drinks/week (1 oz ≈ 2 standard drinks) or binge drinking, which at that time was defined as ≥5 drinks/occasion during pregnancy. All women who reported heavy drinking during pregnancy were advised to stop or reduce their intake and were offered referral for treatment. Women <18 years of age and those with diabetes, epilepsy, or cardiac problems requiring treatment were not included in the study.

Prenatal alcohol exposure for the 16 retrospectively-recruited adolescents was estimated using the following approach. First of all, all 74 mothers were interviewed regarding their current alcohol consumption and retrospectively regarding their alcohol consumption during pregnancy using the timeline follow-up interview. They were also administered the Structured Clinical Interview for DSM-IV Disorders (SCID-I; First et al., 1995) to diagnose lifetime alcohol abuse and/or dependence and were asked how many years they had been drinking and the largest quantity of alcohol they had consumed on a single occasion. To provide a reliable estimate of PAE for the newly recruited adolescents, data from all the prospectively-recruited mothers (including the one whose child had the incidental imaging finding) were examined in linear regression models constructed to "predict" their alcohol use during pregnancy from current drinking, retrospectively-reported drinking during pregnancy, history of alcohol abuse or dependence (yes/no), years of drinking, and most drinks on a single occasion. Multiple *R*s for AA/day, AA/occasion, and days/week of drinking were 0.68, 0.66, and 0.76, respectively. These regression models were then used to estimate the three measures of maternal alcohol use during pregnancy for the participants recruited during adolescence. All the mothers were also asked how many cigarettes they smoked/day and how many days/week they used marijuana ("dagga"), methaqualone ("mandrax"), cocaine, and any other illicit drugs during pregnancy.

2.3. FAS/PFAS diagnosis

In September 2005, we organized a clinic in which each child from the prospectively recruited cohort was independently examined for growth and the anomalies seen in FAS and PFAS using a standard protocol (Hoyme et al., 2005) by two expert FAS dysmorphologists (H. Eugene Hoyme, MD, and Luther K. Robinson, MD), who subsequently reached agreement regarding FASD diagnosis (see S. W. Jacobson et al., 2021; S. W. Jacobson et al., 2008). Interobserver reliability between these dysmorphologists was substantial, including palpebral fissure length and philtrum and vermilion ratings based on the Astley and Clarren (2001) rating scales (*r*'s = 0.80, 0.84, and 0.77, respectively). Participants were re-examined by the same two dysmorphologists in a second clinic in 2009 (Suttie et al., 2013) and by dymorphologists led by Dr. Hoyme in clinics held in 2013 and 2016. Dr. Hoyme subsequently reviewed the diagnoses from all four assessments in case conferences with Drs. S. W. and J. L. Jacobson, and they assigned a final diagnosis to each participant (S. W. Jacobson et al., 2021). The 16 adolescents who were recruited retrospectively were diagnosed by Dr. Hoyme using the same protocol in 2017.

2.4. Attention-deficit/hyperactivity disorder (ADHD) comorbidity

Due to the high comorbidity of FASD and ADHD (Kingdon et al., 2016), all participants were screened for ADHD using the Disruptive Behaviors Disorders Checklist (Pelham et al., 1992). Participants were assigned an ADHD classification following procedures we developed in collaboration with Joel Nigg, Ph.D., and Rafael Klorman, Ph.D., two licensed clinicians widely recognized for their expertise in ADHD research (see J. L. Jacobson et al., 2011). Symptom counts were computed separately for inattention and hyperactivity at each age by totaling how many of the nine DSM-IV behavioral criteria for each

ADHD subtype were endorsed as ''often'' or ''very often'' by the mother and the child's classroom teacher. An ADHD classification was assigned based on DSM-IV criteria if (a) 6 of 9 symptoms of inattention and/or 6 of 9 symptoms of impulsivity/hyperactivity was endorsed (''pretty much'' or ''very much'' true of child) by the mother or teacher and (b) at least 2 symptoms were endorsed by the other informant, ensuring that the behavior was observed in at least two different settings. Because 11 (42%) FAS/PFAS and 13 (45%) HE participants were diagnosed with ADHD, participants with ADHD were oversampled in the control group to match the ratio of ADHD diagnoses in the other two groups ($X^2 = 0.05$, $p > 0.9$, see Table 1).

2.5. Behavioral and socioenvironmental assessments

Reading proficiency was assessed using the Test of Word Reading Efficiency (TOWRE, Torgesen et al., 1999), in which participants are asked to name real words ("sight word efficiency") or pronounceable pseudowords ("phonemic decoding efficiency") as quickly and accurately as possible within 45 s. The obtained raw scores for each task were converted to standard scores with a mean of 100 and a standard deviation (SD) of 15 for subsequent analyses. High reliability (alternate-form reliability: 0.93–0.96; test-retest reliability: 0.82–0.97) and validity (concurrent validity: 0.89–0.96) were reported in the TOWRE assessment manual. All control participants scored in the normal range, defined as within or above one SD from the mean of both tasks (i.e., standard scores >85). General cognitive functioning was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) IQ test (Wechsler, 2011), which was also converted to standard scores (mean = 100, SD = 15) for statistical analyses. These assessments were conducted by neuropsychology-trained Masters-level graduate research assistants, who were blind to the participants' PAE.

It should be noted that because parents can choose between Afrikaans and English as their child's primary language of instruction in the public schools in Cape Town, the psychometric assessments were conducted in the primary language (Afrikaans or English) of instruction used in each participant's school. The Afrikaans versions of the reading assessments and the fMRI task were translated by a graduate research assistant, Landi Meiring, M.S., who majored in neuropsychology and linguistics, under the supervision of and in collaboration with Simone Conradie, Ph.D., a linguist on faculty at Stellenbosch University. Care was taken to match words for semantic category, linguistic difficulty, number of syllables, and word familiarity. Adjustments were made to the English items when Afrikaans items could not be matched to the existing items, and items were culturally adjusted where appropriate for a South African sample (e.g., 'lion' instead of 'bear'). Moreover, to ensure that the observed effects were independent of language influences, additional analyses were performed on the participants who were tested using the English version of the assessments and fMRI tasks to see if they were comparable to the overall findings (see *Follow-up analyses based on data of English-assessed participants only*).

Socioeconomic status (SES) was assessed using the Hollingshead Index (Hollingshead, 2011), based on parental occupational status and years of education. Each of the continuous demographic, prenatal exposure, and behavioral measures were subjected to analysis of variance (ANOVA) with group as the between-subject factor. *Post-hoc* analyses (two-sample tests) were performed for measures with significant group effects. Dichotomous variables were analyzed using chi-square tests.

2.6. Imaging acquisition

Neuroimaging data were collected on a 3 T Siemens Skyra MRI scanner with a standard Siemens 32-channel head coil at the Cape Universities Body Imaging Centre. Structural images were acquired using a multi echo MPRAGE sequence (van der Kouwe et al., 2008) with parameters of 176 slices, TR = 2530 ms, TEs = 1.67/3.52/5.37/7.22 ms, flip angle = 7°, field of view (FOV) = 230 mm^2, voxel size = 1.0 × 1.0 × 1.0 mm^3, GRAPPA 2. For fMRI data acquisition, a behavior interleaved gradient (BIG) imaging design was applied with the following parameters: TR = 6000 ms; TA = 2000 ms; TE = 30 ms; flip angle = 90°; FOV = 250 mm^2; in-plane resolution = 3 × 3 mm^2, slice thickness = 4 mm, slice gap = 1 mm. Diffusion data were collected in two sequences with opposite phase encoding directions (i.e., anterior–posterior and posterior–anterior). Each sequence included 5 non-diffusion-weighted volumes (b = 0) and 30 diffusion-weighted volumes acquired with non-colinear gradient directions (b = 1000 s/mm^2), all at 122 × 122 base resolution and isotropic voxel resolution of 2.0 mm isotropic.

2.7. fMRI

2.7.1. fMRI task procedure. A first sound matching (FSM) task was presented in a block design to examine the neural mechanisms underlying phonological processing (see Fig. 1 for an example trial). During each trial, participants listened to two sequentially presented words for two common objects (e.g., goat vs. gorilla), spoken by either a male or a female. The corresponding pictures appeared simultaneously on the left and right side of the screen. Participants were instructed to decide whether the two names were matched on the same first sound (FSM) in the experimental condition, and spoken by the same gender's voice (i.e., voice matching (VM)) in the control condition via button-press. Each trial lasted 6 s (equal to the length of one TR), containing 4s stimulus (2s for each word) and 2s response periods. Application of the BIG design ensured that the actual scanning time was synchronized with the response period, allowing the auditory stimuli to be presented when the scanner background noise was reduced (Gaab et al., 2007a, 2007b, 2008; Hall et al., 1999). Each task block was comprised of 4 trials, lasting 24 s. Each run consisted of seven task blocks alternating with seven fixation blocks of the same length (24s). Given the low executive functioning and cognitive abilities of these participants as revealed by their atypical IQ scores and high ADHD comorbidity, experimental and control conditions were presented in separate runs to minimize the executive function demands and to ensure that participants understood the task. The same task design has been previously adopted by our group (e.g., Langer et al., 2019; Raschle et al., 2012, 2013; Yu et al., 2018, 2020; Zuk et al., 2018) and others in atypical pediatric populations (e.g., Dębska et al., 2016). The order of these runs was counterbalanced across participants.

2.7.2. fMRI image analyses. Functional imaging data were acquired from all participants. Data were excluded for one subject due to poor image quality and for one, due to a technical problem. fMRI data from the remaining 72 participants (25 FAS/PFAS, 29 HE, 18 controls) were analyzed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8), based on Matlab (Mathworks). A standard preprocessing pipeline was applied, which included 1) removal of initial volumes due to T1 equilibration effects; 2) correction for head movement (realignment); 3) normalization to the Montreal Neurological Institute (MNI) space via the high-resolution structural images using the Computational Anatomy Toolbox (Gaser and Dahnke, 2016); 4) smoothing with a Gaussian kernel with full-width at half maximum of 8 mm. Moreover, scans with excessive motion, defined as 1.5 mm (translational) and/or 2° (rotational) from the beginning scan of each run, were identified. All participants had less than 15% scans with excessive motion (mean = 0.7% ± 0.02). The three groups did not differ significantly in either the number of removed scans ($F_{2,69} = 1.2$, $p = 0.3$) or the head movement of remaining images ($F_{2,69} = 1.1$, $p = 0.3$). Preprocessed images were then submitted to a general linear model with experimental (FSM and VM) and rest conditions as regressors of interest, along with nuisance covariates for run effect and an intercept term. To minimize the potential effects of head movement, six motion parameters and binary regressors, each coding one image with excessive motion, were also included. After model estimation, neural responses for phonological processing were computed by contrasting the beta map of FSM with that of VM for each

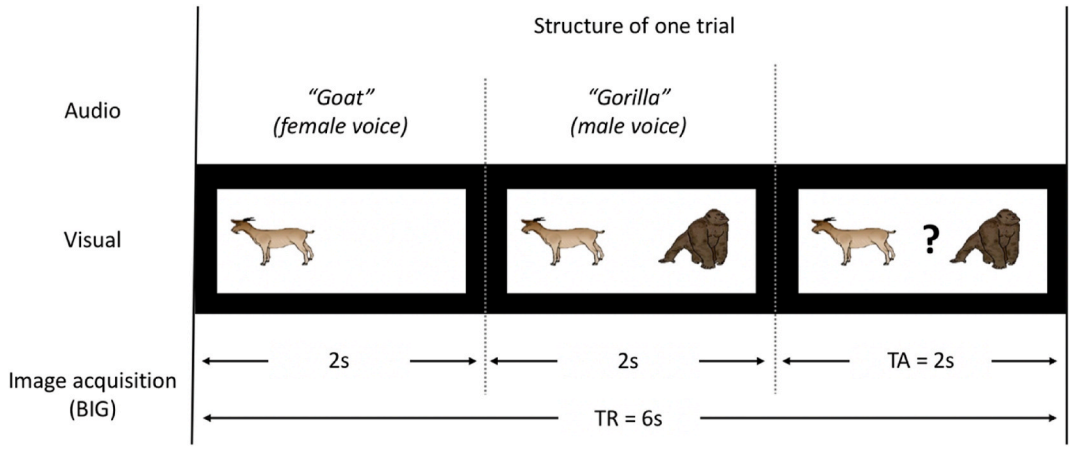

Fig. 1. An example trial of the fMRI task.

participant.

The neural correlates of phonological processing in the three groups (FAS/PFAS, HE, controls) were investigated using two analytic approaches assessing the group-level characteristics and inter-subject variability, respectively. Specifically, a one-way ANOVA model was first built with an *F* contrast to identify regions showing differences in the mean activation magnitudes between the three groups. Second, the potential differences in the brain-behavior relations between the three groups were examined in analyses of covariance (ANCOVA) for the behavioral variables "phonemic decoding efficiency" and "sight word efficiency performance", respectively. Each ANCOVA model included three binary regressors for the three participant groups and three continuous regressors, each representing the individual performance on the phonemic decoding efficiency or sight word efficiency tests within one group. An *F* contrast derived from the continuous regressors was then computed to identify neural regions with a significant group by reading performance interaction effect, indicating differentiated neural mechanisms underlying the individual differences between the three groups. For both analyses, the significant whole-brain results were reported at a cluster-level significance of $p < 0.05$ (voxel-level $p < 0.001$), Monte-Carlo corrected for multiple comparisons.

To further explore the specific patterns of the significant group effect observed in the whole brain analyses, region-of-interest (ROI) analyses were subsequently conducted. Mean contrast estimates of FSM > VM were extracted for every participant in each identified ROI. For regions with significant ANOVA effects, two-sample *t*-tests were performed to assess the differences in activation magnitudes for each group pair (i.e., FAS/PFAS vs. HE, HE vs. controls, FAS/PFAS vs. controls). The same analyses were also performed for each group pair to examine whether the neural associations with the reading scores (phonemic decoding efficiency or sight word efficiency) were different between FAS/PFAS and HE, HE and controls, FAS/PFAS and controls in each of the ANCOVA-derived ROIs. These analyses were followed by correlation analyses relating neural activation magnitudes to the reading scores within each group in order to interpret any observed interaction effects.

2.8. Diffusion image analyses

In contrast to the left-hemispheric dominance that characterizes typical reading development, the current fMRI experiment revealed right-hemispheric reliance in adolescents with FAS and PFAS during phonological processing (see *fMRI results below*). This finding suggests atypical functional lateralization associated with PAE-associated reading impairments, which is consistent with the reduced brain asymmetries associated with FASD reported previously. We, therefore, set out to systematically examine structural lateralization in the key white matter tracts underlying reading development. DTI data collected from 69 participants were first corrected for susceptibility distortions, eddy current and subject movements using the FSL toolbox (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Volumes with artifacts caused by persistent head motion (>2mm/0.5°) after correction, interlace-wise "venetian blind", slice-wise and gradient-wise intensity inconsistencies were removed (DTIprep, Liu et al., 2010). Three adolescents (2 FAS/PFAS, 1 control) with more than 15% gradients removed were excluded, resulting in a final sample of 66 participants (23 FAS/PFAS, 26 HE, 17 controls, see supplementary Table S1 for similar sample characteristics of these subject as those based on the whole sample). The three groups did not differ significantly in either the number of removed gradients ($F_{2,63} = 0.64$, $p = 0.5$) or head movement in the remaining images ($F_{2,63} = 2.1$, $p = 0.13$). The corrected DTI images were aligned to the corresponding structural images via the b0 images. They were then fitted using a linear least-squares fit, and fractional anisotropy (FA) maps were calculated for all subjects (Basser et al., 1994).

White matter tracts were identified using the Automated Fiber Quantification toolbox (Yeatman et al., 2012a,b). Specifically, whole-brain tractography was first estimated using a deterministic streamline tracking algorithm (Basser et al., 2000) with FA = 0.2/angle = 40° termination thresholds. Fiber tract segmentation was then performed based on the waypoint ROIs (two for each tract) that were predefined on a group-averaged DTI dataset in the MNI space and transformed back to each subject's native space using an inversion of their normalization parameters. The tracts identified in the native space were subsequently refined with reference to the manually segmented fiber tract probability maps (Hua et al., 2008) and then were sampled to 100 equidistant nodes. FA, as an indication of the fiber directionality, was estimated for each node, producing a detailed "tract profile" for each tract. We then computed the left-lateralization index (LI) of each node using the following formula: LI = [left FA– right FA]/[left FA + right FA] (Vandermosten et al., 2013). In the current study, four pairs of white matter tracts that underlie the neural reading network were reconstructed in both hemispheres; namely, the arcuate fasciculus (AF) that connects the inferior frontal with the middle temporal lobe, superior longitudinal fasciculus (SLF) linking the inferior parietal with the anterior frontal areas, as well as inferior longitudinal fasciculus (ILF) and inferior frontal-occipital fasciculus (IFOF) that underlie the temporo-occipital circuits with the latter extending to the anterior frontal regions (Fig. 2). These eight fiber tracts of interest were successfully delineated in all participants, except one (FAS/PFAS) for the left ILF and nine (4 FAS/PFAS and 5 HE) for the right AF.

Group comparisons were first performed with the diffusion characteristics, the FA values, of each identified tract. As in the fMRI analyses, the FA values of each node were subjected to the ANOVA and ANCOVA models to evaluate group differences in diffusion measures and the associations with reading performances (phonemic decoding efficiency

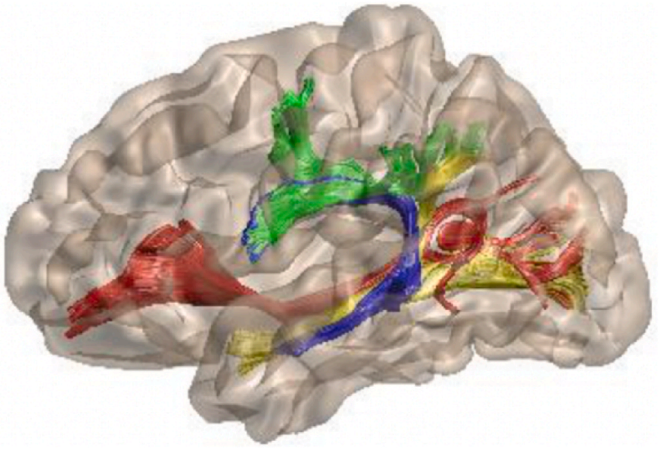

Fig. 2. 3D projections of the four white matter tracts underlying the canonical reading circuits, including the arcuate fasciculus (blue), superior longitudinal fasciculus (green), inferior longitudinal fasciculus (yellow) and inferior frontal-occipital fasciculus (red). Only left-hemispheric tracts are present for better illustration. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and sight word efficiency). Significant results were reported at a cluster-level $p < 0.05$ (a node-level $p < 0.05$), family-wise error corrected for multiple comparisons (Nichols and Holmes, 2002). In the subsequent ROI analyses, two-sample *t*-tests were conducted for each group pair (FAS/PFAS vs. HE, HE vs. controls, FAS/PFAS vs. controls) in white matter segments with significant ANOVA results. For ANCOVA-derived results, interaction effects were examined for each group pair, followed by correlation analyses within each group. Moreover, to further evaluate the white matter asymmetries among these groups, the LI values of the four white matter tracts were analyzed using the same procedures. Specifically, the ANOVA and ANCOVA analyses were carried out, and significant results were reported using the same cluster-level $p < 0.05$ after correction for multiple comparisons. ROI analyses were then performed to identify the specific group difference patterns in each significant segment. Finally, since the LI reflected comparisons between left- and right-hemispheric tract characteristics, hemisphere-specific FA values for the significant tract segments were additionally analyzed to identify the group differences in each tract.

3. Results

3.1. Sample characteristics (Table 1)

SES was higher in the control group than in both the FAS/PFAS ($t_{43} = 3.7$; $p < 0.001$) and HE ($t_{46} = 2.5$; $p = 0.02$) groups, and the latter two groups did not differ significantly from each other ($t_{53} = 1.5$; $p = 0.14$). Maternal alcohol consumption during pregnancy was similar in the FAS/PFAS and HE groups in terms of average AA/day ($t_{53} = 0.68$, $p = 0.50$), AA/occasion ($t_{53} = 0.52$, $p = 0.61$) and frequency ($t_{53} = 1.0$, $p = 0.32$), and all of the control mothers abstained from drinking alcohol during pregnancy (all 0). Mothers of adolescents from the FAS/PFAS and HE groups smoked similar numbers of cigarettes per day ($t_{53} = 0.1$, $p = 0.9$), and both groups smoked more than the mothers of the control participants (FAS/PFAS vs. Control: $t_{43} = 3.9$, $p < 0.001$; HE vs. Control: $t_{46} = 3.8$, $p < 0.001$). Marijuana use during pregnancy was reported by 9 mothers (2 FAS/PFAS and 7 HE) with no significant differences in frequency between FAS/PFAS and HE groups ($t_{53} = 1.8$, $p = 0.07$). Four mothers reported using illicit drugs (1 from the FAS/PFAS group used cocaine 2.6 days/week during pregnancy; 3 from the HE group used methaqualone 1.9 ± 1.7 days/week).

Reading performance scores were successfully obtained from all but one subject (FAS/PFAS) for the sight word efficiency (SWE) test and all but three (one from each group) for the phonemic decoding efficiency (PDE) test. Significant group effects were observed on both tests. *Post-hoc* analyses revealed the same pattern for both tests; while the FAS/PFAS and HE groups did not differ from each other (SWE: $t_{52} = 1.6$; $p = 0.11$; PDE: $t_{51} = 1.6$, $p = 0.12$), both groups performed more poorly than the controls (FAS/PFAS vs. Control: SWE: $t_{42} = 6.6$, $p < 0.001$, PDE: $t_{41} = 4.9$, $p < 0.001$; HE vs. Control: SWE: $t_{46} = 4.7$, $p < 0.001$, PDE: $t_{44} = 2.7$, $p = 0.01$). The WASI IQ test also showed a significant group effect, but here the FAS/PFAS group performed more poorly than both the HE ($t_{53} = 3.8$, $p < 0.001$) and control ($t_{43} = 4.6$, $p < 0.001$) groups, and the latter two groups did not differ from each other ($t_{46} = 1.3$, $p = 0.19$). Finally, it should be noted that, while Afrikaans was the primary language for the FAS/PFAS group, English was the primary language for the control group (Table 1). Therefore, the replication analyses based on only the data of participants assessed in English were further conducted for the observed findings. These analyses were conducted to ensure that the observed results reflect neural characteristics inherent to FASD instead of being driven by language differences (see *Results 3.4. Follow-up analyses based on data of English-assessed participants only*).

3.2. fMRI results

3.2.1. Behavioral performance

Adolescents from all three groups performed well on the phonological processing task (mean accuracies = 94% ± 0.09) with no significant differences between groups (Table 1).

3.2.2. fMRI imaging results (Fig. 3A and B)

The *F* contrast derived from the ANOVA model revealed a significant group effect on activation magnitudes among the three groups in the right precentral gyrus (RPrecentral, [42, −9, 63], k = 41). The ROI analyses showed significantly higher activation for the FAS/PFAS than for both the HE ($t_{52} = 4.9$, $p < 0.001$) and control groups ($t_{41} = 3.0$, $p = 0.005$), whereas the latter two groups did not differ from each other ($t_{45} = 0.8$, $p = 0.4$).

The *F* effect derived from the ANCOVAs revealed significant group differences in the neural correlates of performance on the phonemic decoding efficiency test in the left angular gyrus (LAG, [−51, −54, 36], k = 71) and bilateral precuneus cortex (BiPrecuneus, [−3, −48, 48], k = 168). ROI analyses of the LAG revealed significant interaction effects between the FAS/PFAS and control groups ($F_{1,37} = 28.2$, $p < 0.001$) and between the FAS/PFAS and HE groups ($F_{1,48} = 13.1$, $p = 0.001$), driven by the negative association between group and phonemic decoding efficiency scores in the FAS/PFAS group ($r_{22} = -0.50$, $p = 0.01$) in contrast to the positive associations in the HE ($r_{26} = 0.44$, $p = 0.019$) and control ($r_{15} = 0.70$, $p = 0.002$) groups (Fig. 3B). There was also a significant interaction effect between the HE and control groups ($F_{1,41} = 14.4$, $p < 0.001$) due to a greater positive association between neural magnitude and PDE scores in the control than the HE group. For BiPrecuneus, significant interaction effects were observed between group and phonemic decoding efficiency scores when controls were compared with the FAS/PFAS ($F_{1,37} = 28.1$, $p < 0.001$) and HE groups ($F_{1,41} = 29.7$, $p < 0.001$) due to the significantly positive correlation in the controls ($r_{15} = 0.84$, $p < 0.001$) not seen in the FAS/PFAS ($r_{22} = 0.22$, $p = 0.31$) and HE ($r_{26} = 0.17$, $p = 0.39$) groups. The FAS/PFAS and HE groups did not differ in their associations of BiPrecuneus activations with the phonemic decoding efficiency scores ($F_{1,48} = 0.05$, $p = 0.83$).

The ANCOVAs for the sight word efficiency scores revealed a significant interaction effect in the right anterior temporal lobe (RATL, [54, 9, −30], k = 37). ROI analyses showed that both the FAS/PFAS and HE groups differed from the controls in the associations between neural activation and single word efficiency scores (FAS/PFAS: $F_{1,38} = 27.9$, $p < 0.001$; HE: $F_{1,43} = 30.2$, $p < 0.001$), due to a negative correlation in the controls ($r_{16} = -0.75$, $p < 0.001$) not seen in either the FAS/PFAS ($r_{22} = 0.30$, $p = 0.16$) or HE ($r_{27} = 0.12$, $p = 0.54$) groups. No significant interaction effect was observed for the comparison between the FAS/

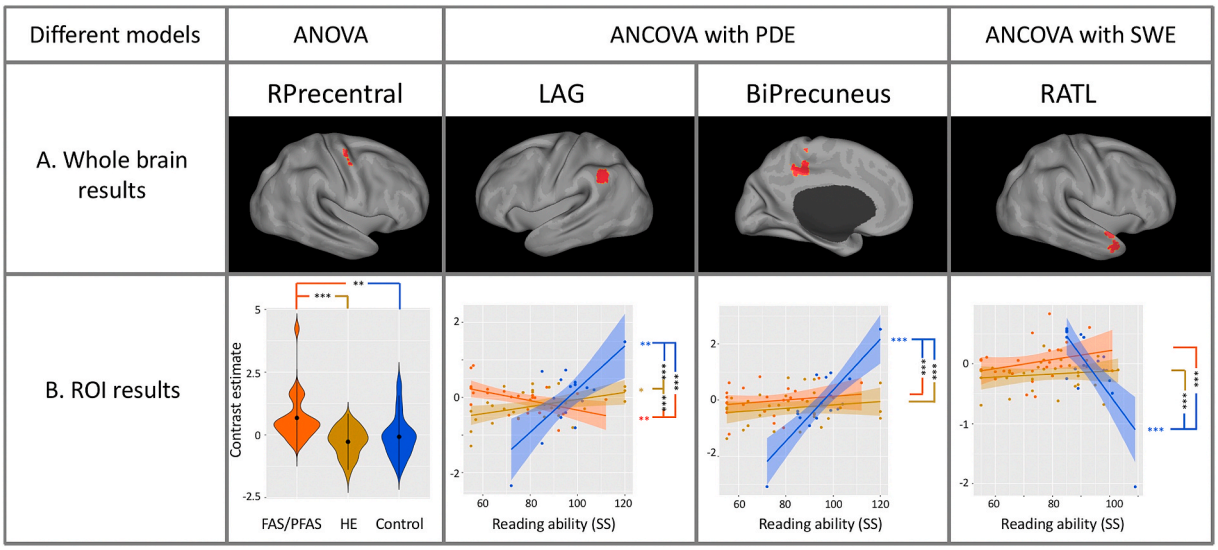

Fig. 3. Distinctive neural responses during the phonological processing task between adolescents with full or partial fetal alcohol syndrome (FAS/PFAS, red), non-syndromal heavily exposed (HE, yellow), and controls (blue). Panel A shows the whole-brain results derived from 1) the ANOVA tests that evaluated the differences in the activation magnitudes among the three groups; 2) the ANCOVA tests that examined the group differences in the associations between the neural activation and the individual differences in reading skills, measured by the phonemic decoding efficiency (PDE) and sight word efficiency (SWE) tests, respectively. The whole-brain results were reported at a cluster-level significance of $p < 0.05$ (voxel-level $p < 0.001$), Monte-Carlo corrected for multiple comparisons. Panel B illustrates the group-specific neural characteristics in each region and the results of pairwise comparisons (FAS/PFAS vs. HE, HE vs. controls, FAS/PFAS vs. controls) based on the two-sample *t*-tests and ANCOVA for the whole brain ANOVA and ANCOVA results, respectively. Moreover, in regions derived from the ANCOVA analyses, results of correlations of neural measures with reading performance are also presented to further explain the observed group differences. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

PFAS and HE groups ($F_{1,49} = 0.70$, $p = 0.41$).

3.3. DTI results

3.3.1. FA results

The ANOVA analyses on the FA of the eight reading-related white matter tracts revealed significant group effects in the middle portion of the right ILF (nodes 46–63, Fig. 4). No other tracts showed significant FA differences among three groups (see supplementary Figure S1). Subsequent ROI analyses demonstrated that the FAS/PFAS groups had significantly higher FA values in the identified right ILF segment than the HE ($t_{47} = 2.6$, $p = 0.01$) and control ($t_{38} = 2.3$, $p = 0.03$) groups, whereas the latter two groups did not differ from each other ($t_{41} = 0.03$, $p = 0.98$).

The ANCOVA analyses revealed significant interaction effects between group and reading performance on the sight word efficiency (SWE) scores in the middle portion of the left ILF (nodes 44–59), a large section of the left SLF (nodes 23–74), as well as the anterior (parietal) portion of the right SLF (nodes 8–33, Fig. 5). Subsequent ROI analyses in the significant segment of the left ILF demonstrated that the neural correlations of the SWE scores differed between the FAS/PFAS and HE groups ($F_{1,44} = 9.5$, $p = 0.004$), but not between the FAS/PFAS and control groups ($F_{1,35} = 2.5$, $p = 0.12$) or between the HE and control groups ($F_{1,39} = 0.04$, $p = 0.85$). Further within-group correlation analyses revealed that the associations between the FA values and the SWE scores were positive in the HE ($r_{24} = 0.42$, $p = 0.03$), negative in the FAS/PFAS group ($r_{20} = -0.43$, $p = 0.05$) and nonsignificant in the control ($r_{15} = 0.19$, $p = 0.47$) groups, contributing to the observed interaction effects in the left ILF. For the significant segment of the left SLF, the FA associations of the SWE scores in the HE group were different from those in the FAS/PFAS ($F_{1,45} = 9.2$, $p = 0.004$) and the control ($F_{1,39} = 12.8$, $p < 0.001$) groups, whereas the latter two were not different from each other ($F_{1,36} = 2.1$, $p = 0.16$). Specifically, the correlations between FA and SWE were positive in the control ($r_{15} = 0.48$, $p = 0.05$), negative in the HE ($r_{24} = -0.61$, $p < 0.001$), and nonsignificant in the FAS/PFAS ($r_{21} = 0.23$, $p = 0.29$) groups. Finally, the same ROI analyses on the right SLF revealed significant interactions between the FAS/PFAS and control groups ($F_{1,36} = 4.1$, $p = 0.05$) and between the HE and the control groups ($F_{1,39} = 9.8$, $p = 0.003$), but not between the two alcohol-exposed groups ($F_{1,45} = 3.4$, $p = 0.07$). These interactions were driven by the positive associations between the FA values and the SWE scores in the control groups ($r_{15} = 0.63$, $p = 0.007$) that were not observed in either the FAS/PFAS ($r_{21} = 0.26$, $p = 0.24$) or the HE ($r_{24} = -0.28$, $p = 0.17$) groups.

The ANCOVA analyses with the phonemic decoding efficiency scores did not reveal any significant results.

3.3.2. LI results

ANOVAs of the LI values for the four reading-related tract pairs identified significant group effects in the middle portion of the ILF (nodes 48–61, Fig. 4) that was similar to those (in the right hemisphere) based on the FA values. Subsequent ROI analyses showed significantly lower LI values for the FAS/PFAS than for the control ($t_{37} = 2.9$, $p = 0.006$) groups; whereas the other two comparisons were not significant (FAS/PFAS vs. HE: $t_{46} = 1.9$, $p = 0.06$; HE vs. Controls: $t_{41} = 1.6$, $p = 0.11$). Consistent with the FA results, analyses of the hemisphere-specific FA metrics showed a significant group effect in the right ILF ($F_{2,63} = 3.7$, $p = 0.03$) due to higher FA values in the FAS/PFAS than the HE ($t_{47} = 2.4$, $p = 0.02$) and control ($t_{38} = 2.4$, $p = 0.02$) groups; whereas the HE and control groups did not differ from each other ($t_{41} = 0.16$, $p = 0.88$). No significant group differences were observed for the left ILF ($F_{2,62} = 0.66$, $p = 0.52$).

Similar segments of ILF showed significant interaction effects between group and reading performance on the phonemic decoding efficiency (nodes 43–57) and sight word efficiency (nodes 42–61) tests (Fig. 6). ROI analyses revealed that the neural associations with the phonemic decoding efficiency scores differed between the FAS/PFAS and HE groups ($F_{1,43} = 10.5$, $p = 0.002$), and between the FAS/PFAS and control groups ($F_{1,34} = 10.5$, $p = 0.003$), but not between the HE and control groups ($F_{1,37} = 0.90$, $p = 0.35$). These interaction effects were driven by group-specific association patterns between the LI values and the phonemic decoding efficiency scores, which were positive in the

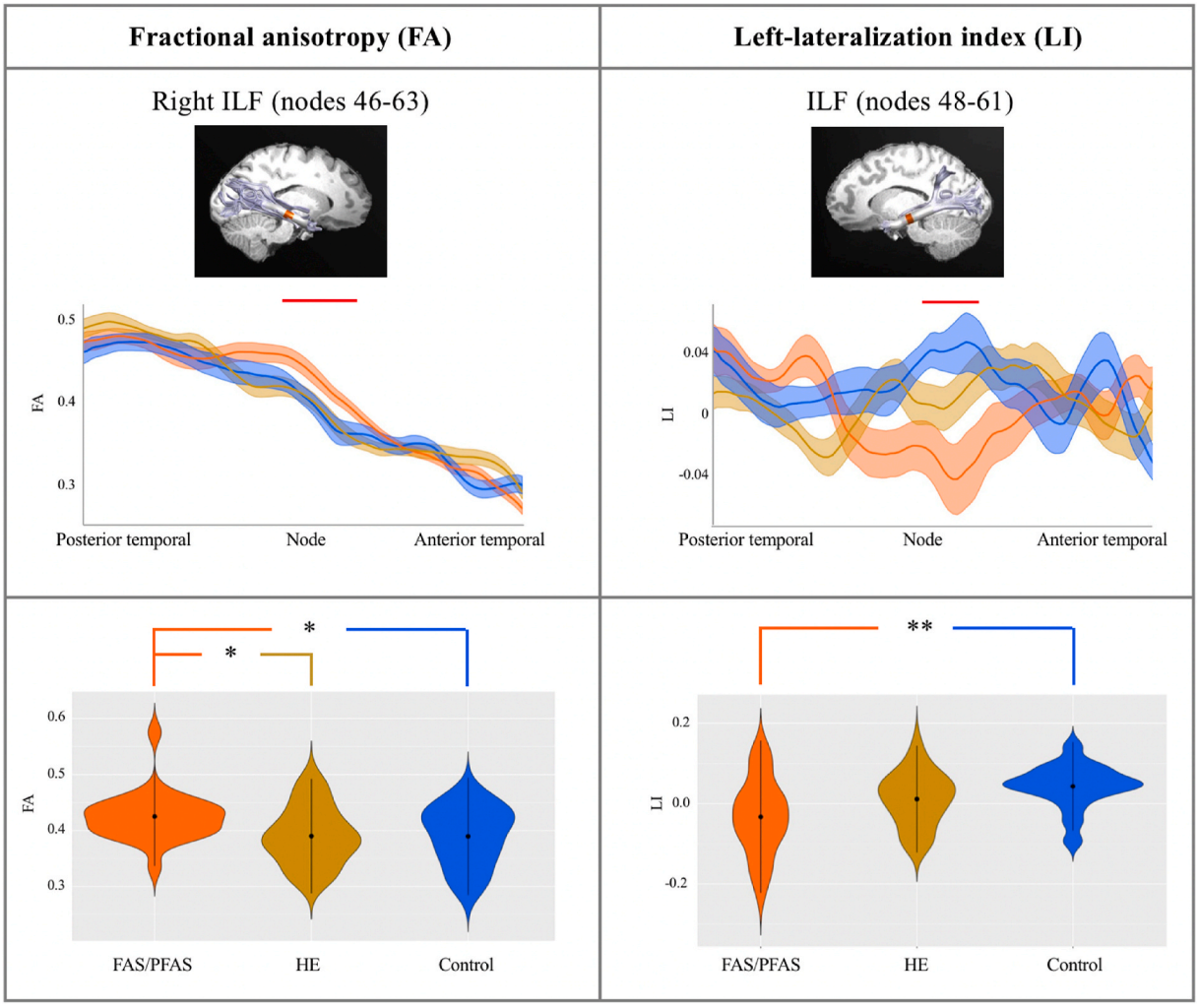

Fig. 4. Atypical white matter characteristics of the inferior longitudinal fasciculus (ILF) in adolescents with full or partial fetal alcohol syndrome (FAS/PFAS, red), as compared to those in non-syndromal heavily exposed (HE, yellow) and controls (blue). The left column illustrates the FA values of the right ILF, and the right column the hemispheric-lateralization index (LI) values of ILF. Significant group results revealed by ANOVA were reported at a cluster-level $p < 0.05$ (a node-level $p < 0.05$), family-wise error corrected for multiple comparisons. The top panel represents the tract profiles of the ILF in terms of the node-specific FA or LI values along the tracts. Nodes with significant group effects are indicated by red lines and highlighted in red in the sagittal views of the rendered tracts. The bottom panel shows the group-specific white matter characteristics in each identified segment with significant pairwise comparisons marked in *.*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

control ($r_{14} = 0.60$, $p = 0.015$), negative in the FAS/PFAS ($r_{20} = -0.55$, $p = 0.009$), and nonsignificant in the HE groups ($r_{23} = 0.31$, $p = 0.14$). Follow-up analyses based on the FA values of the corresponding segment in each hemisphere identified a significant interaction effect in the left ($F_{2,57} = 5.8$, $p = 0.005$). This effect was driven by significant differences in the neural association patterns with the phonemic decoding efficiency scores between the FAS/PFAS and HE ($F_{1,43} = 10.4$, $p = 0.002$) groups, due to a significantly positive association in the HE ($r_{23} = 0.57$, $p = 0.003$) but not in the FAS/PFAS ($r_{20} = -0.32$, $p = 0.14$) group. The other two comparisons were not significant (FAS/PFAS vs. controls: $F_{1,34} = 2.71$, $p = 0.11$; HE vs. controls: $F_{1,37} = 0.24$, $p = 0.63$), nor was the association between the FA values of the ILF and the phonemic decoding efficiency scores in the controls ($r_{14} = 0.30$, $p = 0.26$). Finally, no significant interactions were seen in the right hemisphere ($F_{2,58} = 1.3$, $p = 0.28$).

The ILF segment showing significant interaction effects with the sight word efficiency scores was largely overlapping with the area of the left ILF reported in the FA results. The ROI analyses identified significant differences in the neural associations with task performance between the FAS/PFAS and HE groups ($F_{1,44} = 12.9$, $p < 0.001$), driven by a significantly negative association in the FAS/PFAS ($r_{20} = -0.56$, $p = 0.007$), but not HE ($r_{24} = 0.36$, $p = 0.07$) group. No significant interaction effects were found in the other two comparisons (FAS/PFAS vs. controls: $F_{1,35} = 0.47$, $p = 0.50$; HE vs. controls: $F_{1,39} = 2.8$, $p = 0.10$), and the correlation in the control group was not significant ($r_{15} = -0.28$, $p = 0.29$). In line with the FA results, further analyses based on the hemisphere-specific FA values of this identified segment of ILF revealed the same pattern in the left ILF ($F_{2,59} = 4.8$, $p = 0.012$), where a significant interaction effect was observed only when FAS/PFAS and HE were compared ($F_{1,44} = 8.7$, $p = 0.005$), but not in the other two group comparisons (FAS/PFAS vs. controls: $F_{1,35} = 2.4$, $p = 0.13$; HE vs. controls: $F_{1,39} = 0.018$, $p = 0.89$). This pattern of effects was due to a positive association in the HE ($r_{24} = 0.40$, $p = 0.045$), a negative association in the FAS/PFAS ($r_{20} = -0.42$, $p = 0.05$), and a nonsignificant in the control ($r_{15} = 0.19$, $p = 0.46$) groups. Finally, no significant interaction effect was evident in the right ILF ($F_{2,60} = 0.74$, $p = 0.48$).

3.4. Follow-up analyses based on data of English-assessed participants only

Afrikaans was the primary language in the FAS/PFAS group; English was the primary language for the controls. We, therefore, performed

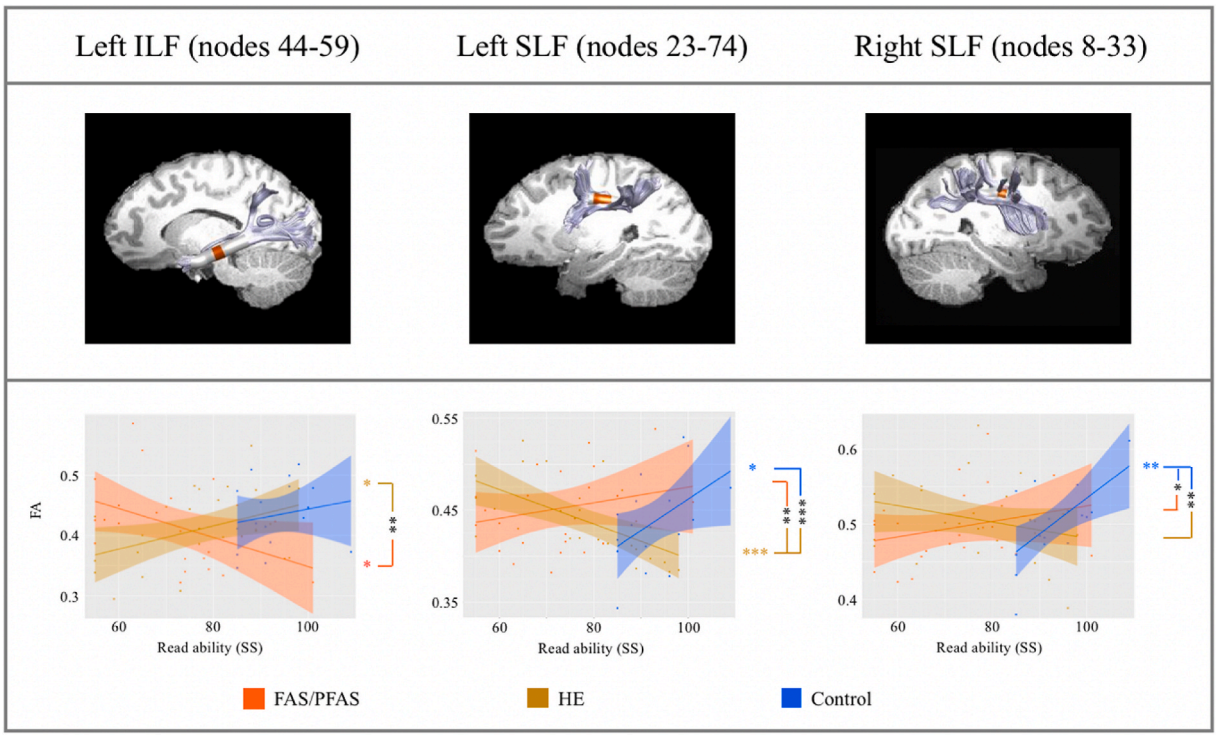

Fig. 5. Distinctive DTI correlates of reading abilities on the sight word efficiency (SWE) between the full or partial fetal alcohol syndrome (FAS/PFAS), the non-syndromal heavily exposed (HE) and control groups. The top panel illustrates the sagittal views of the rendered tracts. Segments showing significant interactions between the FA values and the reading abilities, as revealed by the ANCOVA analyses, are highlighted in red. Significant results were reported at a cluster-level $p < 0.05$ (a node-level $p < 0.05$), family-wise error corrected for multiple comparisons. The bottom panel represents the group-specific associations between the FA values and the SWE scores. Both the significant pairwise comparisons and within-group associations are shown.*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

follow-up analyses of the fMRI data from the 40 adolescents (8 FAS/PFAS, 16HE, 16 controls) who were tested in English to ensure the observed group differences were not caused by language differences. The same group effect was seen in the RPrecentral ROI ($F_{2,37} = 3.2$, $p = 0.05$) and the same interaction effects between group and phonemic decoding efficiency score were seen in both the LAG ($F_{2,32} = 4.5$, $p = 0.02$) and BiPrecuneus ($F_{2,32} = 7.1$, $p = 0.003$). Similarly, the same interaction between group and sight word efficiency score was seen in the RATL ($F_{2,34} = 4.6$, $p = 0.02$).

Re-analyses of the DTI data were performed with 36 participants tested in English (7 FAS/PFAS, 14 HE, 15 controls). Similar to the results based on the whole sample, significant group effects were evident on the mean FA values of the middle right ILF segment (nodes 46–63, $F_{2,33} = 3.9$, $p = 0.03$), as well as on the mean LI values of the corresponding ILF section (nodes 46–63, $F_{2,33} = 15.3$, $p < 0.001$). Among the white matter tract segments with FA values showing significant interactions between group and the SWE scores in the whole sample, the same effect was seen in the left SLF (nodes 28–74, $F_{2,30} = 7.0$, $p = 0.003$) but not in the right SLF (nodes 8–33, $F_{2,30} = 2.0$, $p = 0.16$) and left ILF (nodes 44–59, $F_{2,30} = 2.4$, $p = 0.11$). Nevertheless, the significant interaction effects observed in the LI values of the ILF based on the whole sample were replicated in the subsample of English-assessed participants when both the PDE (nodes 43–57, $F_{2,28} = 4.4$, $p = 0.02$) and SWE (nodes 42–61, $F_{2,30} = 6.3$, $p = 0.005$) scores were evaluated. Subsequent discussion is therefore focused on the results confirmed in the subsample of English-assessed participants to ensure minimal influences of language spoken on the observed group differences.

4. Discussion

This study is the first to identify distinctive neural mechanisms associated with atypical reading skills and the associated sub-components in adolescents with FAS/PFAS and nonsyndromal HE adolescents when compared to nonexposed controls. Specifically, using a phonological processing task that assessed sub-components of reading acquisition, we observed significantly greater activation in the right precentral gyrus (RPrecentral) in adolescents in the FAS/PFAS group than both the HE and control groups. Moreover, the correlations of neural activation magnitudes during phonological processing with reading performance measured behaviorally outside the scanner were also different among the three groups. More specifically, while correlations of better performance on the phonetic decoding test with increased activation in the left angular gyrus (LAG) and the bilateral precuneus (BiPrecuneus) were observed in the controls, these associations were weaker for the HE group and in the opposite direction, i.e., increased LAG activation with lower phonetic decoding scores, in adolescents with FAS/PFAS. Finally, the correlation of better performance in the sight word efficiency test with decreased activation in the right anterior temporal lobe (RATL) among the controls was not observed in the FAS/PFAS and HE groups.

DTI analyses further revealed atypical white matter organization associated with reading impairments in adolescents with FASD. Specifically, less left-lateralization was observed in the inferior longitudinal fasciculus (ILF) in the FAS/PFAS group compared with both the HE and controls groups, an effect driven by FAS/PFAS-specific increases in FA values in the right ILF. Moreover, while higher FA in the left ILF was associated with better reading performance (phonetic decoding and sight word efficiency) in the HE and control groups, it was associated with poorer performance on both reading tests in the FAS/PFAS group. Finally, significant group differences in the FA correlates of sight word efficiency scores were further observed in the left superior longitudinal fasciculus, where positive associations were only observed in the control groups, but absent in the FAS/PFAS group, and even negative in the HE group.

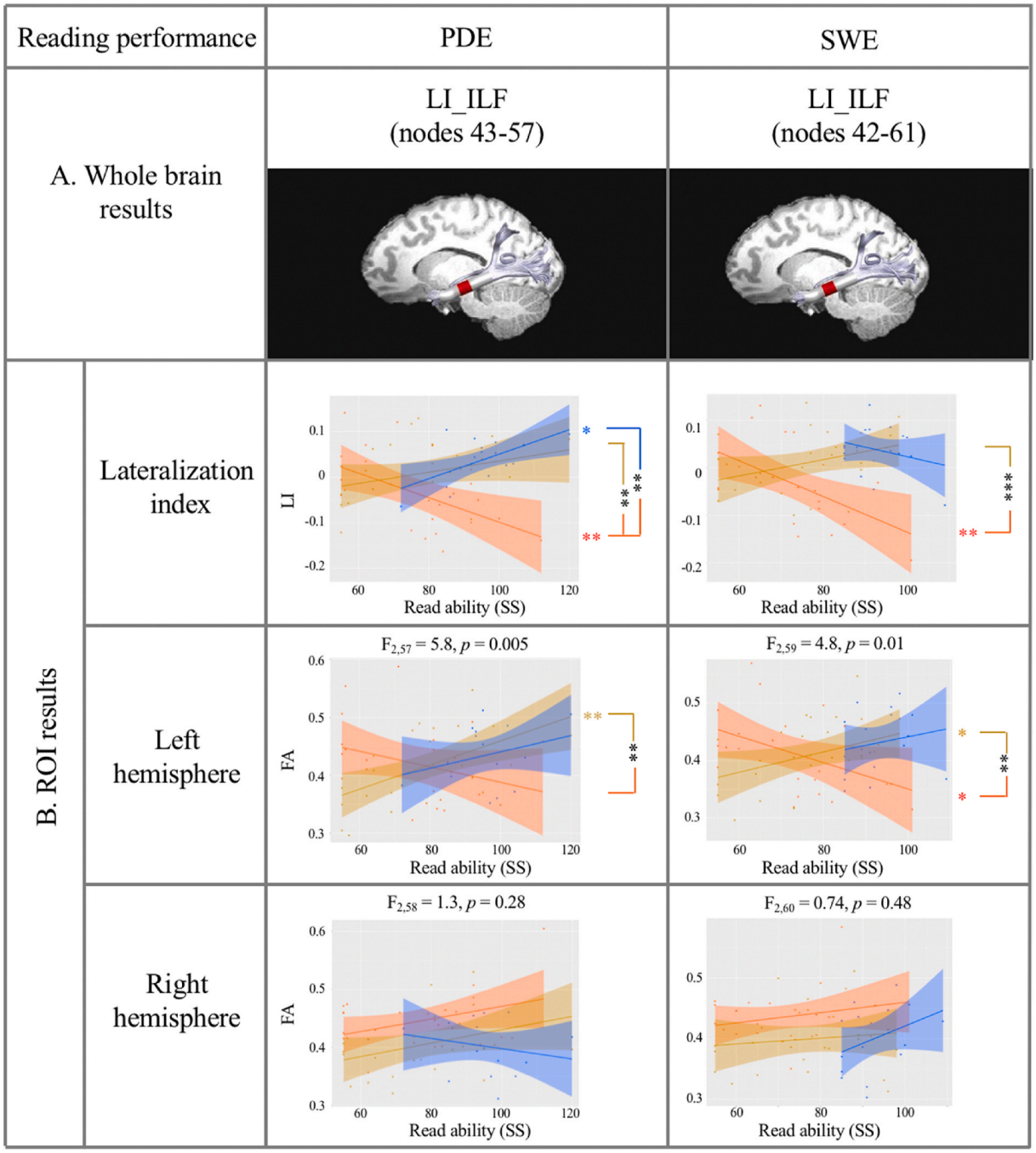

Fig. 6. Atypical hemispheric-lateralization of the inferior longitudinal fasciculus (ILF) in adolescents with full or partial fetal alcohol syndrome (FAS/PFAS, red), as compared to those in non-syndromal heavily exposed (HE, yellow) and controls (blue). Panel A presents the specific segments of the ILF that show significant group differences in the associations between the LI values and the reading performance of the phonemic decoding efficiency (PDE) and sight word efficiency (SWE) tests, as demonstrated by the ANCOVA tests. Significant DTI results were reported at a cluster-level $p < 0.05$ (a node-level $p < 0.05$), family-wise error corrected for multiple comparisons. Panel B illustrates the group-specific white matter characteristics, including the LI values and hemispheric-specific fractional anisotropy (FA) values in each identified segment. For the LI measures, significant between-group differences in LI values and within-group associations between LI and reading measures are shown. For hemispheric-specific measures, both the main effects of group and significant pairwise comparisons are shown.*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Two analytic approaches were utilized in this study to characterize different yet complementary aspects of the neural substrates underlying reading development among adolescents with FASD. The ANOVA models were applied to identify regions showing significant differences in the *group-mean* activation magnitudes among the FAS/PFAS, HE, and control groups. This approach has often been applied in previous studies on FASD (e.g., Lindinger et al., 2021; Meintjes et al., 2010; Nguyen et al., 2017) or other disabilities (e.g., developmental dyslexia, (Martin et al., 2016), with the aim of identifying the neuropathology associated with a clinical diagnosis. However, this approach does not consider *inter-subject variability* that might be meaningful in revealing etiological mechanisms. This issue was considered in our second set of analyses, which examined group differences in the correlations of neural activation magnitude or white matter organization with behavioral performance on two reading tests using the ANCOVA tests (see similar analyses in Gautam et al., 2015; Sowell et al., 2008). These analyses examined

brain-behavior relations across individuals within each of the groups, revealing the functional significance of the PAE-associated neural alterations (Lebel et al., 2011). The application of analytic methods that consider both group-level properties and individual differences provides a more comprehensive delineation of the neural anomalies in individuals with FASD exhibiting a continuum of reading impairments.

Compared to the left-lateralized neural network underlying phonological processing in typically developing individuals, the adolescents with FASD seem to recruit a more wide-spread cortical network, involving the right hemisphere. In the control group, we saw the expected positive associations between phonemic decoding scores and levels of neural activation in the LAG and BiPrecuneus, brain regions underlying phonological processing (Bitan et al., 2007; Church et al., 2008; Yu et al., 2018). Our findings that these associations were altered in adolescents with FASD are consistent with previous reports of PAE-related structural alterations in these regions (De Guio et al., 2014; Sowell et al., 2001, 2002), suggesting high vulnerability of the left posterior temporoparietal cortex to PAE insult.

In the HE group, level of activation in the LAG was positively correlated with phonemic decoding efficiency, but the correlation was weaker than among the controls, suggesting less efficient functioning of underlying neural mechanisms, which likely contributed to their observed reading impairments. By contrast, a different neural activation pattern was seen in the participants with FAS or PFAS, who showed greater activation in the right precentral gyrus than the other two groups, suggesting increased reliance on right frontal areas. Previous studies have reported greater activation of right frontal regions in individuals with FASD during verbal learning than in controls (Sowell et al., 2007) and that verbal skills were positively correlated with cortical thickness in right frontal regions in FASD (Sowell et al., 2008a, b), suggesting a potential neuroplastic change in the function of these regions for language processing. The current findings suggest that the verbal-related involvement of the right frontal cortex may be important in a critical reading-related function, i.e., phonological processing. Alternatively, it is possible that the greater activation in the right precentral gyrus might reflect heightened articulatory effort that may play a facilitative role in phonological processing in response to the PAE-associated alterations in the left-hemispheric reading network (see similar accounts for hyper right hemispheric activation in dyslexia in Martin et al., 2016). The rightward activation was observed only in the syndromal alcohol-exposed individuals, who exhibited facial dysmorphology, implying an atypical lateralization pattern specific to this group. Consistent with this interpretation, in FASD only children with FAS have shown less left-lateralized dichotic listening asymmetry (Domellöf et al., 2009) and greater bilateral frontal activation during classical eyeblink conditioning (Cheng et al., 2017). Moreover, previous studies have indicated a higher risk of hearing loss in children with facial dysmorphology compared to other FASD subtypes (Church et al., 1997; McLaughlin et al., 2019). Although all the adolescents included in the current study attended regular public schools and none exhibited significant hearing dysfunctions, milder auditory processing deficits not detected in their daily life might have contributed to their atypical development of phonological skills. Future investigation with more systematic assessments on the basic auditory processing abilities is needed to evaluate this potential link. Overall, different functional mechanisms underlying phonological processing were observed among individuals with and without facial dysmorphology; whereas a left-lateralized neural network was observed in the HE group (albeit weaker than in controls), the FAS/PFAS group relied on additional neural resources in the right hemisphere to support their reading performance.

The atypical neural mechanisms underlying reading development in subjects with FASD are further evident in their alterations in the left-hemispheric white matter correlates of reading abilities. The adolescents from the control group showed positive correlations between their SWE scores and the FA values of the left SLF, consistent with its critical role in reading abilities evident in both developmental and adult populations (Frye et al., 2011; Zhang et al., 2014). By contrast, this positive relationship was not detected among adolescents with FASD in the current study. Previous studies have shown that the SLF underlying reading development in individuals with FASD (Treit et al., 2013, 2017) were vulnerable to the teratogenic effects associated with PAE. Both lower FA values (Lebel et al., 2008) and atypical growth rates (Treit et al., 2013, 2017) have been observed in PAE individuals when compared to controls, potentially linking to their reading deficits. Our findings provide additional support for the functional relevance of the SLF in the alcohol-associated reading impairments. Moreover, it is worth noting that the PAE-associated neural atypicalities in the white matter tract connecting the anterior frontal and inferior parietal cortices also align with the functional deficits of the latter area (left angular gyrus) during the phonological processing task, proving further evidence for the alcohol-related disruptions in the posterior association cortices that were commonly observed in previous studies (e.g., Chen et al., 2012; Donald et al., 2015a,b; Lebel et al., 2012; Sowell et al., 2002a,b).

Furthermore, left dominance alterations are observed in the inferior longitudinal fasciculus (ILF) among adolescents with FAS and PFAS. The left ILF provides the ventral reading pathway from the temporo-occipital cortex to the anterior temporal lobe that has been associated with reading abilities among typically developing children (Vanderauwera et al., 2018; Wang et al., 2016; Yeatman et al., 2012a,b). The ILF has previously been implicated in white matter alterations associated with PAE (Lebel et al., 2008; Sowell et al., 2008a,b) and has been shown to have atypical developmental trajectories in individuals with FASD compared to controls (Treit et al., 2017). The current study extends these PAE-associated alterations to the lateralization characteristics of the ILF (the middle segment) specifically in the FAS/PFAS group (compared to both the HE and controls), driven by atypically higher FA values in the right ILF. It is important to note that our results are not necessarily in contrast with the previous studies that adopted a voxel-based approach and identified FA reductions in regions on the bilateral ILF pathways not overlapping with the current identified location (Fan et al., 2016; Sowell et al., 2008a,b). Rather, our findings provide additional information about the alcohol teratogenic effects on the coordination of bilateral brain characteristics important for reading development. Specifically, these PAE-related alterations in the leftward lateralization of ILF may disrupt the development of white matter mechanisms underlying typical reading development. Accordingly, by contrast to the positive correlations between reading performance (both phonemic decoding and sight word efficiency scores) and the FA values in the left ILF in the HE and control groups, the FAS/PFAS group exhibited a negative association, suggesting atypical involvement of the ILF in reading specific to this group. Overall, the white matter patterns observed in the adolescents with FAS/PFAS, combined with their functional characteristics during phonological processing, collectively suggesting the development of alternative brain mechanisms in the right hemisphere to compensate (albeit not entirely successfully) for PAE-associated neural alterations in the left-hemispheric reading network.

Overall, combining the fMRI and DTI findings, the current study revealed dissociable neural correlates of atypical reading development between prenatally alcohol-exposed adolescents with FAS or PFAS and those without the characteristic pattern of facial anomalies (i.e., the HE group), suggesting that distinctive brain mechanisms are employed in different subtypes of FASD. While early neuroimaging studies often combined all individuals with FASD into one group due to limited sample size (see Lebel et al., 2011; Wozniak and Muetzel, 2011 for reviews), recent investigations examining different FASD subtypes have found differences in neural activation patterns or/and structural characteristics (e.g., Astley et al., 2009; Cheng et al., 2017; Diwadkar et al., 2013). The current study is the first to provide evidence of FASD subtype-specific neural mechanisms related to reading. Importantly, since individuals in our FAS/PFAS and HE groups were similar in their

levels of PAE and their reading abilities, the observed group differences cannot be attributed to different levels of exposure but instead provide compelling evidence supporting differentiated alterations in cortical engagement for reading function in adolescents with and without FAS dysmorphology. These findings are consistent with studies that have linked more severe facial dysmorphology, such as higher lip/philtrum scores and reduced palpebral fissure length, to greater brain structural alterations (Lebel et al., 2012; Roussotte et al., 2011; Yang et al., 2012a, b), including increased cortical thickness in the right frontal area (Yang et al., 2012a,b). Finally, it is critical to note that the neural differences between the FAS/PFAS and HE groups were further confirmed in the subset of participants whose primary language was English. This demonstrates that the observed group differences are not attributable to between-group differences in the proportion of adolescents whose primary language was Afrikaans or English. Altogether, the current findings lend strong support for the dissociable neural mechanisms underlying atypical reading development between adolescents with FAS and PFAS and individuals with PAE who lack the distinctive fetal alcohol-related facial dysmorphology.

5. Limitations and future directions

This study identified dissociable brain structural and functional alterations associated with reading impairments in prenatally alcohol-exposed adolescents with and without fetal alcohol-related facial dysmorphology. One potential confounding influence is our sample's high rate of comorbidity (~40%) of FASD with ADHD, however, it is similar to that reported in other studies (e.g., Kingdon et al., 2016). Although ADHD was oversampled in the control group to match the clinical groups, the potential influences of ADHD might have confounded group contrasts due to the unknown neural mechanisms underlying FASD and ADHD comorbidity. Future studies recruiting separate groups with single and co-morbid diagnoses are warranted to directly examine the neuropathology associated with FASD and ADHD comorbidity (see a similar study for dyslexia and ADHD comorbidity in Langer et al., 2019). Second, the fMRI images of the current study were acquired at a relatively low spatial resolution (3×3 x4 mm^3), limiting fine-grain delineation of the functional mechanisms underlying reading development in adolescents with FASD. Moreover, the participants with FASD in our study exhibited variable reading skills, with about half of the adolescents (13 FAS/PFAS and 12 HE) able to read fewer than 30 words in either reading task. Therefore, a phonological processing task was used in the current fMRI experiment. This task enabled characterization of the neural correlates of the foundational literacy skills important for reading acquisition and ensured optimal task performance during scanning. Nevertheless, further investigation should consider a reading comprehension task and employ a more advanced imaging acquisition sequences with high spatial resolutions, in order to more precisely characterize the neural etiologies underlying reading comprehension associated with prenatal alcohol insults and whether distinctive neural correlates are seen in different fetal alcohol-related disorders. Finally, the challenges in recruiting clinical and control populations with comparable demographic backgrounds and well-characterized PAE estimates led to relatively small sample sizes in the current study, limiting the result generalizability. Due to the same reason, adolescents with two languages of instruction in schools were recruited, possibly confounding the group comparisons with the primary language spoken. We conducted additional analyses using data from a subset of participants with the same primary language (English) to confirm that the main effects obtained based on the whole sample were independent of the language of instruction used in school. However, future studies are needed to determine whether different mechanisms underlying reading impairments are seen among individuals with different primary languages. Collaborations and open science efforts (Allen and Mehler, 2019) will be essential for circumventing the recruitment difficulties on special populations and achieving large datasets in order to promote reliable scientific discoveries. Findings derived from these efforts may have important implications for developing treatment plans more suitable for alcohol-exposed individuals with different language backgrounds.

6. Conclusions

In summary, utilizing both fMRI and DTI, this study is the first to characterize brain functional and structural alterations associated with atypical reading development and its sub-components in adolescents with prenatal alcohol insults. Specifically, atypical functional and white matter characteristics of the left association cortex were evident in both groups with FASD, suggesting a general alcohol-associated vulnerability in this area. Moreover, while the HE group exhibited the functional correlates of phonological processing and the ventral reading pathway (in the left ILF) that were similar to, albeit somewhat weaker than those seen in the control group, the FAS/PFAS group exhibited greater reliance on right frontal regions. Since the FAS/PFAS and HE groups in this sample were similar in terms of levels of prenatal alcohol exposure and proficiency in basic reading skills (phonemic decoding and sight word reading), these observed differences presumably reflect distinctive neural mechanisms engaged by different FASD subtypes during atypical reading and phonological processing. Given the essential role of reading proficiency for academic, vocational, economic outcomes and societal functioning generally, it is important to further understand the etiology of reading difficulties in individuals with FASD. Future studies with larger samples from socioeconomically and culturally different populations are warranted to better understand the neural etiologies of reading impairment in FASD, which might have the potential to inform the design of customized treatment strategies for PAE-related reading deficits.

Data availability statement

The data sets generated during this study are available at https://osf.io/re7s9/.

Credit author statement

Xi Yu: Methodology, Formal analysis, Writing - Original Draft, Review & Editing; **Jade Dunstan:** Data Curation and Methodology; **Sandra W. Jacobson:** Conceptualization, Writing- Review & Editing, Funding acquisition, Recruitment supervision of assessments of the cohort; **Christopher D. Molteno:** Methodology; **Nadine M. Lindinger:** Data Curation, Project administration; **TedK. Turesky:** Software and Methodology; **Ernesta M. Meintjes:** Methodology; **Joseph L. Jacobson**: Conceptualization, Writing- Review & Editing, Funding acquisition, Supervision, Recruitment supervision of assessments of the cohort, and **Nadine Gaab**: Conceptualization, Writing- Review & Editing, Funding acquisition, Supervision.

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Appendix A. Supplementary data

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