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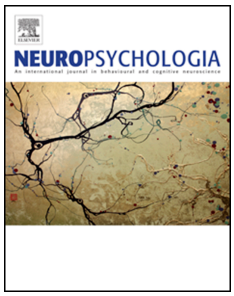

The neural basis of nonword repetition in children with developmental speech or language disorder: An fMRI study

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The neural basis of nonword repetition in children with Developmental Speech or Language Disorder: An fMRI study

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1. Introduction (1190 words)

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Developmental language disorder (DLD) and developmental speech disorder (DSD) are common during childhood, with prevalence rates estimated between 2-15% (Campbell et al., 2003; Eadie et al., 2015; McLeod & Harrison, 2009; Shriberg, Tomblin, & McSweeny, 1999). Children with DLD have significant difficulty acquiring and using language in the absence of hearing, intellectual or neurological impairment (Bishop, Snowling, Thompson, & Greenhalgh, 2016; Bishop, Snowling, Thompson, Greenhalgh, & Catalise-consortium., 2017). Children with DSD have difficulty accurately producing the speech sounds of their native language compared to same age peers, also in the absence of a clear aetiology (Dodd et al., 2018). DLD and DSD are associated with an increased risk of psychosocial, academic, and occupational difficulties (Conti-Ramsden, Durkin, Toseeb, Botting, & Pickles, 2018; Law, Rush, Schoon, & Parsons, 2009; Lewis et al., 2015; McKean et al., 2017; Mok, Pickles, Durkin, & Conti-Ramsden, 2014; Schoon, Parsons, Rush, & Law, 2010). DLD and DSD are thought to be influenced by a complex interaction between genetics, environmental and neurobiological factors (Graham & Fisher, 2013; Morgan, 2013). While a considerable amount of research has focussed on genetic and environmental risk factors, there are only a handful of studies that have examined the neurobiological basis of these disorders, and findings to date are equivocal (for review see: Liégeois, Mayes, & Morgan, 2014; Mayes, Reilly, & Morgan, 2015; Morgan, Bonthrone, & Liegeois, 2016). Furthermore, functional imaging studies have only studied DLD or DSD in isolation, when compared to typical controls. Given that these disorders often co-occur (Eadie et al., 2015; McKean et al., 2017; Shriberg et al., 1999) and show overlap in their symptomology and etiological risk factors (Peterson, McGrath, Smith, & Pennington, 2007), examining whether these two groups share functional anomalies, when compared to controls, would improve our understanding of these conditions.

Speech and language processes in the 'normal' brain involve multiple and interacting neural networks (Guenther, 2006; Skeide & Friederici, 2016). These networks include inferior frontal (inferior frontal gyrus, anterior insula), premotor (including supplementary motor area) and motor cortex, as well as superior, middle and inferior temporal regions and inferior parietal regions (Hickok, 2009; Hickok & Poeppel, 2007; Price, 2012). There is also evidence that a subcortical network, including the basal ganglia and cerebellum are involved in both speech (Hickok, 2012) and language processes (Mariën et al., 2014; Watkins, 2011). Individuals with DLD and DSD have been shown to engage similar neural networks during speech and language tasks (Badcock, Bishop, Hardiman, Barry, & Watkins, 2012; de Guibert et al., 2011; Preston et al., 2012; Tkach et al., 2011; Weismer, Plante, Jones, & Tomblin, 2005), however subtle differences in brain activation patterns have been reported in these groups relative to typical controls (Badcock et al., 2012; de Guibert et

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al., 2011; Preston et al., 2012; Tkach et al., 2011; Weismer et al., 2005). Although findings are mixed (for reviews see: Liégeois et al., 2014; Mayes et al., 2015), there is some evidence to suggest that children with DLD or DSD have reduced brain activation in the inferior frontal and posterior temporal regions (Badcock et al., 2012; de Guibert et al., 2011; Preston et al., 2012; Tkach et al., 2011; Weismer et al., 2005). However, interpretations of these studies are limited by the use of different speech/language tasks, and within and between group variability in the participant's age (e.g., 7-18 years or 8-17 years), speech/language phenotype, and co-occurring diagnoses/difficulties. In addition, the majority of these studies have used DLD or DSD samples of 10 participants or less, which has the potential to impact on statistical power and the generalisability of these findings (Badcock et al., 2012; Tkach et al., 2011; Weismer et al., 2005).

Nonword repetition is a task that involves listening to and immediately repeating multisyllabic nonsense words that match the phonological rules of a specific language (e.g., perplisteronk; Gathercole & Baddeley, 1996a). The repetition of novel speech sounds (i.e., nonwords) activates regions implicated in the dorsal language network which is involved in converting auditory speech sounds into articulatory-based representations (Hickok & Poeppel, 2004, 2007; Shuster, 2009; Strand, Forssberg, Klingberg, & Norrelgen, 2008; Tkach et al., 2011). The dorsal network includes the posterior superior temporal cortex, tempo-parietal junction, and left frontal lobe (including the inferior frontal gyrus, supplementary motor area, premotor and motor cortex; Hickok & Poeppel, 2004, 2007). The thalamus, putamen and cerebellum have also been shown to be activated by nonword repetition tasks using fMRI (Buchsbaum, Olsen, Koch, & Berman, 2005; Liegeois, Morgan, Connelly, & Vargha-Khadem, 2011; Shuster, 2009). Nonword repetition provides a good tool for investigating underlying functional differences in the brains of children with DLD and DSD because it is a highly sensitive clinical marker for speech and language disorders (Graf Estes, Evans, & Else-Quest, 2007). Furthermore, this task has also been shown to be a reliable phenotypic marker in individuals with genetically inherited speech and language disorder (Watkins, Dronkers, & Vargha-Khadem, 2002). Nonword repetition is the core task that co-segregates affected vs unaffected KE family members who present with an inherited mutation in *FOXP2,* resulting in childhood apraxia of speech (CAS) and language disorder (Watkins et al., 2002). Functional brain imaging studies with the KE family using nonword repetition have reported that relative to controls, affected members have reduced activation in the premotor, supplementary and primary motor cortices, as well as cerebellum and basal ganglia (Liegeois et al., 2011). While the primary deficit in the affected members of the KE family is CAS, these individuals also show language difficulties similar to those seen in individuals with DLD (Vargha-Khadem, Watkins, Alcock, Fletcher, &

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Passingham, 1995; Watkins et al., 2002). To date, the fMRI correlates of nonword repetition have not yet been investigated in a community-ascertained sample of children with DLD or DSD.

The aim of this study was to compare the fMRI correlates of nonword repetition in children with DLD, DSD, and typically developing speech and language ('typical controls'). At the behavioural level, we hypothesised that children with DLD and children with DSD would show poorer performance on the nonword repetition task compared to typical controls. On fMRI, we expected that typical controls would show task-related activation in the posterior temporal lobe bilaterally (superior temporal gyrus/sulcus), left tempo-parietal junction, as well as a network of regions in the frontal lobe (precentral gyrus, premotor cortex, supplementary motor area, and anterior insula), basal ganglia (thalamus and putamen) and cerebellum (Buchsbaum et al., 2005; Liegeois et al., 2011; Shuster, 2009). It was hypothesised that the DLD and DSD groups would show hypo-activation compared to controls in the inferior frontal and posterior temporal regions, as well as basal ganglia and cerebellum. In particular, we expected to see atypical cortical activation in regions implicated in the dorsal pathway such as bilateral posterior temporal region (superior temporal gyrus/sulcus and left tempo-parietal junction) and left frontal regions (posterior inferior frontal gyrus, premotor regions and anterior insula). Given the frequent co-morbidity (Eadie et al., 2015; Shriberg et al., 1999) and shared deficits on nonword repetition in DLD and DSD (Adams & Gathercole, 1995; Graf Estes et al., 2007; Munson, Edwards, & Beckman, 2005), our final hypothesis was that no functional activation differences would be detected between the DLD and DSD groups.

2. Materials and methods (1876 words)

2.1 Participant inclusion/exclusion criteria

Participants were identified from a larger longitudinal community cohort study of speech, language and communication which commenced when the children were 8-10 months of age (Early Language in Victoria Study (ELVS; Reilly et al., 2018). Children in the ELVS cohort who met the selection criteria for the current study were invited to participate. Children were excluded if they did not speak English, were a twin or multiple birth, had a neurological condition (e.g., epilepsy or acquired brain injury), hearing impairment, persistent stuttering (i.e., after the age of 5 years), or other neurodevelopmental disorder (e.g., Autism Spectrum Disorder, Attention Deficit Hyperactive Disorder). To be included children had to pass an MRI safety screen, and have a non-verbal IQ standard score of ≥ 80 on the Kaufman Brief Intelligence Test, Second Edition (KBIT-II; Kaufman & Kaufman, 2004) at age 4 and the Wechsler Abbreviated Scales of Intelligence (WASI; Wechsler, 1999) at age 7 years.

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Additional group-specific criteria were required. For the DSD group this included the presence of articulation and/or phonological errors at 4 years of age and at time of scanning (9-11 years), which was assessed by two raters using the Goldman Fristoe Test of Articulation, second Edition (GFTA-2; Goldman & Fristoe, 2000) and a connected speech sample. Children with speech sound errors were classified according to the DSD subtypes outlined in Dodd et al. (2018) and Morgan et al. (2017). All children in the DLD group were required to have a score at least one standard deviation below the mean on the receptive or expressive language index score of the Clinical Evaluation of Language Fundamentals (CELF; Semel, Wiig, & Secord, 2006; Wiig, Secord, & Semel, 2006) at ages 4 and 7 years or 5 and 7 years, and at the time of MRI scanning (9-11 years). All children in the DSD and typical control group scored within the average range on receptive and expressive language indices of the CELF (Semel et al., 2006; Wiig et al., 2006) at 4, 5, 7 and 9-11 years.

2.2 Participant characteristics

Seventy nine children (mean age = 10;3 years, range = 9;3 to 11;2 years) participated in this study. This included *n* = 19 with DLD, *n* = 15 with DSD and *n* = 45 typical controls. Four of these children were excluded from the analysis due to excessive movement (i.e., >3mm maximum inter-scan displacement), including three typical controls and one participant from the DLD group. Participant characteristics for the final sample are summarised in Table 1. The TC-reduced group is a subset of the typical control group that was included for comparison with the DLD and DSD groups in order to explore whether any differences in activation patterns were related to differences in the group sizes. Note that some participants in this study were also included in structural MRI focused publications (Kurth et al., 2018; Luders et al., 2017; Morgan et al., 2018).

Table 1. Participant characteristics

		TC	DLD	DSD	TC-reduced
N		42	18	15	17
Age in months		123(6)	124(3)	123(4)	123(5)
Sex (M:F)		22:20	10:8	5:10	8:9
Left, mixed, right handed		3, 2, 37	4, 1, 13	0, 1, 14	2, 1 ,14
CNRep		34(4)	25(4)	30(4)	33(3)
CELF-4 (Language)	Rec	105(8)	83(9)	103(6)	106(10)
	Exp	109(10)	80(9)	105(10)	109(11)
	Core	107(9)	80(7)	104(9)	108(10)

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WASI-2 PRI (NVIQ)	102(10)	92(8)	105(11)	107(7)

Values are Mean (Standard Deviation).
CELF-4 standard index scores and WASI-2 standard index scores are reported with a mean of 100 and a standard deviation of 15. CELF-4 = Clinical Evaluation of Language Fundamentals, Fourth Edition; WASI-2 PRI = Wechsler Abbreviated Scale of Intelligence, Second Edition Perceptual Reasoning Index; Rec = receptive; Exp = expressive; NVIQ = nonverbal IQ; M:F = male:female; CNRep = Children's Nonword Repetition Test; TC = Typical controls; DLD = Developmental Language Disorder; DSD = Developmental Speech Disorder; TC-reduced = a subset of the typical control group, matched as closely as possible in age and gender to both the DSD and DLD groups.

In the current sample, there were no group differences in age ($\chi^2(2, 72) = .44$, $p = .804$), sex ratio ($\chi^2(2, 72) = 1.97$, $p = .373$) or handedness ($\chi^2(4, 72) = 4.91$, $p = .214$). However, there were group differences on the measures of non-verbal intellectual abilities ($F(2, 72) = 9.05$, $p < .001$) and language (Core: $F(2, 72) = 69.06$, $p < .001$; Receptive: $F(2, 72) = 49.09$, $p < .001$; Expressive: $F(2, 72) = 58.99$, $p < .001$). As expected, post hoc comparisons using Tukey's HSD revealed the language scores for the DLD group were significantly lower than for the DSD and typical control groups ($p<.05$). The DLD group also showed lower scores on the measure of non-verbal intellectual abilities when compared to the DSD and typical control groups ($p<.05$). However this is not unusual in DLD groups (Bishop et al., 2017) and non-verbal ability of the DLD group remained in the "Average" normative range. Children in the DLD group were classified as having a primary receptive language deficit (n = 4), a primary expressive language deficit (n = 9), or both (n = 5) based on their CELF-4 Index scores at the time of MRI scanning. All children in the DSD group had speech sound errors consistent with either articulation disorder (n = 10), phonological delay (n = 3), or both (n = 1). One additional child presented with sub-clinical inconsistent sound distortions. Eight children in the DLD group also presented with speech sound errors consistent with phonological delay (n = 1), phonological delay *and* phonological disorder (n = 1) or articulation disorder (n = 6). This is consistent with the high co-occurrence of speech/language difficulties in children within the normal population (Eadie et al., 2015; McKean et al., 2017; Shriberg et al., 1999). More than 80% of the parents of children with DLD and more than 50% with DSD had received a referral to a speech and language pathologist or had sought professional assistance relation to their child's speech or language difficulties.

2.3 Ethics

This study was approved by the Human Research Ethics Committee at the Royal Children's Hospital in Melbourne Australia (HREC31225). Informed consent was obtained from each child's parent/guardian and verbal assent from each child.

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2.4 Testing session

Participants completed a mock and real MRI session, followed by standardised testing of their speech, language and non-verbal intellectual abilities. The mock scan, as well as training in the fMRI task was conducted in order to familiarize children with the MRI process, maximise compliance of the fMRI task and minimize head motion artefacts during data acquisition. Receptive and expressive language skills were evaluated with the Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4; Semel et al., 2006) and nonverbal intellectual abilities were assessed with the Perceptual Reasoning Index (PRI) of the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-2; Wechsler, 2011). Participants completed the Children's Nonword Repetition Test (CNRep; Gathercole & Baddeley, 1996a) outside the scanner (after completion of the MRI session) to measure nonword repetition performance without the confound of the MRI. The nonwords from the CNRep were recorded by an Australian English speaker and presented via a laptop using the same procedures outlined in the manual (Gathercole & Baddeley, 1996a). Participant responses were recorded online, as well as audio and video recorded for additional scoring. If a child had a consistent substitution or distortion error on the GFTA-2, this error was scored as correct on the CNRep as recommended in the manual (Gathercole & Baddeley, 1996a). As noted previously, speech sound errors were assessed using the GFTA-2 Sounds in Words subtest and a connected speech sample (see section 2.1).

2.5 fMRI: Stimuli design and task procedures /paradigm

The presentation of the fMRI paradigm during MRI data acquisition was controlled by the E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA). The child was required to listen to and repeat multi-syllable nonwords (active condition) or passively listen to pink noise (baseline condition) which was matched to each non-word on frequency, amplitude and length. The nonword stimuli were between two and five syllables in length and included 28 words from the CNRep (Gathercole & Baddeley, 1996a) and seven words from the Nonword Memory Test (Gathercole & Baddeley, 1996b) recorded in a typical English Australian accent. The fMRI task was administered in two six minute runs for each participant, with each run containing 70 unique stimuli (i.e., 35 active and 35 baseline). Auditory stimuli (i.e., nonwords or pink noise) were presented over 5 active (nonword) and 5 baseline (pink noise) blocks, with 7 stimuli in each block. There was a one-second gap between each block. Each stimulus was presented for a maximum of 2000ms and the response period was 3000ms. The child was instructed to either repeat out loud the non-words or to just listen to the "shh" sound (i.e., pink noise). A white "X" on a black computer screen was presented via a head coil mounted mirror, and participants were instructed to look at it for the duration of the

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task. Spoken responses were monitored via a custom-made microphone mounted on the head coil to ensure task compliance, however the quality of recordings was not always of adequate quality to score the accuracy of the responses. The auditory stimuli was presented via MRI compatible in-ear buds. Sound attenuating headphones were also worn to minimise the effects of the ambient scanner noise. Padding was inserted around the head to restrict movement.

2.6 Data acquisition

MRI data were collected on a Siemens 3 Tesla Skyra scanner (Erlangen, Germany) with 20-channel receiver head coil at the Florey Institute of Neuroscience and Mental Health, Melbourne. High resolution T1 weighted MPRAGE images were acquired with the following parameters: echo time (TE): 2.49 ms, repetition time (TR): 1900 ms, inversion time (TI): 900 ms, flip angle=9°, matrix: 256 x 256 x 192, and voxel size: 0.9 mm isotropic. The blood–oxygen level-dependent (BOLD) images were generated using a whole brain echo planer imaging (EPI) gradient echo sequence with the following scan parameters: TE: 30ms, TR: 3000ms, flip angle: 90^{o}, 44 interleaved slices, 3mm isotropic voxels, number of volumes per run: 120.

2.7 Data analysis

2.7.1 Behavioural data analysis

Behavioural data were analysed in IBM SPSS version 24. Group differences in age were assessed using a Kruskal-Wallis test due to a violation in assumptions for parametric statistical tests. The Freeman-Halton extension of the Fisher's Exact Tests was used to examine group differences in handedness. A between subjects ANOVA was used to test for group differences in nonword repetition accuracy.

2.7.2. Pre-processing

Imaging data was analysed using SPM8 (http://fil.ion.ucl.ac.uk/spm/software/spm8) running in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States). Images were spatially realigned to the first image of each run to correct for subject movement. Spatial normalisation was performed using the DARTEL (Diffeometric Anatomical Registration Through Exponentiated Lie Algebra) Toolbox, which enables precise inter-subject alignment to be achieved (Ashburner 2007). A customised DARTEL T1 template was created based on segmentations from the MPRAGE images for all subjects. The normalised fMRI images were then re-sampled at 2x2x2mm isotropic voxels and smoothed with an 8mm full width at half maximum Gaussian kernel. Participants that had a maximum inter-scan displacement that exceeded 3mm were excluded.

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2.7.3 First-level analysis

A first-level statistical analysis was conducted for each subject with a comparison between the active condition (nonword repetition) and baseline condition (pink noise). The BOLD response was modelled using the canonical hemodynamic response function and temporal derivative. A high pass filter with a cut off of 128 seconds was applied to remove low frequency drift. Preprocessing included de-correlating the motion regressors with the task regressors in order to minimise the regressors of no-interest causing reduction of task related activations due to task-correlated motion. One sample t-tests were used to test for significant task-related activation for each group. A threshold of $p<.05$ family-wise error (FWE) corrected and minimum cluster criteria of 10 contingent voxels was used to determine significant task-based within group activation (task > baseline).

2.7.4. Second-level analysis

The first-level contrasts were then analysed at the second level to generate group activation maps and comparisons. Hypotheses were tested using independent sample t-tests with age, sex, nonverbal intellectual abilities and handedness as covariates. A whole-brain voxel-level FWE corrected significance was set at $p<.05$ (including Bonferroni correction for testing both volume increases and decreases) and a minimum cluster criteria of 10 contiguous voxels.

3. Results (418 words)

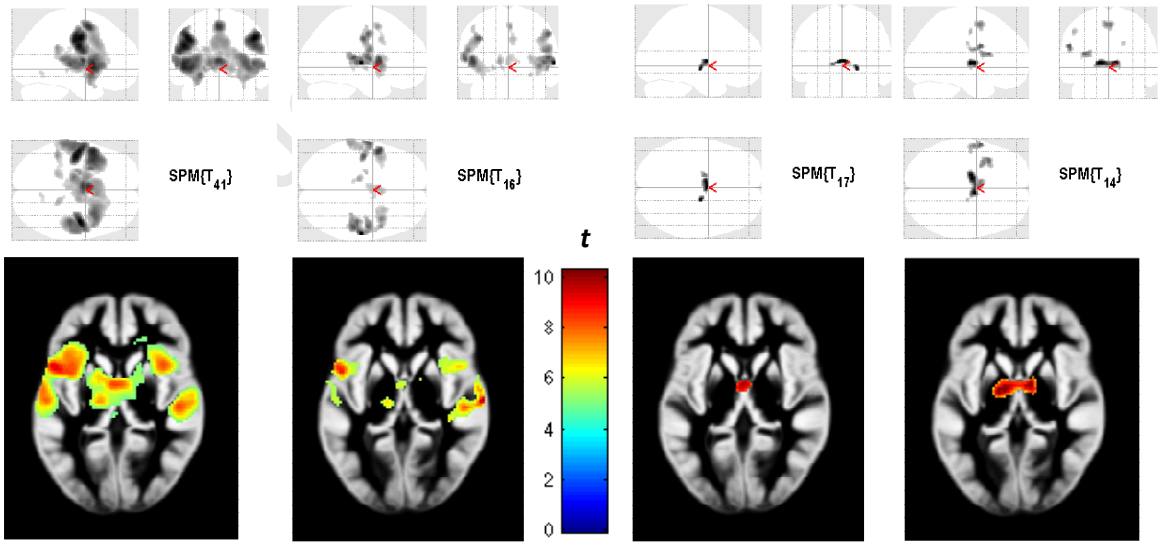
3.1 Nonword repetition performance (outside the scanner)

A significant group difference was detected in nonword repetition accuracy (i.e., CNRep) when performed outside of the scanner ($F(2, 72) = 31.91$, $p < .001$, $\eta_p^2 = .47$). Tukey's HSD post-hoc comparison indicated that nonword repetition accuracy was greater in typical controls compared with the DLD ($p < .001$) and DSD ($p = .025$) groups. Furthermore, the DSD group demonstrated greater repetition accuracy than the DLD group ($p < .001$). Means and standard deviations are presented in Table 1.

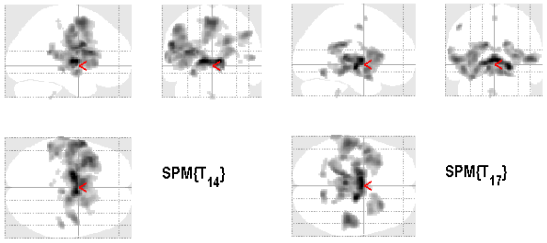
3.2 fMRI results

The first-level analyses for the typical controls revealed activation predominantly in lateral cortical regions including bilateral posterior superior temporal gyrus and superior temporal sulcus, anterior insula (extended into the ventral inferior frontal gyrus, especially on the left), supplementary motor area, precentral gyrus/motor cortex, left tempo-parietal junction, as well as the anterior cingulate and thalamus (See Figure 1). Due to the differences in group size, analysis was also conducted on a

subset of the typical control group (*n*=17), matched as closely as possible in age and gender to both the DLD and DSD groups (see table 1). As shown in Figure 1, the pattern of task-related brain activation for the smaller group of typical controls (TC-reduced) overlapped with that of the larger typical control group, although with lower activation in the thalamus. In contrast to the typical controls, the primary regions of activation for the DLD and DSD groups centred around the subcortical regions including the thalamus and globus pallidus, with the DSD group also displaying activation in the left precentral and post central gyrus, anterior insula and supplementary motor area. Despite these apparent differences, independent samples t-tests revealed no significant differences in brain activation between the a) typical controls and DLD group, b) typical controls and DSD group, or c) DLD and DSD group, following whole brain correction for multiple comparisons and at an uncorrected level of $p<.001$ within brain regions where differences were hypothesised. Similarly, there were no significant differences in activation for the a) TC-reduced controls and DLD and b) TC-reduced controls and DSD group at the same thresholds. Further inspection of the within-group brain activation maps in the DLD and DSD groups at more lenient thresholds (see figure 1bi and ii) revealed that the brain activation pattern for these groups (DLD and DSD) at this reduced threshold overlapped considerably with the typical control group. We also ran the group comparisons without nonverbal intellectual abilities and sex included as covariates, with no significant change in the results.



a) i. TC (*n*=42)*** ii. TC-reduced (*n*=17)*** iii. DLD (*n*=15)*** iv. DSD (*n*=18)***



b) i. DSD (n=15)** ii. DLD (*n*=18)*

Figure 1. Anatomical regions activated during nonword repetition task.

Each of the figures in 1a shows activation at the particular threshold specified, displayed on a "glass brain", as well as relevant activations shown superimposed on the corresponding axial slice from the study-specific grey matter template. Figure 1b is displayed only on a glass brain. In all cases, left side of brain is displayed on left side. Colour scale refers to t-values.
*** p<.05 FWE-corrected
** p<.0001 uncorrected
* p<.001 uncorrected

4. Discussion (1455 words)

Here we compared brain activation patterns during overt nonword repetition in 9-11 year old children with and without developmental language or speech disorder. Behavioural findings revealed that both children with DLD and children with DSD were significantly less accurate at repeating nonwords when compared to typical controls, as hypothesized and in line with previous research (Graf Estes et al., 2007). Imaging findings revealed that the DLD and DSD groups activated primarily sub-cortical regions (with the DSD group also displaying some activation in left lateral cortical regions and supplementary motor area), while the most significant activations in the typical control group were in lateral cortices. However, no statistically significant differences in brain activation patterns were observed on direct comparison between the groups.

Typical controls engaged known speech and language-related brain regions including bilateral posterior temporal cortices (posterior superior temporal gyrus/sulcus), the left tempo-parietal junction, bilateral frontal regions (anterior insula/inferior frontal gyrus, ventral motor cortex, supplementary motor area), bilateral thalamus (although much reduced in the smaller typical control group), and the cingulate gyrus. This pattern of activation is consistent with the adult fMRI literature employing similar tasks (Buchsbaum et al., 2005; Liegeois et al., 2011; Shuster, 2009), and suggests that the functional architecture supporting nonword repetition in typical children aged 9-11 years closely resembles the mature brain. When examined at the same FWE-corrected threshold, the DLD and DSD groups showed strong activation in the thalamus, as well as the globus pallidus. In contrast to controls, the DLD group showed no activation in cortical speech-language networks in the frontal or temporal lobe, and although the DSD group showed activation within this network, it

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was restricted to the left hemisphere. These indicative findings suggest a relatively greater role for sub-cortical structures than the lateral cortices in mediating sub-lexical aspects of language in the DLD and DSD groups. This observation of less detectable activation within the cortical speech/language regions of the DLD and DSD groups is consistent with the results of previous fMRI studies (Badcock et al., 2012; de Guibert et al., 2011; Weismer et al., 2005), including those that have used overt nonword repetition to examine brain activation in individuals with developmental speech and language disorders (Liegeois et al., 2011; Tkach et al., 2011). For example, hypo-activation in contrast to controls has previously been reported in several DLD fMRI studies using language tasks other than nonword repetition (Badcock et al., 2012; de Guibert et al., 2011; Weismer et al., 2005). Imaging findings from affected members of the KE family during nonword repetition reported hypo-activation compared to controls in the right anterior cingulate and right supplementary motor area, and left pre-central gyrus, ventral motor and premotor region (Liegeois et al., 2011). Furthermore, in line with the lack of activation in right cortical regions of the DSD group, Tkach and colleagues (2011) reported hypo-activation (at an uncorrected significance level of $p<.001$) in the right cortical regions (including the inferior frontal gyrus and middle temporal gyrus) for adolescence with a history of DSD when compared to controls.

Despite the apparent variation in activation patterns suggested by visual inspection, the differences between the typical control group and the DLD/DSD groups were not statistically significant. Previous fMRI studies using other speech/language tasks have reported DLD and DSD groups to show significant differences in their brain activation patterns, when compared to controls (Badcock et al., 2012; de Guibert et al., 2011; Preston et al., 2012; Tkach et al., 2011; Weismer et al., 2005). There are several possible explanations for the differences between the current and previous findings. First, previous research has utilised tasks that involve additional cognitive processes (e.g., lexical access, complex attention, visual processing; Badcock et al., 2012; de Guibert et al., 2011; Weismer et al., 2005), that are not required for nonword repetition. Second, average language scores for the DLD groups in previous studies have tended to fall between 1.5 to 2 standard deviations below the mean (e.g., Badcock et al., 2012; de Guibert et al., 2011; Weismer et al., 2005). Children in the present study by contrast, had an average core language index score of around 1.25 standard deviations below the mean, indicating less severe language deficits in our cohort. Third, a stringent statistical criteria was utilised in the present study (FWE corrected level of $p<.05$). Only one of the previous DLD studies utilised a similar criteria (de Guibert et al., 2011) and this study examined group differences within specific regions of interest rather than across the whole brain, which can be more sensitive at detecting group differences. The other two studies (Badcock et al.,

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2012; Weismer et al., 2005) used more lenient statistical thresholds (e.g., uncorrected for multiple comparisons), which may have increased the risk of a false positive result. Finally, most of the previous studies have used very small DLD/DSD samples (e.g., 6-8 participants; Badcock et al., 2012; Tkach et al., 2011; Weismer et al., 2005). In a recent paper by Ramus and colleagues (2018), it was noted that in dyslexia research, small scale imaging studies tend to be more likely to report significant findings, compared to more powered studies that fully correct for multiple comparisons. This highlights a possible false positive reporting problem in studies with very small samples.

It is also possible that within-group variability contributed to the lack of significant group differences in the current study. Within-group homogeneity was attempted to be maximised in this study by restricting the age range, identifying children via longitudinal measures of speech and language, and excluding children with a history of other developmental difficulties. However the DLD and DSD groups in the current study did nevertheless show heterogeneity in their respective phenotypes. For example, the DLD group included children with primary receptive, primary expressive and mixed receptive/expressive language impairments, while the DSD group constituted children who showed errors consistent with articulation disorder, phonological disorder, or both. Limitations in the sample size did not enable comparisons between these different phenotypes. This heterogeneity at the behavioural level is in line with research that reports heterogeneous genetic profiles of children with developmental language and speech disorders (Chen et al., 2017; Eising et al., 2018). It is possible that the underlying brain function and cognitive deficits associated with poor nonword repetition within each of the clinical groups (i.e., DLD & DSD) is variable. This variability could be a function of underlying genetics and speech/language phenotype, as well as further exacerbated by individual differences in the way the brain attempts to compensate for speech or language deficits. Regardless of the underlying mechanism, within-group variability would likely make it more difficult to detect subtle group differences in brain activation. Although previous studies with heterogeneous DLD samples have reported group differences in activation, these studies utilised very small DLD groups (e.g., 6-8 participants; Badcock et al., 2012; Tkach et al., 2011; Weismer et al., 2005), some of whom had difficulties in other areas of development (e.g., ADHD; oromotor difficulties). Thus, these previous findings may not be generalizable to the general DLD population. Future work including larger, well-defined participant samples that enable the investigation of DLD and DSD subgroups would be useful to clarify findings in this area.

Limitations and future directions

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Although one of the largest fMRI studies in DLD and DSD, the sample size in this study was still quite small, which may have resulted in limited power to detect a significant effect. As described above, group sizes also precluded the examination of specific DLD or DSD phenotypes/subgroups within this study (e.g., receptive versus expressive language deficit/articulation versus phonological speech difficulties). Further fMRI research with larger samples is needed to investigate whether such subgroups of DLD or DSD are associated with different functional brain anomalies. Although the inclusion of children with a narrow age range was an important strength of this study, future imaging work that incorporates a longitudinal design is warranted to better understand the development of the functional neural architecture in DLD and DSD.

Summary and implications

This study provided thought-provoking findings in relation to the neural correlates of nonword repetition in children with DLD, DSD and typical controls. Behavioural findings confirmed that the DLD and DSD groups had poorer nonword repetition performance compared to typical controls. FMRI findings revealed no statistically significant group differences in brain activation, despite the groups appearing to engage slightly different regions when compared at identical thresholds. Given the non-significant findings, these results suggest that fMRI during nonword repetition is not a sensitive *brain MRI* marker in DLD or DSD. However, the DLD and DSD groups showed less detectable activation, when compared to controls, within the cortical speech/language regions, together with higher sub-cortical activation. This could suggest a relatively greater role for sub-cortical structures compared to lateral cortices in mediating sub-lexical aspects of language in children with DLD and DSD.

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Highlights

- Nonword repetition a sensitive clinical marker for DLD and DSD
- No significant differences in nonword repetition fMRI for DLD, DSD and controls
- Nonword repetition not a sensitive *brain MRI* marker for children with DLD or DSD

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