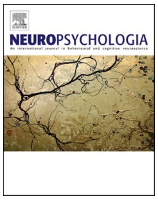
Neuropsychologia 146 (2020) 107543

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: http://www.elsevier.com/locate/neuropsychologia



Differential activation of the visual word form area during auditory phoneme perception in youth with dyslexia

Lisa L. Conant [a,*], Einat Liebenthal [a,b], Anjali Desai [a], Mark S. Seidenberg [c], Jeffrey R. Binder [a]

[a] Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA
[b] Department of Psychiatry, McLean Hospital, Harvard Medical School, Boston, MA, USA
[c] Department of Psychology, University of Wisconsin-Madison, Madison, WI, USA

ARTICLE INFO

Keywords:
Developmental dyslexia
Phoneme perception
Speech perception
Reading development
Visual word form area

ABSTRACT

Developmental dyslexia is a learning disorder characterized by difficulties reading words accurately and/or fluently. Several behavioral studies have suggested the presence of anomalies at an early stage of phoneme processing, when the complex spectrotemporal patterns in the speech signal are analyzed and assigned to phonemic categories. In this study, fMRI was used to compare brain responses associated with categorical discrimination of speech syllables (P) and acoustically matched nonphonemic stimuli (N) in children and adolescents with dyslexia and in typically developing (TD) controls, aged 8–17 years. The TD group showed significantly greater activation during the P condition relative to N in an area of the left ventral occipitotemporal cortex that corresponds well with the region referred to as the "visual word form area" (VWFA). Regression analyses using reading performance as a continuous variable across the full group of participants yielded similar results. Overall, the findings are consistent with those of previous neuroimaging studies using print stimuli in individuals with dyslexia that found reduced activation in left occipitotemporal regions; however, the current study shows that these activation differences seen during reading are apparent during auditory phoneme discrimination in youth with dyslexia, suggesting that the primary deficit in at least a subset of children may lie early in the speech processing stream and that categorical perception may be an important target of early intervention in children at risk for dyslexia.

1. Introduction

1.1. Phonological processing and phoneme perception deficits in developmental dyslexia

Developmental dyslexia is the most common learning disability, with prevalence estimates ranging from 5 to 17% of the population (Lyon, 1995; Shaywitz, 1998). It is not only common but also persistent, with elevated risks for multiple long-term adverse psychosocial and economic outcomes. Deficits in phonological processing historically have been considered to constitute the core area of difficulty in developmental dyslexia (Fletcher et al., 1994; Grigorenko, 2001; Lyon and Chhabra, 1996; Ramus, 2003; Shaywitz, 1998), but there is evidence to suggest that multiple deficits, either alone or in combination, may contribute to a given individual's difficulties in reading acquisition, and the idea of a single deficit underlying all cases of dyslexia is untenable (McGrath et al., 2011; Pennington, 2006; Pennington et al., 2012; van Bergen et al., 2014). Among the potential deficits examined, a number of studies have found a specific difficulty in the categorical perception of phonemes. Categorical phoneme perception refers to a warping of perceptual space based on phoneme categories such that acoustic variations that cross category boundaries are augmented while acoustic variations of the same magnitude within a phonemic category are diminished. Different instances of the same speech utterance inevitably vary acoustically, and categorical perceptions allows the perception of many physically different sounds as exemplars of the same phoneme.

Many studies have found phonemic categorical perception deficits not only in children and adults diagnosed with developmental dyslexia (Bogliotti et al., 2008; Breier et al., 2001; Chiappe et al., 2001; de Gelder and Vroomen, 1998; Godfrey et al., 1981; Lieberman et al., 1985; Noordenbos and Serniclaes, 2015; O'Brien et al., 2018; O'Brien et al., 2019; Serniclaes, Sprenger-charolles, Carré and Démonet, 2001; Steffens et al., 1992; Veuillet et al., 2007; Zhang et al., 2012) but also in young beginning readers considered to be at risk for dyslexia due to a

---

* Corresponding author. Department of Neurology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI, 53226, USA.
E-mail address: lconant@mcw.edu (L.L. Conant).

https://doi.org/10.1016/j.neuropsychologia.2020.107543
Received 17 October 2019; Received in revised form 16 March 2020; Accepted 21 June 2020

phonological awareness deficit (Breier et al., 2004), and in infants (Richardson et al., 2003) or young children (Boets et al., 2007; Noordenbos, Segers, Serniclaes, Mitterer and Verhoeven, 2012a) at familial risk for dyslexia. A recent meta-analysis indicates that the deficit is stronger for discrimination than identification tasks and is present in comparison to both chronological-age and reading-level controls (Noordenbos and Serniclaes, 2015).

In addition to these findings of impairments in individuals with dyslexia, studies have suggested that categorical perception is associated more generally not only with reading ability (Breier et al., 2001; Godfrey et al., 1981; Maassen and Groenen, 2001; O'Brien et al., 2018; Veuillet et al., 2007; Zoubrinetzky et al., 2016), but also phonological awareness (Boets et al., 2007; Breier et al., 2001; Chiappe et al., 2001; Manis et al., 1997; McBride-Chang, 1996; Zoubrinetzky et al., 2016) and rapid naming (McBride-Chang, 1996; O'Brien et al., 2018). Importantly, anomalies in speech perception and associated event-related potentials (ERPs) can be seen in infants at familial risk for dyslexia, and these early differences in speech processing have been found to predict future phonological processing as well as reading performance (for review, see Leppänen et al., 2011; Lyytinen et al., 2004). Specifically, across multiple studies conducted as part of the Jyväskylä Longitudinal Study of Dyslexia, not only was a behavioral difference in categorical perception seen between infants at familial risk for dyslexia relative to control infants (Richardson et al., 2003), but ERP differences were seen suggesting diminished left hemisphere (Leppänen et al., 2002) and enhanced right hemisphere processing during speech perception in the at-risk group (Guttorm et al., 2001; Leppänen et al., 1999). Infant speech perception ERPs were associated with later phonological awareness, rapid serial naming, letter knowledge (Guttorm et al., 2010), and second-grade reading and writing skills (Leppänen et al., 2011). In addition, studies using phoneme discrimination training in non-reading-impaired children (Moore et al., 2005) and children with dyslexia (Hurford, 1990) have shown significant post-training improvements in phonological awareness relative to children who did not receive discrimination training. Improvements in reading abilities in children with dyslexia have also been reported after phoneme identification training (Magnan et al., 2004; Magnan and Ecalle, 2006; Veuillet et al., 2007).

A few attempts have been made to determine whether a phonemic perception deficit in dyslexia was specific to speech or reflected a broader auditory temporal processing deficit. Generally these studies have tended to find greater performance differences with speech stimuli than nonspeech stimuli (Breier et al., 2001; Mody et al., 1997; Rosen and Manganari, 2001). In some studies (Mody et al., 1997; Rosen and Manganari, 2001), the nonspeech stimuli were less acoustically complex than the speech stimuli, leaving open the possibility of a general auditory perceptual difficulty with more complex sounds; however, Serniclaes et al. (2001) precisely matched the complexity of the stimuli across conditions by comparing the AX discrimination performance of children with and without dyslexia on sine wave analogues of speech sounds, which were first described to the participants as electronic whistles (acoustic condition) and later revealed as/ba/and/da/analogues (speech condition). Group differences were observed only in the speech condition, in which the children with dyslexia showed less categorical patterns than the nonimpaired readers. Several other studies have found that, although individuals with dyslexia show diminished discrimination across phonemic categories compared to nonimpaired controls, their within-category discrimination is at or above that demonstrated by nonimpaired readers (de Gelder and Vroomen, 1998; Godfrey et al., 1981; Noordenbos, Segers, Serniclaes, Mitterer and Verhoeven, 2012b; Noordenbos et al., 2012a).

However, while many studies have reported a significant deficit in speech perception in individuals with dyslexia, other studies have only shown them in a subset of individuals (Adlard and Hazan, 1998; Manis and Keating, 2005; Manis et al., 1997; Messaoud-Galusi et al., 2011) or have failed to find difficulties in this area (Brandt and Rosen, 1980; Romanovska et al., 2019, although the latter study did find a correlation with reading ability in typically developing children). Some of the variability may be due to differences in task demands or stimuli (Blomert and Mitterer, 2004; Maassen and Groenen, 2001; Noordenbos and Serniclaes, 2015; Ziegler et al., 2009) or sample characteristics, such as the presence or absence of additional language impairments (Joanisse et al., 2000) or of a family history of dyslexia (Vandermosten et al., 2020). Interestingly, one recent study reported that adults with dyslexia who showed intact performance on a phoneme-discrimination-in-noise task relied on different allophonic cues than non-reading-impaired controls, suggesting the use of a compensatory strategy to attain a similar level of performance (Varnet et al., 2016). Thus, perceptual differences may still exist despite intact behavioral performance on categorical tasks.

1.2. *Functional neuroimaging of categorical perception*

In adults, functional neuroimaging studies suggest that primarily the middle portion of the left ventral superior temporal gyrus and sulcus (STG/STS) is engaged during discrimination of phonemic relative to acoustically matched nonphonemic stimuli, implicating this area in phoneme perception (DeWitt and Rauschecker, 2012; Liebenthal et al., 2010, 2005; Obleser et al., 2007). However, more posterior STS activation has been found in association with phonemic discrimination of sine-wave speech stimuli (Desai et al., 2008) and with emerging categorical perception of nonphonemic stimuli after training (Liebenthal et al., 2010), suggesting the involvement of more posterior superior temporal regions when the discrimination is more challenging or less automatic. In addition, a recent fMRI study found that simultaneous presentation of ambiguous speech sounds falling at the category boundary and text labeling the sounds as exemplars of one or the other category recalibrates the perceptual interpretation of these sounds on subsequent trials, and this recalibration was associated with changes in posterior superior temporal activations and their functional connectivity with dorsal inferior parietal regions (Bonte et al., 2017). This finding further implicates the posterior superior temporal region, and potentially inferior parietal regions, in emerging category representation.

We previously used fMRI to examine the neural correlates of phonemic and nonphonemic perception in 32 children, aged 7–12 years (Conant et al., 2014). Multiple regions in left frontal, temporal, and parietal cortex were found to be more responsive to phonemic than acoustically-matched nonphonemic sounds. In ROI analyses, the children with higher categorical perception performance, as defined by significantly greater between-than within-category discrimination, showed greater left lateralization for phonemic relative to nonphonemic perception in the inferior parietal lobule and the posterior portion of the superior and middle temporal gyri (pSTG/MTG). In addition, activation in the left pSTG/MTG was correlated with the level of categorical perception in children with lower proficiency in this ability. In the whole-brain analyses, an unexpected finding was that categorical perception performance was strongly related to activation in the left posterior occipitotemporal sulcus (pOTS)/fusiform gyrus (FG) area during the phonemic condition relative to baseline, which was observed in both group comparisons of children with high and low categorical perception performance and correlational analyses across the full sample. The location corresponded well to the coordinates reported previously for the putative visual word form area (VWFA) (Cohen et al., 2000; McCandliss et al., 2003). While the precise role of this region and its specificity for processing orthographic input relative to nonorthographic visual stimuli is still debated, there is substantial evidence that this region of left ventral occipitotemporal cortex (vOTC) plays a critical role in reading (Price, 2012; Sandak et al., 2004). It is consistently found to be activated during tasks involving reading visually presented words or pseudowords (Martin et al., 2015; Price, 2012), and damage to this area has been found to disrupt visual word recognition (Binder and Mohr, 1992; Cohen et al., 2003; Leff et al., 2006). As discussed below, this area has also been strongly implicated in the neuropathology of developmental dyslexia.

1.3. Functional neuroimaging in developmental dyslexia

There have been multiple meta-analyses of neuroimaging studies comparing individuals with dyslexia to nonimpaired readers using reading or reading-related tasks with print stimuli (Hancock et al., 2017; Linkersdörfer et al., 2012; Maisog et al., 2008; Martin et al., 2016; Richlan et al., 2011, Richlan et al., 2009), with one meta-analysis also including a minority of studies with solely auditory tasks (Paulesu et al., 2014). Most typically, these studies have reported decreased activation of left vOTC in the vicinity of the VWFA and of left temporoparietal regions in individuals with dyslexia (Hancock et al., 2017; Linkersdörfer et al., 2012; Maisog et al., 2008; Paulesu et al., 2014; Richlan et al., 2011, 2009), with the latter regions most commonly including the posterior STG and STS, extending into the MTG (Hancock et al., 2017; Linkersdörfer et al., 2012; Maisog et al., 2008; Pollack et al., 2015; Richlan et al., 2011, 2009) and the dorsal inferior parietal lobule (IPL) (Hancock et al., 2017; Linkersdörfer et al., 2012; Martin et al., 2016; Paulesu et al., 2014; Richlan et al., 2011, 2009).

Little is known about the neural basis of categorical perception deficits in dyslexia. In an fMRI study in which participants passively listened to sequences of speech syllables (/pa/and/ta/), Ruff et al. (2003) reported greater activation associated with the presentation of across-category stimuli in non-impaired adult readers relative to adults with dyslexia in the left angular gyrus, right mid-cingulate, and right inferior frontal gyrus. In contrast, for a within-category deviant, the individuals with dyslexia showed activation in the posterior cingulate that was not seen in the control group. The activation differences were not in expected locations, which may have been due in part to the passive nature of the task, but did suggest differences in neural regions recruited by individuals with dyslexia relative to non-impaired readers when listening to speech sounds.

Two neuroimaging studies have used active discrimination tasks. The first of these was a magnetoencephalography (MEG) study using a voice-onset-time discrimination task in children (Breier et al., 2003). The results suggested less left lateralization in temporoparietal cortex in children with dyslexia compared to a control group. The hemispheric asymmetry index was significantly related to performance on a phoneme deletion task and marginally related to rapid letter naming. Discrimination functions were not calculated, so the extent of categorical perception demonstrated by the groups is unknown. No nonspeech control task was used, and the precise localization of the anomalous activation remains uncertain given the limited spatial resolution of MEG.

A PET study conducted by Dufor et al. (2007) has been the only study to include an acoustic control task. This study used PET to examine activation in adults with or without dyslexia during an AX discrimination task using sinewave analogues of/ba/and/da/, which were described to participants initially as electronic sounds (acoustic condition) and subsequently as speech syllables (speech condition). Group differences in performance were seen overall, with greater accuracy in the control group relative to the group with dyslexia, but the authors did not report any significant group x condition or pair-type (between-category, within-category, same) interactions. Both groups showed a significant improvement in performance after debriefing. With regard to activation, in the speech condition relative to rest, the controls showed greater activation in left-lateralized regions spanning posterior frontal, inferior parietal, and mid to posterior superior temporal cortices. In contrast, the individuals with dyslexia showed greater activation in the right inferior and middle frontal gyri, right parahippocampal gyrus, right thalamus, left putamen, and both cerebellar hemispheres. For the contrast of the speech relative to the acoustic condition, the controls showed greater activation in bilateral frontal and parietal regions and left posterior superior, middle, and inferior temporal regions, with the latter extending into the upper portion of Brodmann's Area 37. The group with dyslexia showed greater activation in medial occipital cortex, which appeared to primarily reflect a significant deactivation in the acoustic condition relative to rest.

Overall, these studies suggest that there are likely differences in the neural correlates of categorical phoneme perception in individuals with dyslexia relative to typically developing controls; however, there has not yet been a study combining the spatial resolution of fMRI with the use of an active task that compares categorical phoneme discrimination with an acoustically matched nonspeech control condition in children with and without dyslexia. Thus, the goal of the current study was to use fMRI to investigate potential differences between youth with developmental dyslexia and typically developing controls in activation associated with performance of a categorical phoneme perception task. The use of an acoustically-matched nonspeech control condition allows the examination of speech-specific processes after controlling for aspects of complex auditory analysis and more general processes involved in attention to task and decision-making. Based on our previous findings with typically developing children using a categorical perception task (Conant et al., 2014), and results of meta-analyses investigating anomalous patterns of activation in individuals with dyslexia (Hancock et al., 2017; Linkersdörfer et al., 2012; Maisog et al., 2008; Martin et al., 2016; Richlan et al., 2011, 2009), we predicted decreased activation in left vOTC in the vicinity of the VWFA as well as in left temporoparietal regions in the children with dyslexia relative to non-impaired readers.

2. Materials and methods

2.1. Participants

The study was approved by the Children's Hospital of Wisconsin Institutional Review Board, and both informed consent from all parents and informed assent from all minors were obtained. Participants with dyslexia were required to have a documented history of reading difficulties consistent with dyslexia as identified through the school, a reading specialist, or a psychologist/neuropsychologist, and all participants had received some reading intervention prior to this study (mean duration of 3.26 ± 2 years). Their performance at the time of participation had to fall at or below a standard score of 90 (the 25th percentile) on a composite created by averaging three scores: (a) the Basic Reading Skills Composite from the Woodcock-Johnson Tests of Achievement-3rd Edition (WJ-III) (Woodcock et al., 1999), which is comprised of the Letter-Word Identification subtest and the Word Attack subtest; (b) the Spelling subtest from the WJ-III; and (c) Total Reading Efficiency as assessed with the Test of Word Reading Efficiency (TOWRE) (Torgesen et al., 1999). In contrast, the typically developing children were required to have no history of speech, language, reading, or other learning problems and to perform above 90 on the composite measure. Exclusion criteria for both groups were the following: (a) estimated Full Scale IQ below 85; (b) a history of significant sensory impairment, neurological illness or injury, Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder, or psychiatric disorder; (c) the presence of clinically significant attentional concerns as suggested by parent and teacher behavior ratings; (d) the presence of medical or constitutional contraindications for undergoing MRI; or (e) failure of an audiometric screening performed at the time of participation. In addition, participants were required to have English as a primary language because performance and functional neuroanatomy seen with a secondary language may differ from that seen with the primary language, and at least one parent had to be a native American English speaker to ensure that they had early exposure to all American English phonemes.

Twenty-nine children, including 15 with dyslexia and 14 typically developing (TD), completed both a neuropsychological testing session and fMRI scan involving phonemic and nonphonemic perception tasks. To be included in the analyses, participants were required to have at least 32 trials in each condition after removing missed trials or ones with excessive motion. One child in each group was excluded on this basis. An

Table 1

Means and standard deviations (in parentheses) for the demographic variables and behavioral measures for the children with dyslexia and the typically developing children as well as the uncorrected p values for the independent samples t tests, ANCOVAs, or Mann-Whitney U tests.

	Dyslexia (n=12)	TD Controls (n=13)	Test Statistic	p
Age	12.05 (1.66)	13.18 (2.62)	$t(23) = -1.28$	0.214
Sex (F/M)	6/6	4/9		0.428
Hollingshead SES Index	53.75 (8.64)	46.69 (17.67)	$t(17.7) = 1.25$	0.216
WISC-IV Est. Verbal IQ	110.92 (10.89)	121.31 (11.94)	$t(23) = -2.27$	0.033
WISC-IV Est. Nonverbal IQ	104.92 (17.04)	114.46 (12.30)	$t(23) = -1.62$	0.120
WISC-IV Symbol Search	9.92 (1.93)	10.92 (2.02)	$t(23) = -1.27$	0.216
Reading Composite[c]	81.58 (6.30)	113.25 (9.05)	$t(23) = -10.07$	<0.001
WJ-III Basic Reading Skills[c]	85.92 (8.22)	111.69 (8.62)	$t(23) = -7.64$	<0.001
Letter-Word Identification[c]	86.33 (9.58)	109.85 (7.68)	$t(23) = -6.80$	<0.001
Word Attack[c]	87.42 (7.42)	111.08 (9.05)	$t(23) = -7.11$	<0.001
WJ-III Spelling[c]	79.58 (9.12)	119.69 (11.09)	$t(23) = -9.83$	<0.001
TOWRE Total Reading Efficiency[c]	79.25 (5.17)	108.38 (10.28)	$t(18.01) = -9.06$	<0.001
Sight Word Efficiency[c]	85.17 (5.86)	103.23 (10.15)	$t(23) = -5.39$	<0.001
Phonemic Decoding Efficiency[c]	80.17 (4.93)	110.69 (9.82)	$t(23) = -9.69$	<0.001
GORT-4 Fluency[c]	4.58 (2.35)	13.31 (2.50)	$t(23) = -8.97$	<0.001
GORT-4 Comprehension[b]	9.33 (2.64)	12.31 (2.02)	$t(23) = -3.18$	0.004
CTOPP Phonological Awareness	101.75 (15.27)	112.92 (7.59)	$t(15.8) = -2.29$	0.036
CTOPP Rapid Naming[a]	88.75 (13.05)	103.92 (13.44)	$t(23) = -2.86$	0.009
CTOPP Phonological Memory[a]	92.75 (10.96)	104.15 (13.56)	$t(23) = -2.31$	0.030
CELF-4 LMI[b]	100.92 (11.28)	114. 54 (6.77)	$U = 23$	0.002
TOVA d’	80.00 (6.16)	100.23 (15.69)	$U = 24.5$	0.005
TOVA ADHD Score[c]	−2.82 (2.11)	0.95 (2.20)	$U = 15$	<0.001
CBCL Attention-Parent[a]	54.75 (4.07)	51.08 (1.75)	$U = 35$	0.013
CPI (d’)	2.52 (1.85)	3.59 (1.17)	$F(1,22) = 1.70$	0.206
Phonemic Across (d’)	2.92 (1.46)	4.00 (0.89)	$F(1,22) = 4.15$	0.054
Phonemic Within (d’)	0.40 (0.52)	0.45 (0.48)	$F(1,22) = 0.21$	0.650
Nonphonemic (d’)	1.16 (0.83)	1.51 (0.80)	$F(1,22) = 0.53$	0.475
Phonemic RT	1338.92 (238.60)	1282.46 (285.27)	$F(1,22) = 0.21$	0.650
Nonphonemic RT	1301.67 (221.63)	1325.08 (252.46)	$F(1,22) = 2.05$	0.166

Note: WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition; WJ-III: Woodcock-Johnson Tests of Achievement-Third Edition; TOWRE: Test of Word Reading Efficiency; GORT-4: Gray Oral Reading Test-Fourth Edition; CTOPP: Comprehensive Test of Phonological Processing; CELF-4 LMI: Clinical Evaluation of Language Fundamentals-Fourth Edition Language Memory Index; TOVA: Test of Variables of Attention; CBCL Attention: Child Behavior Checklist Attention Problems scale; CPI: Categorical Perception Index; RT: Reaction time.

[a] Corrected $p < .05$.

[b] Corrected $p < .01$.

[c] Corrected $p < .001$.

additional child in the dyslexia group was excluded due to poor image quality and apparent inconsistency regarding which hand was used to indicate which response. Finally, one child in the dyslexia group was eliminated due to excessive translational and rotational motion parameters (described below), resulting in samples of 12 children with dyslexia and 13 TD children. Demographic data are summarized in Table 1.

2.2. Neuropsychological assessment

The participants completed a brief hearing screening, a battery of neuropsychological measures, and a mock scanner training session to familiarize them with the stimuli, tasks, and scanner procedures and to reduce possible anxiety and excess motion during scanning. Standardized neuropsychological measures included the following: a four-subtest short form of the Wechsler Intelligence Scale for Children-Fourth Edition (Wechsler, 2003) or the Wechsler Adult Intelligence Scale-Fourth Edition (Wechsler, 2008); Test of Variables of Attention (TOVA) (Leark et al., 1999); Comprehensive Test of Phonological Processing (CTOPP) (Wagner et al., 1999); WJ-III Tests of Achievement (Woodcock et al., 1999)-Letter-Word Identification, Word Attack, Spelling, and Picture Vocabulary subtests; TOWRE (Torgesen et al., 1999); Gray Oral Reading Tests-4th Edition (GORT-4) (Wiederholt and Bryant, 2001); Clinical Evaluation of Language Fundamentals-4th Edition Language Memory Index (CELF-4 LMI)-Formulated Sentences, Concepts & Following Directions (ages 8–12)/Semantic Relationships (ages 13–17), and Recalling Sentences subtests (Semel et al., 2003); Achenbach Child Behavior Checklist-Parent and Teacher Rating Forms (Achenbach and Rescorla, 2001). Age-corrected standard scores for these measures were used in the analyses. One child with dyslexia did not complete the TOVA due to technical difficulties. For the categorical perception measures, age was added to the analyses as a covariate. All variables were examined for normality using the D’Agostino-Pearson K^2 Test, which is an omnibus test to detect deviations in either skewness or kurtosis. The two attentional measures and the CELF-4 LMI were found to be non-normal in the TD control group, and one attentional measure was non-normal in the dyslexia group. Therefore, Mann-Whitney U Tests were conducted for these variables rather than independent samples *t*-tests.

2.3. Image acquisition

For 18 of the participants (7 with dyslexia and 11 controls), images were acquired using a 3T GE Signa Excite scanner (GE Medical Systems, Milwaukee, WI) and, for the remaining 7 participants (5 participants with dyslexia and 2 controls), a 3T GE Healthcare Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) was used. There was no significant difference between groups in the number of children scanned with the two different scanners (Fisher’s Exact Test, $p = .202$). In addition, voxelwise scaling to percent mean signal was used in the preprocessing. However, to ensure no effects were secondary to differences in scanner type, it was included as a covariate in the analyses. Whole-brain fMRI data were acquired using gradient-echo, echoplanar imaging (TE = 20 ms, flip angle = 80°) at long intervals (TR=7 s; acquisition time=2 s). The clustered acquisition paradigm was used to avoid perceptual masking of the test items and contamination of the BOLD data by the acoustic noise of the scanner (Edmister et al., 1999). Thirty-six axial slices, 3 mm thick, were acquired with 0.5 mm gap between slices to prevent signal bleed. The field of view was 220 mm with a matrix of 64x64, resulting in 3.44 x 3.44 × 3.5 mm voxels covering the whole brain. High resolution, T1-weighted structural images were obtained at each session using a 3D SPGR sequence (TE = 3.9 ms, TR = 9.5 ms, TI = 450 ms, flip angle = 12°, matrix = 256 x 224, NEX = 1, slice thickness 1.2 mm, 106 axial slices, scan time = 6.23 min).

2.4. *Stimulus synthesis and presentation*

Stimuli were created using a cascade/parallel formant synthesizer (SenSyn Laboratory Speech Synthesizer, Sensimetrics Corp., Cambridge, MA). The Phonemic test items consisted of a 7-token continuum from/ba/to/da/. Pitch, intensity, formant bandwidth and formant center frequency parameters for synthesis of the anchor points of the Phonemic continuum were derived from natural utterances of the syllables produced by a male speaker (JRB) and sampled at 44.1 kHz. The pitch, intensity and formant bandwidths of the anchor points, as well as the formant center frequencies throughout the steady-state vowel segment of the syllables were equated across tokens using average values. Tokens were edited to 150 ms duration. The anchor points of the Nonphonemic continuum were constructed by spectrally inverting the first formant of the speech syllables in order to disrupt their phonemic value without altering their general spectrotemporal characteristics. Intermediate tokens for both continua were interpolated as described in a previous study (Liebenthal et al., 2005).

Stimuli were delivered through a pneumatic MRI-compatible audio system (Avotec, Jensen Beach, FL) at approximately 85 dB. This system is equipped with an equalizer to provide a flat frequency response (+/−5 dB) at 150–4500 Hz, well encompassing the information in the speech signals. Stimuli were delivered at intervals between image acquisitions to prevent their contamination by the gradient noise.

During scanning, participants performed a same-different AX discrimination task (i.e., is the second sound in a pair exactly the same or different from the first?). A single trial was presented in each interval between image acquisitions, beginning 490 ms following the completion of an acquisition. The stimuli were 150 ms in duration separated by a 1010 ms interstimulus interval and followed by a 2710 ms response window. Phonemic and Nonphonemic stimuli were presented in blocks of 24 trials. For the Phonemic stimuli, each block consisted of two identical/ba/token pairs (3-3), two identical/da/token pairs (5-5), four pairs within the/ba/category (1–3, 3–1), four pairs within the/da/ category, eight two-step across-category pairs (3–5, 5–3), and four four-step across category pairs (1–5, 5–1, 3–7, 7–3). This distribution of stimulus pairs was selected so that approximately 50% of the Phonemic contrasts would be expected to be perceived as different in TD children (i.e. they span the category boundary), while 50% would be expected to be perceived as the same to prevent response bias. The same distribution of token-pairs was used for the Nonphonemic stimuli. Each run contained one block of Phonemic and one block of Nonphonemic stimuli as well as eight baseline silence trials. Two runs of these conditions were presented, with the order of the conditions counterbalanced across runs and participants. Two additional conditions were also presented in separate, alternating runs, and these results are not discussed here. Participants provided their responses using the thumb or index finger of one hand to indicate "same" and of the opposite hand to indicate "different". The specific hands used for each response option were counterbalanced, with seven participants in each group using the left hand to indicate "same" and right hand to indicate "different", and the remaining participants using the right hand for "same" and left for "different".

To evaluate categorical perception, separate d' scores (Macmillan and Creelman, 2005) were calculated for all sets of two-step pairs in the Phonemic and Nonphonemic conditions. Within each group and each condition, the d' scores for the pairs were compared to each other. Distributions were non-normal for the d' associated with the Phonemic token-pairs 1–3 in the group with dyslexia and the Nonphonemic token-pairs 5–7 in the control group. Therefore, Wilcoxon Signed-Ranks Tests were used to evaluate within-group performance differences across pairs. For the remaining analyses, AX discrimination in the Phonemic condition was expressed in terms of the Categorical Perception Index (CPI). The CPI was the difference between the d' scores for the across- and within-category trials. A larger CPI is indicative of greater categorical perception, i.e. relatively better discrimination across and poorer discrimination within categories. Age was added as a covariate for group comparisons.

2.5. *Image analysis*

Image processing and statistical analysis were performed using the Analysis of Functional Neuroimages (AFNI) software package (Cox, 1996). Within-subject analysis included volumetric image registration to minimize head motion artifacts. Functional volumes were aligned to the T1-weighted anatomical volume and smoothed with a 6 mm FWHM Gaussian kernel. Each voxel time series was then scaled to percent of mean signal level. Individual voxelwise multiple linear regression, with reference functions representing experimental conditions and regressors of no interest (across-condition-mean-removed RTs, global white matter signal, and six motion parameters), was performed. The use of an RT regressor helps to account for variance associated with differences in time-on-task or general task difficulty. With regard to motion, missed trials (i.e., trials on which the participant did not respond) and trials with greater than 10% outlier voxels (as identified using 3dToutcount) were removed from the analyses, and there was no significant difference between groups for either condition with regard to the number of remaining trials. Initially, the groups did significantly differ with regard to mean rotational parameters (root mean square (RMS)). One participant with dyslexia was an outlier (RMS > 4°). This participant was also an outlier with regard to translational parameters (RMS > 4 mm), and was removed from the analyses. Group differences were no longer significant after removal of this participant. A general linear test was conducted for the contrast between the Phonemic and Nonphonemic conditions. Individual anatomical scans and beta coefficient maps were transformed into standard stereotaxic space (Talairach and Tournoux, 1988).

Group maps were generated using random effects analysis. Age and scanner type were included as covariates in the analyses. 3dFWHMx was run using the residuals from both the individual and group-level analyses, which yielded similar results. The largest estimate of the smoothness of the noise in the data (from the group-level residuals), thus resulting in the most stringent threshold, was used for all analyses in order to be more conservative. Recent work has shown that the spatial autocorrelation function of fMRI noise does not follow a Gaussian shape, but rather has heavier tails (Eklund et al., 2016). Therefore, 3dClustSim with a spatial autocorrelation function of a mixed Gaussian plus mono-exponential form, which has longer tails than the Gaussian model, was used to generate the noise random fields, yielding a cluster threshold of 1931 mm^3 with a voxelwise $p < .01$ to achieve a mapwise threshold of $p < .05$. Differences between the typically developing and dyslexia groups, using age and scanner type as covariates, were examined. In addition, regression analyses were performed using the reading composite as a continuous variable across the full sample of 25 participants, with age and scanner type included as regressors of no interest. Follow-up analyses including CPI as a moderating variable and the TOVA ADHD score to examine and control for any potential effects of attention on the identified effects were also performed.

In an effort to balance the probability of Type I and Type II error, across the behavioral and follow-up fMRI analyses, Benjamini-Hochberg false discovery rate (FDR) correction (Benjamini and Hochberg, 1995) was done separately for each set of analyses (e.g., the set of behavioral differences across groups, the set of within-group categorical perception analyses, regressors of interest and post-hoc analyses for the regression analyses).

3. Results

3.1. Behavioral results

The demographic information and behavioral performances for both groups are summarized in Table 1. The children with dyslexia and the TD controls did not significantly differ with regard to age, sex, or socioeconomic status as measured using the Hollingshead Index (Hollingshead, 1975). On tests of intellectual functioning, the two groups did not significantly differ with regard to nonverbal intellectual abilities (corrected $p = .156$), but the group with dyslexia showed borderline significantly lower verbal intellectual abilities than the control group (corrected $p = .050$). There was no significant group difference seen on a nonverbal processing speed measure (corrected $p = .244$).

As expected, the dyslexia group performed significantly more poorly on all word and nonword reading decoding and fluency measures (corrected $ps < .001$) as well as measures of rapid naming abilities, phonological memory, and reading comprehension (corrected $ps = .017$, .049, and 0.009, respectively). The difference for phonological awareness was borderline significant after correction (corrected $p = .052$). The group with dyslexia also performed significantly below the TD group on the CELF-4 Language Memory Index, a composite score comprised of oral language tasks dependent on verbal working memory (corrected $p = .005$), although mean performance in the former group fell solidly in the average range. In addition, the groups showed significant differences on a formal test of attentional abilities (corrected $ps \leq .01$), as well as parent report of attentional difficulties (corrected $p = .023$). Importantly, while the group mean for the children with dyslexia on the formal attentional measure exceeded the cut-off indicative of ADHD-like performance (−1.80), mean and all individual parental ratings of attentional problems for the children in this group fell within the normal range. Teacher ratings were also available for all but three of the children with dyslexia, and these fell within the normal range as well.

With regard to the categorical discrimination tasks, both groups showed significantly greater discrimination of the between-category Phonemic token-pairs (3–5) than either of the within-category Phonemic pairs (1–3 or 5–7) (Dyslexia: corrected $ps < .05$, Control: corrected $ps < .001$), with no significant differences between the two within-category Phonemic pairs (corrected $ps > .4$). In contrast, there were no significant differences in discrimination among the three token-pairs for the Nonphonemic condition for either group (corrected $ps > .2$). Thus, both groups showed categorical perception of the Phonemic but not the Nonphonemic sounds. These results are shown in Table 2 and Fig. 1. The two groups did not significantly differ with regard to the response time on either the Phonemic or Nonphonemic discrimination tasks (corrected $ps = .650$ and .206, respectively). They also did not significantly differ with regard to the CPI for Phonemic sounds (corrected $p = .243$), the discrimination of within-category pairs (corrected $p = .650$), or the discrimination of the across-category pairs (corrected $p = .074$). Within- and across-boundary are not meaningful for the Nonphonemic condition; therefore, performance across the three types of 2-step pairs were averaged, and there were no significant group differences (corrected $p = .515$). In addition, they did not significantly differ with regard to the number of missed trials (i.e., the number of trials on which they did not respond) for either discrimination task, or to the number of responses or response times to any trial type in either condition (see Supplemental Table S1).

Table 2
Regions showing a significant group difference in the whole-brain analyses, with cluster size (volume in mm^3), z-scores (Max), Talairach coordinates (x, y, z), and location of local maxima.

Cluster Size	Max	x	y	z	Location
Dyslexia > Control					
Phonemic-Baseline					
2650 mm^3	−4.3	−7	−12	59	L supplementary motor area
	−3.5	−5	−4	43	L cingulate s
	−3.4	5	6	36	R cingulate g
Control > Dyslexia					
Phonemic-Nonphonemic					
2069 mm^3	3.4	−47	−46	−18	L inferior temporal g/ occipitotemporal s
	3.4	−49	−61	−6	L inferior temporal s
	3.0	−42	−58	−18	L fusiform g/occipitotemporal s
	3.0	−52	−53	−12	L inferior temporal g

Note. L = Left, R = Right, g = gyrus, s = sulcus.

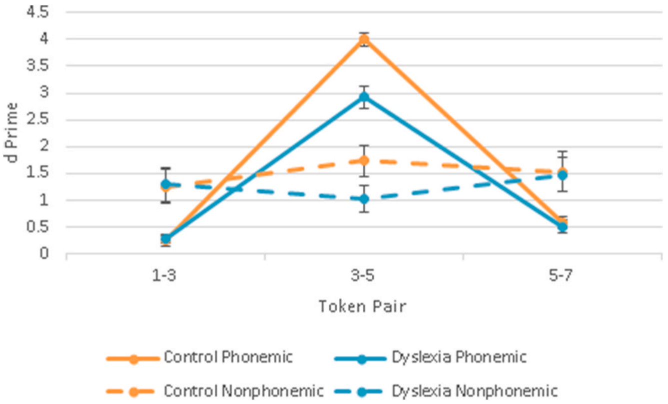


Fig. 1. Discrimination functions for the typically developing control group and the group with dyslexia in the Phonemic and Nonphonemic conditions. Error bars reflect standard error of measurement.

3.2. FMRI results

3.2.1. Group differences

In both the Phonemic and Nonphonemic conditions relative to baseline, both groups showed extensive bilateral perisylvian activation including frontal, temporal, and parietal regions, as well as activation in the anterior cingulate, insula, thalamus, and cerebellum (see Supplemental Fig. S1 and Supplemental Table S2). There were no significant group differences in the Nonphonemic condition relative to baseline. In the Phonemic condition relative to baseline (see Fig. 2A and Table 2), the dyslexia group showed significantly greater activation than the controls in the bilateral caudal anterior cingulate cortex and left supplementary motor area.

In the Phonemic relative to the Nonphonemic condition (see Fig. 2B and Table 2), significantly greater activation for the TD group than the group with dyslexia was seen in left vOTC, extending from the FG through the pOTS to the posterior inferior temporal gyrus (pITG) and inferior temporal sulcus (ITS). The average beta coefficients for the Phonemic and Nonphonemic conditions relative to baseline in this area were extracted to examine the simple effects. Age and scanner type were not significantly correlated with the beta coefficients and therefore were not included in the analyses. The TD group showed significantly greater activation than the group with dyslexia during the Phonemic condition relative to baseline ($t(23) = 3.728$, uncorrected $p = .001$, corrected $p = .004$). The group difference for the Nonphonemic condition relative to baseline was not significant ($t(23) = -1.830$, uncorrected $p = .08$, corrected $p = .08$). Within the dyslexia group, activation was significantly greater in the Nonphonemic than Phonemic condition ($t(11) = -2.813$, uncorrected $p = .017$, corrected $p = .023$), whereas activation was significantly greater in the Phonemic than Nonphonemic condition in the TD children ($t(12) = 3.459$, uncorrected $p = .005$, corrected $p = .01$).

3.2.2. Regression analyses across the full sample

Relationships between activation and performance on the reading composite were also examined at the voxel level across the full group of

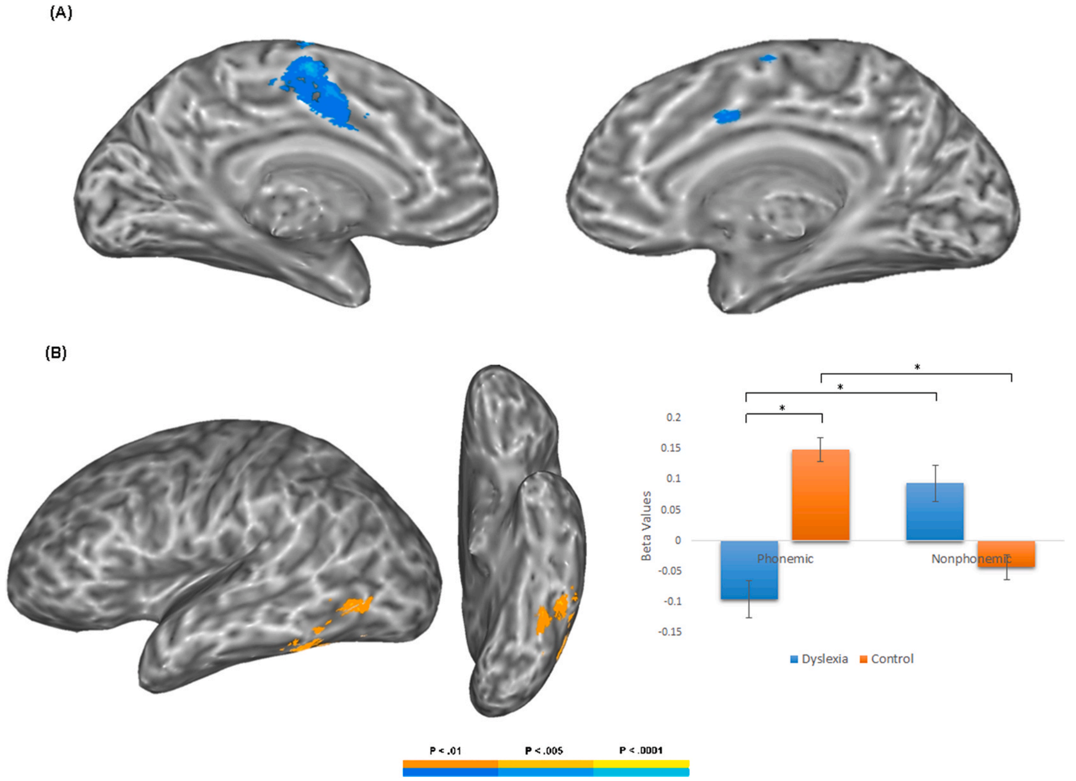


Fig. 2. Regions showing significant group differences in the whole-brain analyses in the (A) Phonemic condition relative to Baseline and in the (B) Phonemic relative to the Nonphonemic condition. Hot colors indicate greater activation in the typically developing controls than the group with dyslexia, and cool colors indicate the reverse. A graph of the simple effects is also shown for the latter contrast. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

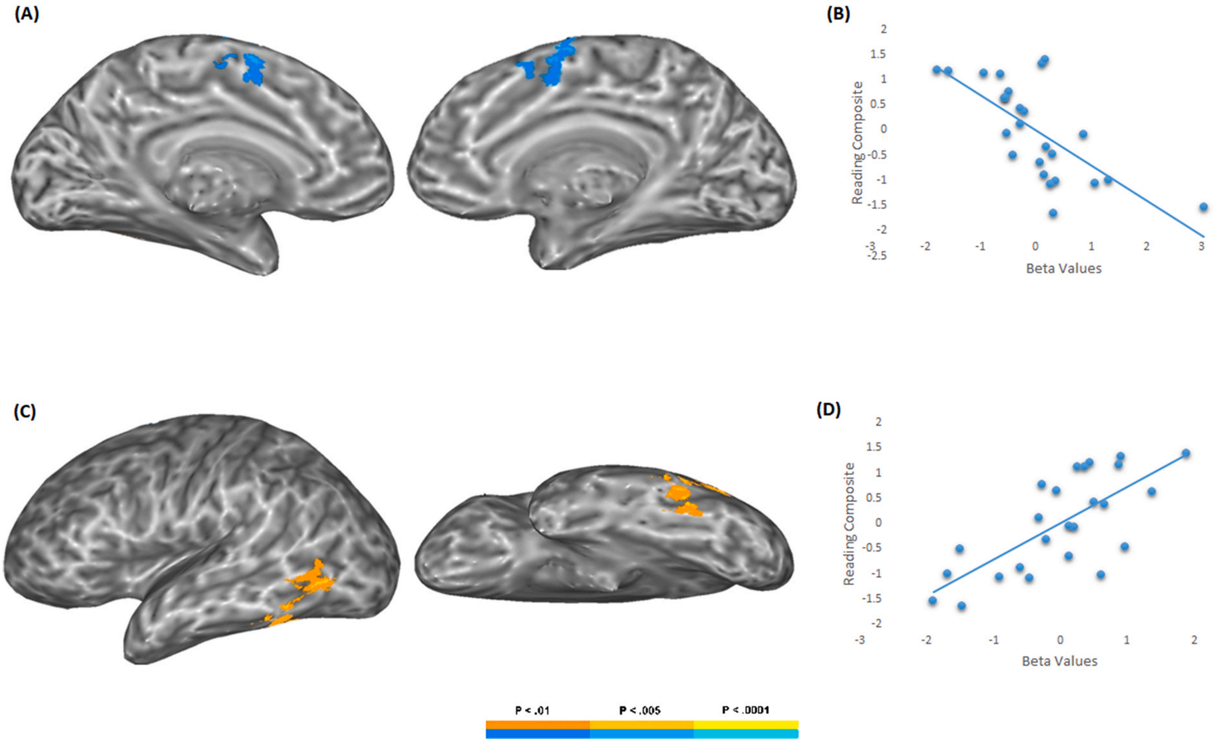


Fig. 3. Relationships between the Reading Composite and activation in the Phonemic condition relative to the Nonphonemic condition across the full sample while controlling for age and scanner type, showing clusters in the medial frontal cortex (A and B) and left occipitotemporal cortex (C and D).

25 participants in the Phonemic relative to the Nonphonemic condition, while controlling for age and scanner type. Similar to the group differences in the Phonemic relative to baseline condition, greater activation was seen in association with poorer reading performance in the bilateral supplementary motor area, extending into the pre-supplementary motor area on the right (see Fig. 3A and B). In addition, similar to the group comparison in the Phonemic relative to the Nonphonemic condition, greater activation in association with stronger reading performance was seen in the left vOTC, including the pOTS, FG, pITG, and ITS (see Fig. 3C and D). Evaluation of the relationship between reading performance and activation in the individual conditions relative to baseline controlling for age revealed a significant positive relationship between reading and activation in the Phonemic condition relative to baseline ($pr = .631$, uncorrected $p = .001$, corrected $p = .002$), while the relationship in the Nonphonemic condition was not significant ($pr = -.310$, uncorrected $p = .140$).

To investigate the nature of the relationships among activation associated with phoneme perception, reading performance, and categorical perception performance, a regression analysis was performed using the beta coefficients extracted from the left vOTC region found in the whole-brain analysis. In addition to age and the reading composite, CPI, and the CPI x reading composite interaction were included. There was a significant interaction between reading performance and CPI ($\beta = -.496$, $pr = -.651$, uncorrected $p = .001$, corrected $p = .004$). To elucidate this effect, the sample was split into high and low reading groups, which were the same whether identified using the original criteria for group membership or a median split of the reading composite scores (median = 94.7). Because age was significantly correlated with CPI scores across the full sample ($r = .406$, uncorrected $p = .044$), the correlations between CPI and activation in the left vOTC in each group were performed on the age-residualized values of each variable (across the full sample). The results, as shown in Fig. 4, showed a strong positive correlation between CPI and activation in the dyslexia group ($r = .693$, uncorrected $p = .012$, corrected $p = .021$), with a nonsignificant negative correlation observed in the control group ($r = -.439$, uncorrected $p = .133$, corrected $p = .186$).

In order to rule out the possibility that differences in attention accounted for the left vOTC findings, the TOVA ADHD score was first added to the regression equation using only age and the reading composite, and subsequently to the equation that included the CPI × reading interaction effect. The attention variable had no significant effect in either regression analysis (uncorrected $ps > .5$), and the effects of reading performance and the interaction remained significant (corrected $ps < .005$) after controlling for attention.

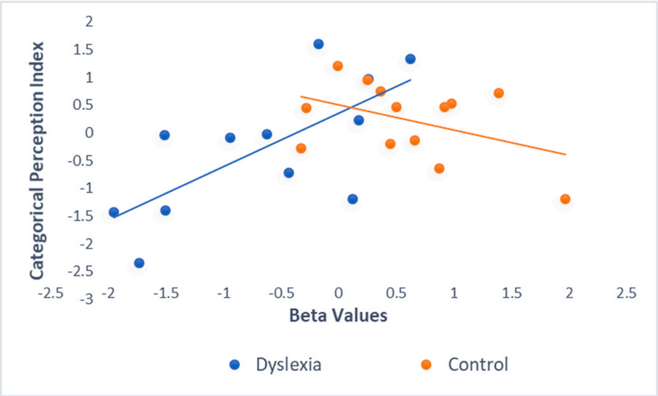


Fig. 4. Relationships between age-residualized CPI scores and activation in the left vOTC in the Phonemic relative to the Nonphonemic condition in low performing and high performing readers.

3.2.3. *Relationships with age in the TD group*

Because a significant relationship between CPI and activation in the left vOTC during the Phonemic task was seen in a previous study with TD children (Conant et al., 2014) with ages ranging from 7 through 12 years, but no significant relationship was seen in the TD children in the current study, which had a broader age range, the possibility that the relationship between these two variables changes with age was examined more closely. As an exploratory analysis, each of the groups was divided at the overall median for the entire sample (age 12.58 years), and the relationships between CPI and activation in the left vOTC for the Phonemic condition were examined in each subgroup using Spearman rank-order correlations given the very small sample sizes. In the dyslexia group, strong positive correlations were seen in both the younger ($n = 7$, $\rho = .536$, uncorrected $p = .215$) and older groups ($n = 5$, $\rho = .900$, uncorrected $p = .037$, corrected $p = .046$), although only the latter attained significance. In the TD group, both correlations attained significance but showed opposite directions of effects. Specifically, there was a strong positive correlation in the younger group ($n = 5$, $\rho = .900$, uncorrected $p = .037$, corrected $p = .046$), consistent with our previous findings (Conant et al., 2014), and a strong negative correlation in the older group ($n = 8$, $\rho = -.747$, uncorrected $p = .033$, corrected $p = .046$). The difference between these correlations was also significant ($z = 2.91$, uncorrected $p = .004$, corrected $p = .018$), suggesting that there may be a nonlinear relationship between CPI and activation in this region across age in typically developing children. In addition, if only the 15 children under the age of 13 from both groups were included in the regression, there was a significant effect of CPI on activation in the left vOTC region in the Phonemic relative to Nonphonemic condition ($\beta = .411$, $pr = .627$, $p = .016$) after controlling for the reading composite. CPI uniquely accounted for 16.3% of the variance in left vOTC activation above and beyond the 45.5% of the variance uniquely accounted for by reading performance ($\beta = .687$, $pr = .803$, $p = .001$).

Of note, while the two groups did not significantly differ in age, the age range was more limited at the upper end in the dyslexia group, with all children falling below the age of 15 years (dyslexia age range: 8.8–14.7; TD age range: 8.8–17.8). Although age was used as a covariate, it is clear that a nonlinear relationship may be present. To ensure that this difference did not account for the group findings, the analyses were re-run with the three members of the TD group above this age removed (TD age range: 8.8–14.5). These analyses revealed the same group difference in the left vOTC for the Phonemic relative to Nonphonemic condition contrast, and, in fact, significant activation was seen in this region for the TD group in the Phonemic condition relative to baseline (see Supplementary Fig. S2).

4. Discussion

Children with dyslexia showed significant differences with regard to brain activation during a speech perception task, and these differences overlapped with regions found in previous studies to differ between individuals with and without dyslexia when performing reading or phonological tasks with print stimuli, predominantly in the left vOTC. Specifically, for Phonemic relative to Nonphonemic discrimination, significant group differences were observed in the pOTS, FG, and ITG. In this area, the TD group showed significantly greater activation than the group with dyslexia for the Phonemic condition, while the difference for the Nonphonemic condition was not significant. Similar findings were obtained in a regression analysis examining activation associated with reading performance across the full sample. In addition, within the dyslexia group, greater activation in the left vOTC for the Phonemic relative to Nonphonemic condition was associated with better categorical perception of phonemes. Thus, increasing specialization of this region for phonemic relative to nonphonemic perception was associated with more categorical phoneme perception in the group with dyslexia and stronger reading performance across the full group.

Although significantly greater activation was seen in this region for the Phonemic relative to the Nonphonemic condition in the TD group, activation was not correlated with the CPI in this group. However, in a previous study with 7- to 12-year-old TD children (Conant et al., 2014), a positive relationship was found between categorical perception performance and activation in the left pOTS/FG in the Phonemic condition relative to baseline. The current study includes a wider age range, and it is possible that the relationship between phoneme perception and activation in this region changes nonlinearly with age. Preliminary analyses in the current sample in combination with the results of the prior study suggest that there may be a positive relationship between activation in this region and categorical perception of phonemes in the early stages of reading development, but this relationship may change direction around the age of 13 during typical reading development, as reading abilities are approaching more adult-like levels, and the region becomes more specialized for orthographic processing. At later ages, it may no longer be recruited or may only be recruited when the individual has not developed proficient categorical perception or reading abilities. Support for the possibility of a developmental change in the recruitment of the left vOTC for auditory language tasks comes from findings of greater involvement of this region during both visual and auditory word processing tasks in children but only during the visual tasks in adults (Booth et al., 2001; Church et al., 2008).

Of note, greater activation in this area for auditory words relative to nonspeech stimuli has also been reported in adults using tasks such as rhyming (Yoncheva et al., 2010), one-back matching (Ludersdorfer et al., 2013), and repetition (Price et al., 2003); however, in these studies, the differential activation across tasks actually reflected less de-activation relative to baseline in the word conditions than in the nonspeech conditions. Complex auditory tasks or selective attention to the auditory modality have been associated with suppression of activation in visual regions (Laurienti et al., 2002; Mozolic et al., 2008). These studies in adults suggest that, at later ages, while this area is not significantly activated in auditory phonological tasks, it may be selectively spared from suppression relative to other auditory tasks and other extrastriate regions (Yoncheva et al., 2010). In the previous study in younger typically developing children, the relationships between activation and categorical perception performance were strongest in the Phonemic relative to baseline condition, while they were more strongly seen in the Phonemic relative to Nonphonemic contrast in the current study. This may reflect an age-related trend toward reduced recruitment of this area in auditory phonological tasks and increased active suppression of this region in auditory non-speech tasks in typical development.

The relationship between left vOTC activation and categorical perception in children may reflect multiple different processes and could potentially be bidirectional in influence. One possibility is that the greater activation in TD children, particularly younger TD children, does not contribute to speech perception but simply reflects incidental retrieval of the orthographic representation during speech perception. This may be more likely to occur as phoneme-to-grapheme mappings are in the process of being established and subsequently decrease after a high degree of automaticity in both speech perception and reading have been achieved.

Alternatively, one of the proposed functions of the VWFA is the extraction of abstract orthographic representations (Dehaene et al., 2001, 2004; Polk and Farah, 2002), and it is possible that speech perception abilities are important for development in this domain. Similar to phonemes in the auditory modality, different instances of the same letters or frequently encountered letter sequences must be recognized quickly, despite variations in visual appearance, in order for fluent reading to occur. Activation in the VWFA has been found to be invariant to many visual characteristics that are irrelevant to letter identification, such as case, size, vertical or horizontal orientation, and retinal location (Cai et al., 2010; Dehaene et al., 2004, 2001; Polk and Farah, 2002), while showing significant sensitivity to statistical familiarity of letter sequences (Binder et al., 2006). Phonology may play an integral role in the development of abstract orthographic representations (Bowers and Michita, 1998), and the importance of phonology to the development of activation in left vOTC was suggested by a study in which activation was found in a region just lateral to the left pOTS in adults for newly learned letters but only if learned in association with speech sounds as opposed to nonspeech sounds (Hashimoto and Sakai, 2004). Other studies in adults have suggested that the VWFA region is sensitive to the presence of phonological task demands (Mano et al., 2013) and spelling-sound consistency (Graves et al., 2010), providing further support for a role of this region in linking phonology and orthography. Thus, in development, strong phoneme category representations may be directly related to optimal development of abstract orthographic representations in the left vOTC and/or of the mapping between orthographic and phonological representations during reading acquisition.

A reverse directional relationship, in which activation in the left vOTC supports the development of phoneme perception in children, is also possible. Given that speech perception undergoes substantial development prior to reading acquisition, and deficits in this area have been seen in prereaders at risk for dyslexia, an examination of whether abnormalities exist in the structure and function of the VWFA region in individuals with dyslexia prior to literacy instruction may help to elucidate this area's potential role in speech perception. Structural studies are somewhat mixed regarding the presence of abnormalities in this area in children at risk for dyslexia prior to reading experience. Clark et al. (2014) only found cortical thickness differences in this area in males with dyslexia relative to TD children after the age of 11, and not in the full group at that age nor in the 6-year-old children who would later develop dyslexia. In contrast, Raschle et al. (2011) reported decreased gray matter volume in the left vOTC in pre-reading children with a family history of dyslexia (FHD+) relative to those without a family history (FHD-). With regard to possible functional differences, Debska et al. (2016) used fMRI prior to and after initial formal literacy instruction in groups of children who were either at familial risk for dyslexia (FHD+) or not at risk (FHD-). In the kindergarten group, who had not yet started formal reading instruction, there was greater activation in multiple regions bilaterally, including the left fusiform gyrus and more posterior inferior occipital and lingual gyri in the FHD-group relative to the FHD + group during an auditory rhyming task relative to a voice gender matching task. In addition, within the FHD + group, activation specifically in these left vOT regions was correlated with performance on an auditory pseudoword rhyming task. This would suggest that the left vOTC is involved in phonological tasks prior to the establishment of orthographic representations.

This leads to the question of how this more visual region might be involved in the development or refinement of speech perception or phonological processing prior to reading acquisition. In this regard, Saygin et al. (2016) used fMRI in TD children at age 5 before they learned to read and again at age 8 to examine the pre-reading functional connectivity of the vOT region that would later show orthographic selectivity. They found significantly greater connectivity of this region with multiple brain areas implicated in auditory, speech, and language processing, including the left transverse temporal gyrus, superior and middle temporal gyri, and the angular gyrus, than seen in a neighboring, more medial area, known as the fusiform face area (FFA), which shows preferential activation for faces. Similar connectivity findings have been reported in anatomical (Bouhali et al., 2014) and functional (Stevens et al., 2017) studies of the VWFA in adults, but this study suggests that these connectivity patterns predate reading instruction.

It is possible that these connections subserve the audiovisual integration of speech sounds with facial articulatory movements early in development (Hannagan et al., 2015). As noted, the VWFA is in close proximity to the left hemisphere FFA. The FFA is generally considered to be bilateral but with a rightward predominance (Kanwisher and Yovel, 2006), while the more lateral VWFA is left lateralized. A study in children found a correlation between susceptibility to the McGurk effect, which requires audiovisual integration of speech sounds and facial articulatory movements, and activation not only in the left superior temporal sulcus, as has been seen in adults, but also in the bilateral FG, with the left-sided region of activation falling in the vicinity of the VWFA (Nath et al., 2011). Similarly, an fMRI study using independent component analysis of data obtained during an audiovisual speech integration task in adults with and without dyslexia found a main effect of group in a component containing bilateral FG, including a left hemisphere region also in the vicinity of the VWFA (Russeler et al., 2018). In addition, a close relationship between the neuroanatomical substrates of speechreading and reading in adults was suggested by a clinical case study that showed a double dissociation between the pattern of impairments of two patients with posterior cerebral artery infarcts resulting in vOT lesions in opposite hemispheres (Campbell et al., 1986). The patient with right occipitotemporal damage demonstrated prosopagnosia and topographagnosia with intact lipreading but impaired recognition and classification of facial expressions, whereas the patient with a left-hemisphere lesion showed alexia and impaired lipreading with intact face recognition and interpretation of facial expressive gestures. Furthermore, both children and adults with dyslexia have been found to benefit significantly less from lip-read information that would disambiguate noise-masked speech (van Laarhoven et al., 2018). Thus, it is possible that this region contributes to the development and refinement of speech perception through face-to-speech circuitry and that early dysfunction in this region or its connectivity may contribute to speech perception difficulties in at least some individuals with dyslexia. In typical development, this region may continue to be recruited during speech perception until full maturation or automaticity of the latter is reached, with gradual lessening of its involvement as the region becomes increasingly selective for audiovisual mapping of orthographic visual input to phonological forms.

The greater deactivation of the left vOTC in the Nonphonemic condition relative to the Phonemic condition in the children with dyslexia may reflect cross-modal suppression associated with attention to the auditory modality in the context of less categorical perception of phonemes and decreased audiovisual integration for speech perception. The children with dyslexia may recognize the phonemic sounds as familiar but may need to devote greater attentional resources to the auditory processing of these stimuli in an effort to discriminate the phonemes. This may result in greater de-activation of visual regions in the Phonemic condition than the Nonphonemic condition. In support of this interpretation, regions in bilateral medial frontal cortex, including the SMA and dorsal anterior cingulate, were more activated for the group with dyslexia than the TD children in the Phonemic condition relative to baseline and showed an inverse relationship with reading ability in the Phonemic condition relative to the Nonphonemic condition in the full sample. Greater activation in right medial frontal cortex in individuals with dyslexia has been reported in two previous meta-analyses (Paulesu et al., 2014; Richlan et al., 2009). In addition, greater activation in the left SMA for words and bilateral SMA for pseudowords was seen in individuals with dyslexia relative to controls when performing a phonological lexical decision task (Richlan et al., 2010). In typical development, activation in the SMA is routinely observed during both covert and overt speech production tasks and has been thought to potentially reflect articulatory planning (Brown et al., 2009; Indefrey and Levelt, 2004). Importantly, this area has also been implicated in aspects of auditory processing, including speech processing under challenging conditions such as distortion or decreased intelligibility of the speech stimuli (Adank, 2012; Lima et al., 2016). The role of this area may reflect not only its involvement in articulation but also more executive control processes (Lima et al., 2016). With regard to the latter, the anterior cingulate cortex has also been implicated in conflict monitoring, error monitoring, and the allocation of cognitive control (Heilbronner and Hayden, 2016; Shenhav et al., 2013). Thus, the greater activation of these regions in the group with dyslexia for the phonemic stimuli may reflect the increased difficulty of this task for this group and associated need for greater allocation of resources to the auditory discrimination of the phonemes, potentially involving auditory-motor associations as opposed to auditory-visual ones.

4.1. Limitations and future directions

In the current study, a significant limitation is the small sample size and resulting low power. However, the findings from the small group comparisons were also replicated using a regression analysis in the full sample of 25 participants. In addition, the finding of activation in the left vOTC during performance of a categorical phoneme perception task is consistent with a previous finding by our group in a completely separate sample of typically developing children (Conant et al., 2014), which provides support for the reliability of this finding. The comparison of the pattern of results across studies did highlight the need for larger samples in different age ranges to examine the developmental trajectory of the relationships between categorical perception ability and activation in TD children and children with dyslexia.

There were insufficient trials to separately examine activation associated with across-category and within-category judgments. The perceptual warping that characterizes categorical perception occurs for both types of trials, but in different directions (i.e., stronger across- and weaker within-category perception), and categorical perception is defined by the discrepancy between the two. Thus, this discrepancy was the focus in the current study. In addition, in our previous work with a similar paradigm in adults (Liebenthal et al., 2005), we did not find any significant differences in activation between the two types of trials. Furthermore, using a voice-onset-time discrimination task, Hutchison and colleagues (Hutchison et al., 2008) found no significant differences in activation between their across-category and within-category trials, although additional activation was seen in the right inferior and middle frontal gyri for the more difficult 15-ms across-category trials, but not the within-category trials or 30-ms across category trials, when contrasted with a tone discrimination task. The latter likely reflected more domain-general decision-making processes, which were not the focus of the current investigation. However, given that Ruff et al. (2003) did find differential patterns of activation between groups when passively listening to the different sets of stimuli, there could be group differences specific to the different trial types, which may be useful to investigate in future work.

In addition, investigation of activation associated with categorical phoneme perception in pre-readers with and without a familial history of dyslexia will be important in order to determine whether the relationship between vOTC activation and categorical phoneme perception precedes reading acquisition. It is possible that activation differences associated with categorical perception may represent a subtype, or specific phenotype, that could be beneficial in identifying genetic risk alleles and developing targeted interventions that could then be implemented early in development. Segregation analyses, twin studies, and molecular-genetic studies have provided substantial evidence of genetic influences on reading, reading-related subskills, and dyslexia (for review, see Schumacher et al., 2007). The genetic basis of this disorder is complex, and progress in this area has been hindered by the lack of homogeneous phenotypes and the developmental variability in behavioral manifestations (Skiba et al., 2011). The identification of specific patterns of activation associated with the performance of contributing skills may ultimately assist in delineating subgroups with more similar genetic bases despite the development of disparate reading performances over time. The identification of genetic markers associated with very specific phenotypes would allow for earlier identification of children at risk for dyslexia and the implementation of targeted interventions even before children are faced with the task of learning to read.

Declaration of competing interest

None.

CRediT authorship contribution statement

Lisa L. Conant: Conceptualization, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration, Funding acquisition. **Einat Liebenthal:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition. **Anjali Desai:** Data curation, Formal analysis, Investigation. **Mark S. Seidenberg:** Writing - review & editing. **Jeffrey R. Binder:** Conceptualization, Writing - review & editing.

Acknowledgments

This work was supported by the National Institute of Child Health and Human Development (R21 HD054824 to LC) and CTSA Grant Number 1UL1RR031973 from the National Center for Research Resources. The authors are grateful for the generous donation of time and effort made by the children and parents who participated in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2020.107543.

References

Achenbach, T.M., Rescorla, L.A., 2001. Manual for the ASEBA School-Age Forms & Profiles. University of Vermont, Research Center for Children, Youth, and Families, Burlington, VT.

Adank, P., 2012. The neural bases of difficult speech comprehension and speech production: two Activation Likelihood Estimation (ALE) meta-analyses. Brain Lang. 122, 42–54. https://doi.org/10.1016/j.bandl.2012.04.014.

Adlard, A., Hazan, V., 1998. Speech perception in children with specific reading difficulties (dyslexia). Q. J. Exp. Psychol. 51, 153–177. https://doi.org/10.1080/713755750.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B 57, 289–300.

Binder, J.R., Medler, D. a, Westbury, C.F., Liebenthal, E., Buchanan, L., 2006. Tuning of the human left fusiform gyrus to sublexical orthographic structure. Neuroimage 33, 739–748. https://doi.org/10.1016/j.neuroimage.2006.06.053.

Binder, J.R., Mohr, J.P., 1992. The topography of callosal reading pathways. A case-control analysis. Brain 115, 1807–1826. https://doi.org/10.1093/brain/115.6.1807.

Blomert, L., Mitterer, H., 2004. The fragile nature of the speech-perception deficit in dyslexia: natural vs synthetic speech. Brain Lang. 89, 21–26. https://doi.org/10.1016/S0093-934X(03)00305-5.

Boets, B., Ghesquière, P., van Wieringen, A., Wouters, J., 2007. Speech perception in preschoolers at family risk for dyslexia: relations with low-level auditory processing and phonological ability. Brain Lang. 101, 19–30. https://doi.org/10.1016/j.bandl.2006.06.009.

Bogliotti, C., Serniclaes, W., Messaoud-Galusi, S., Sprenger-Charolles, L., 2008. Discrimination of speech sounds by children with dyslexia: comparisons with chronological age and reading level controls. J. Exp. Child Psychol. 101, 137–155. https://doi.org/10.1016/j.jecp.2008.03.006.

Bonte, M., Correia, J.M., Keetels, M., Vroomen, J., Formisano, E., 2017. Reading-induced shifts of perceptual speech representations in auditory cortex. Sci. Rep. 7, 1–11. https://doi.org/10.1038/s41598-017-05356-3.

Booth, J.R., Burman, D.D., Van Santen, F.W., Harasaki, Y., Gitelman, D.R., Parrish, T.B., Marsel Mesulam, M.M., 2001. The development of specialized brain systems in reading and oral-language. Child Neuropsychol. 7, 119–141. https://doi.org/10.1076/chin.7.3.119.8740.

Bouhali, F., Thiebaut de Schotten, M., Pinel, P., Poupon, C., Mangin, J.-F., Dehaene, S., Cohen, L., 2014. Anatomical connections of the visual word form area. J. Neurosci. 34, 15402–15414. https://doi.org/10.1523/JNEUROSCI.4918-13.2014.

Bowers, J., Michita, Y., 1998. An investigation into the structure and acquisition of orthographic knowledge: evidence from cross-script Kanji-Hiragana priming. Psychon. Bull. Rev. 5, 259–264. https://doi.org/10.3758/BF03212948.

Brandt, J., Rosen, J.J., 1980. Auditory phonemic perception in dyslexia: categorical identification and discrimination of stop consonants. Brain Lang. 9, 324–337. https://doi.org/10.1016/0093-934x(80)90152-2.

Breier, J.I., Fletcher, J.M., Denton, C., Gray, L.C., 2004. Categorical perception of speech stimuli in children at risk for reading difficulty. J. Exp. Child Psychol. 88, 152–170. https://doi.org/10.1016/j.jecp.2004.03.003.

Breier, J.I., Gray, L., Fletcher, J.M., Diehl, R.L., Klaas, P., Foorman, B.R., Molis, M.R., 2001. Perception of voice and tone onset time continua in children with dyslexia with and without attention deficit/hyperactivity disorder. J. Exp. Child Psychol. 80, 245–270. https://doi.org/10.1006/jecp.2001.2630.

Breier, J.I., Simos, P.G., Fletcher, J.M., Castillo, E.M., Zhang, W., Papanicolaou, A.C., 2003. Abnormal activation of temporoparietal language areas during phonetic analysis in children with dyslexia. Neuropsychology 17, 610–621. https://doi.org/10.1037/0894-4105.17.4.610.

Brown, S., Laird, A.R., Pfordresher, P.Q., Thelen, S.M., Turkeltaub, P., Liotti, M., 2009. The somatotopy of speech: phonation and articulation in the human motor cortex. Brain Cognit. 70, 31–41. https://doi.org/10.1016/j.bandc.2008.12.006.

Cai, Q., Paulignan, Y., Brysbaert, M., Ibarrola, D., Nazir, T. a, 2010. The left ventral occipito-temporal response to words depends on language lateralization but not on visual familiarity. Cerebr. Cortex 20, 1153–1163. https://doi.org/10.1093/cercor/bhp175.

Campbell, R., Landis, T., Regard, M., 1986. Face recognition and lipreading. A neurological dissociation. Brain 109, 509–521. https://doi.org/10.1093/brain/109.3.509.

Chiappe, P., Chiappe, D.L., Siegel, L.S., 2001. Speech perception, lexicality, and reading skill. J. Exp. Child Psychol. 80, 58–74. https://doi.org/10.1006/jecp.2000.2624.

Church, J.A., Coalson, R.S., Lugar, H.M., Petersen, S.E., Schlaggar, B.L., 2008. A developmental fMRI study of reading and repetition reveals changes in phonological and visual mechanisms over age. Cerebr. Cortex 18, 2054–2065. https://doi.org/10.1093/cercor/bhm228.

Clark, K.A., Helland, T., Specht, K., Narr, K.L., Manis, F.R., Toga, a W., Hugdahl, K., 2014. Neuroanatomical precursors of dyslexia identified from pre-reading through to age 11. Brain 137, 3136–3141. https://doi.org/10.1093/brain/awu229.

Cohen, L., Dehaene, S., Naccache, L., Lehéricy, S., Dehaene-Lambertz, G., Hénaff, M. a, Michel, F., 2000. The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain 123 (Pt 2), 291–307. https://doi.org/10.1093/brain/123.2.291.

Cohen, L., Martinaud, O., Kener, C., Lehericy, S., Samson, Y., Obadia, M., Slachevsky, A., Dehaene, S., 2003. Visual word recognition in the left and right hemispheres: anatomical and functional correlates of peripheral alexias. Cerebr. Cortex 13, 1313–1333. https://doi.org/10.1093/cercor/bhg079.

Conant, L.L., Liebenthal, E., Desai, A., Binder, J.R., 2014. FMRI of phonemic perception and its relationship to reading development in elementary-to middle-school-age children. Neuroimage 89, 192–202. https://doi.org/10.1016/j.neuroimage.2013.11.055.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173. https://doi.org/10.1006/cbmr.1996.0014.

de Gelder, B., Vroomen, J., 1998. Impaired speech perception in poor readers: evidence from hearing and speech reading. Brain Lang. 64, 269–281. https://doi.org/10.1006/brln.1998.1973.

Debska, A., Łuniewska, M., Chyl, K., Banaszkiewicz, A., Zelechowska, A., Wypych, M., Marchewka, A., Pugh, K.R., Jednoróg, K., 2016. Neural basis of phonological awareness in beginning readers with familial risk of dyslexia-Results from shallow orthography. Neuroimage 132, 406–416. https://doi.org/10.1016/j.neuroimage.2016.02.063.

Dehaene, S., Jobert, A., Naccache, L., Ciuciu, P., Poline, J.-B., Le Bihan, D., Cohen, L., 2004. Letter binding and invariant recognition of masked words: behavioral and neuroimaging evidence. Psychol. Sci. 15, 307–313. https://doi.org/10.1111/j.0956-7976.2004.00674.x.

Dehaene, S., Naccache, L., Cohen, L., Bihan, D.L., Mangin, J.F., Poline, J.B., Rivière, D., 2001. Cerebral mechanisms of word masking and unconscious repetition priming. Nat. Neurosci. 4, 752–758. https://doi.org/10.1038/89551.

Desai, R., Liebenthal, E., Waldron, E., Binder, J.R., 2008. Left posterior temporal regions are sensitive to auditory categorization. J. Cognit. Neurosci. 20, 1174–1188. https://doi.org/10.1162/jocn.2008.20081.

DeWitt, I., Rauschecker, J.P., 2012. Phoneme and word recognition in the auditory ventral stream. Proc. Natl. Acad. Sci. U.S.A. 109, E505–E514. https://doi.org/10.1073/pnas.1113427109.

Dufor, O., Serniclaes, W., Sprenger-Charolles, L., Démonet, J.-F., 2007. Top-down processes during auditory phoneme categorization in dyslexia: a PET study. Neuroimage 34, 1692–1707. https://doi.org/10.1016/j.neuroimage.2006.10.034.

Edmister, W.B., Talavage, T.M., Ledden, P.J., Weisskoff, R.M., 1999. Improved auditory cortex imaging using clustered volume acquisitions. Hum. Brain Mapp. 7, 89–97. https://doi.org/10.1002/(SICI)1097-0193(1999)7:2<89::AID-HBM2>3.0.CO;2-N.

Eklund, A., Nichols, T.E., Knutsson, H., 2016. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proceedings of the National Academy of Sciences. https://doi.org/10.1073/pnas.1602413113.

Fletcher, J.M., Shaywitz, S.E., Shankweiler, D.P., Katz, L., Liberman, I.Y., Stuebing, K.K., Francis, D.J., Fowler, A.E., Shaywitz, B.A., 1994. Cognitive profiles of reading disability: comparisons of discrepancy and low achievement definitions. J. Educ. Psychol. 86, 6–23. https://doi.org/10.1037/0022-0663.86.1.6.

Godfrey, J.J., Syrdal-Lasky, A.K., Millay, K.K., Knox, C.M., 1981. Performance of dyslexic children on speech perception tests. J. Exp. Child Psychol. 32, 401–424. https://doi.org/10.1016/0022-0965(81)90105-3.

Graves, W.W., Desai, R., Humphries, C., Seidenberg, M.S., Binder, J.R., 2010. Neural systems for reading aloud: a multiparametric approach. Cerebr. Cortex 20, 1799–1815. https://doi.org/10.1093/cercor/bhp245.

Grigorenko, E.L., 2001. Developmental dyslexia: an update on genes, brains, and environments. JCPP (J. Child Psychol. Psychiatry) 42, 91–125. https://doi.org/10.1111/1469-7610.00704.

Guttorm, T.K., Leppänen, P.H.T., Hämäläinen, J.A., Eklund, K.M., Lyytinen, H.J., 2010. Newborn event-related potentials predict poorer pre-reading skills in children at risk for dyslexia. J. Learn. Disabil. 43, 391–401. https://doi.org/10.1177/0022219409345005.

Guttorm, T.K., Leppanen, P.H.T., Richardson, U., Lyytinen, H., 2001. Event-related potentials and consonant differentiation in newborns with familial risk for dyslexia. J. Learn. Disabil. 34, 534–544. https://doi.org/10.1177/002221940103400606.

Hancock, R., Richlan, F., Hoeft, F., 2017. Possible roles for fronto-striatal circuits in reading disorder. Neurosci. Biobehav. Rev. 72, 243–260. https://doi.org/10.1016/j.neubiorev.2016.10.025.

Hannagan, T., Amedi, A., Cohen, L., Dehaene-Lambertz, G., Dehaene, S., 2015. Origins of the specialization for letters and numbers in ventral occipitotemporal cortex. Trends Cognit. Sci. 19, 374–382. https://doi.org/10.1016/j.tics.2015.05.006.

Hashimoto, R., Sakai, K.L., 2004. Learning letters in adulthood: direct visualization of cortical plasticity for forming a new link between orthography and phonology. Neuron 42, 311–322. https://doi.org/10.1016/S0896-6273(04)00196-5.

Heilbronner, S.R., Hayden, B.Y., 2016. Dorsal anterior cingulate cortex : a bottom-up view. Annu. Rev. Neurosci. 39, 149–170. https://doi.org/10.1146/annurev-neuro-070815-013952.

Hollingshead, A.B., 1975. Four Factor Index of Social Status. Yale University, Department of Sociology, New Haven, CT. Unpublished Manuscript.

Hurford, D.P., 1990. Training phonemic segmentation ability with a phonemic discrimination intervention in second-and third-grade children with reading disabilities. J. Learn. Disabil. 23, 564–569. https://doi.org/10.1177/002221949002300906.

Hutchison, E.R., Blumstein, S.E., Myers, E.B., 2008. An event-related fMRI investigation of voice-onset time discrimination. Neuroimage 40, 342–352. https://doi.org/10.1016/j.neuroimage.2007.10.064.

Indefrey, P., Levelt, W.J.M., 2004. The spatial and temporal signatures of word production components. Cognition 92, 101–144. https://doi.org/10.1016/j.cognition.2002.06.001.

Joannisse, M.F., Manis, F.R., Keating, P., Seidenberg, M.S., 2000. Language deficits in dyslexic children: speech perception, phonology, and morphology. J. Exp. Child Psychol. 77, 30–60. https://doi.org/10.1006/jecp.1999.2553.

Kanwisher, N., Yovel, G., 2006. The fusiform face area: a cortical region specialized for the perception of faces. Philos. Trans. R. Soc. B Biol. Sci. 361, 2109–2128. https://doi.org/10.1098/rstb.2006.1934.

Laurienti, P.J., Burdette, J.H., Wallace, M.T., Yen, Y.-F., Field, A.S., Stein, B.E., 2002. Deactivation of sensory-specific cortex by cross-modal stimuli. J. Cognit. Neurosci. 14, 420–429. https://doi.org/10.1162/089892902317361930.

Leark, R.A., Dupuy, T.R., Greenberg, L.M., Corman, C.L., Kinschi, C.L., 1999. T.O.V.A. Test of variables of attention. Universal Attention Disorders. Inc., Los Alamitos, CA.

Leff, A.P., Spitsyna, G., Plant, G.T., Wise, R.J.S., 2006. Structural anatomy of pure and hemianopic alexia. J. Neurol. Neurosurg. Psychiatry 77, 1004–1007. https://doi.org/10.1136/jnnp.2005.086983.

Leppänen, P.H., Pihko, E., Eklund, K.M., Lyytinen, H., 1999. Cortical responses of infants with and without a genetic risk for dyslexia: II. Group effects. Neuroreport 10, 969–973. https://doi.org/10.1097/00001756-199904060-00014.

Leppänen, P.H.T., Hämäläinen, J.A., Guttorm, T.K., Eklund, K.M., Salminen, H., Tanskanen, A., Torppa, M., Puolakanaho, A., Richardson, U., Pennala, R., Lyytinen, H., 2011. Infant brain responses associated with reading-related skills before school and at school age. Neurophysiol. Clin. 42, 35–41. https://doi.org/10.1016/j.neucli.2011.08.005.

Leppänen, P.H.T., Richardson, U., Pihko, E., Eklund, K.M., Guttorm, T.K., Aro, M., Lyytinen, H., 2002. Brain responses to changes in speech sound durations differ between infants with and without familial risk for dyslexia. Dev. Neuropsychol. 22, 407–422. https://doi.org/10.1207/S15326942dn2201_4.

Liebenthal, E., Binder, J.R., Spitzer, S.M., Possing, E.T., Medler, D.A., 2005. Neural substrates of phonemic perception. Cerebr. Cortex 15, 1621–1631. https://doi.org/10.1093/cercor/bhi040.

Liebenthal, E., Desai, R., Ellingson, M.M., Ramachandran, B., Desai, A., Binder, J.R., 2010. Specialization along the left superior temporal sulcus for auditory categorization. Cerebr. Cortex 20, 2958–2970. https://doi.org/10.1093/cercor/bhq045.

Lieberman, P., Meskill, R.H., Chatillon, M., Schupack, H., 1985. Phonetic speech perception deficits in dyslexia. J. Speech Hear. Res. 28, 480–486. https://doi.org/10.1044/jshr.2804.480.

Lima, C.F., Krishnan, S., Scott, S.K., 2016. Roles of supplementary motor areas in auditory processing and auditory imagery. Trends Neurosci. 39, 527–542. https://doi.org/10.1016/j.tins.2016.06.003.

Linkersdörfer, J., Lonnemann, J., Lindberg, S., Hasselhorn, M., Fiebach, C.J., 2012. Grey matter alterations co-localize with functional abnormalities in developmental dyslexia: an ALE meta-analysis. PloS One 7, e43122. https://doi.org/10.1371/journal.pone.0043122.

Ludersdorfer, P., Schurz, M., Richlan, F., Kronbichler, M., Wimmer, H., 2013. Opposite effects of visual and auditory word-likeness on activity in the visual word form area. Front. Hum. Neurosci. 7, 491. https://doi.org/10.3389/fnhum.2013.00491.

Lyon, G.R., 1995. Research initiatives in learning disabilities: contributions from scientists supported by the national Institute of child Health and human development. J. Child Neurol. 10 (Suppl. 1), S120–S126. https://doi.org/10.1177/08830738950100S126.

Lyon, G.R., Chhabra, V., 1996. The current state of science and the future of specific reading disability. Ment. Retard. Dev. Disabil. Res. Rev. 2, 2–9. https://doi.org/10.1002/(SICI)1098-2779(1996)2:1<2::AID-MRDD2>3.0.CO;2-X.

Lyytinen, H., Ahonen, T., Eklund, K., Guttorm, T., Kulju, P., Laakso, M.L., Leiwo, M., Leppänen, P., Lyytinen, P., Poikkeus, A.M., Richardson, U., Torppa, M., Viholainen, H., 2004. Early development of children at familial risk for dyslexia–follow-up from birth to school age. Dyslexia 10, 146–178. https://doi.org/10.1002/dys.274.

Maassen, B., Groenen, P., 2001. Identification and discrimination of voicing and place-of-articulation in developmental dyslexia. Clin. Linguist. Phon. 15, 319–339. https://doi.org/10.1080/02699200010026102.

Macmillan, N.A., Creelman, C.D., 2005. Detection Theory: A User's Guide, second ed. Lawrence Erlbaum Associates, Inc., Mahwah, NJ.

Magnan, A., Ecalle, J., 2006. Audio-visual training in children with reading disabilities. Comput. Educ. 46, 407–425. https://doi.org/10.1016/j.compedu.2004.08.008.

Magnan, A., Ecalle, J., Veuillet, E., Collet, L., 2004. The effects of an audio-visual training program in dyslexic children. Dyslexia 10, 131–140. https://doi.org/10.1002/dys.270.

Maisog, J.M., Einbinder, E.R., Flowers, D.L., Turkeltaub, P.E., Eden, G.F., 2008. A meta-analysis of functional neuroimaging studies of dyslexia. Ann. N. Y. Acad. Sci. 1145, 237–259. https://doi.org/10.1196/annals.1416.024.

Manis, F., Keating, P., 2005. Speech perception in dyslexic children with and without language impairments. In: Catts, H.W., Kamhi, H.G. (Eds.), The Connections between Language and Reading. Lawrence Erlbaum, Mahwah, NJ, pp. 77–99.

Manis, F.R., Mcbride-Chang, C., Seidenberg, M.S., Keating, P., Doi, L.M., Munson, B., Petersen, A., 1997. Are speech perception deficits associated with developmental dyslexia? J. Exp. Child Psychol. 66, 211–235. https://doi.org/10.1006/jecp.1997.2383.

Mano, Q.R., Humphries, C., Desai, R.H., Seidenberg, M.S., Osmon, D.C., Stengel, B.C., Binder, J.R., 2013. The role of left occipitotemporal cortex in reading: reconciling stimulus, task, and lexicality effects. Cerebr. Cortex 23, 988–1001. https://doi.org/10.1093/cercor/bhs093.

Martin, A., Kronbichler, M., Richlan, F., 2016. Dyslexic brain activation abnormalities in deep and shallow orthographies: a meta-analysis of 28 functional neuroimaging studies. Hum. Brain Mapp. 2699, 2676–2699. https://doi.org/10.1002/hbm.23202.

Martin, A., Schurz, M., Kronbichler, M., Richlan, F., 2015. Reading in the brain of children and adults: a meta-analysis of 40 functional magnetic resonance imaging studies. Hum. Brain Mapp. 36, 1963–1981. https://doi.org/10.1002/hbm.22749.

McBride-Chang, C., 1996. Models of speech perception and phonological processing in reading. Child Dev. 67, 1836–1856. https://doi.org/10.1111/j.1467-8624.1996.tb01831.x.

McCandliss, B.D., Cohen, L., Dehaene, S., 2003. The visual word form area: expertise for reading in the fusiform gyrus. Trends Cognit. Sci. 7, 293–299. https://doi.org/10.1016/S1364-6613(03)00134-7.

McGrath, L.M., Pennington, B.F., Shanahan, M. a, Santerre-Lemmon, L.E., Barnard, H.D., Willcutt, E.G., Defries, J.C., Olson, R.K., 2011. A multiple deficit model of reading disability and attention-deficit/hyperactivity disorder: searching for shared cognitive deficits. JCPP (J. Child Psychol. Psychiatry) 52, 547–557. https://doi.org/10.1111/j.1469-7610.2010.02346.x.

Messaoud-Galusi, S., Hazan, V., Rosen, S., 2011. Investigating speech perception in children with dyslexia: is there evidence of a consistent deficit in individuals? J. Speech Lang. Hear. Res. 54, 1682–1701. https://doi.org/10.1044/1092-4388(2011/09-0261).

Mody, M., Studdert-Kennedy, M., Brady, S., 1997. Speech perception deficits in poor readers: auditory processing or phonological coding? J. Exp. Child Psychol. 64, 199–231. https://doi.org/10.1006/jecp.1996.2343.

Moore, D.R., Rosenberg, J.F., Coleman, J.S., 2005. Discrimination training of phonemic contrasts enhances phonological processing in mainstream school children. Brain Lang. 94, 72–85. https://doi.org/10.1016/j.bandl.2004.11.009.

Mozolic, J.L., Joyner, D., Hugenschmidt, C.E., Peiffer, A.M., Kraft, R.A., Maldjian, J.A., Laurienti, P.J., 2008. Cross-modal deactivations during modality-specific selective attention. BMC Neurol. 8, 1–11. https://doi.org/10.1186/1471-2377-8-35.

Nath, A.R., Fava, E.E., Beauchamp, M.S., 2011. Neural correlates of interindividual differences in children's audiovisual speech perception. J. Neurosci. 31, 13963–13971. https://doi.org/10.1523/JNEUROSCI.2605-11.2011.

Noordenbos, M.W., Segers, E., Serniclaes, W., Mitterer, H., Verhoeven, L., 2012a. Allophonic mode of speech perception in Dutch children at risk for dyslexia: a longitudinal study. Res. Dev. Disabil. 33, 1469–1483. https://doi.org/10.1016/j.ridd.2012.03.021.

Noordenbos, M.W., Segers, E., Serniclaes, W., Mitterer, H., Verhoeven, L., 2012b. Neural evidence of allophonic perception in children at risk for dyslexia. Neuropsychologia 50. https://doi.org/10.1016/j.neuropsychologia.2012.04.026, 2010–2017.

Noordenbos, M.W., Serniclaes, W., 2015. The categorical perception deficit in dyslexia: a meta-analysis. Sci. Stud. Read. 19, 1–20. https://doi.org/10.1080/10888438.2015.1052455.

O'Brien, G.E., McCloy, D.R., Kubota, E.C., Yeatman, J.D., 2018. Reading ability and phoneme categorization. Sci. Rep. 8, 16842. https://doi.org/10.1038/s41598-018-34823-8.

Obleser, J., Zimmermann, J., Van Meter, J., Rauschecker, J.P., 2007. Multiple stages of auditory speech perception reflected in event-related FMRI. Cerebr. Cortex 17, 2251–2257. https://doi.org/10.1093/cercor/bhl133.

O'Brien, G.E., McCloy, D.R., Yeatman, J.D., 2019. Categorical phoneme labeling in children with dyslexia does not depend on stimulus duration. J. Acoust. Soc. Am. 146, 245–255. https://doi.org/10.1121/1.5116568.

Paulesu, E., Danelli, L., Berlingeri, M., 2014. Reading the dyslexic brain: multiple dysfunctional routes revealed by a new meta-analysis of PET and fMRI activation studies. Front. Hum. Neurosci. 8, 830. https://doi.org/10.3389/fnhum.2014.00830.

Pennington, B.F., 2006. From single to multiple deficit models of developmental disorders. Cognition 101, 385–413. https://doi.org/10.1016/j.cognition.2006.04.008.

Pennington, B.F., Santerre-lemmon, L., Rosenberg, J., Macdonald, B., Boada, R., Friend, A., Leopold, D., Samuelsson, S., Byrne, B., Willcutt, E.G., Olson, R.K., 2012. Individual prediction of dyslexia by single vs. multiple deficit models. J. Abnorm. Psychol. 121, 212–224. https://doi.org/10.1037/a0025823.Individual.

Polk, T.a., Farah, M.J., 2002. Functional MRI evidence for an abstract, not perceptual, word-form area. J. Exp. Psychol. Gen. 131, 65–72. https://doi.org/10.1037//0096-3445.131.1.65.

Pollack, C., Luk, G., Christodoulou, J.A., 2015. A meta-analysis of functional reading systems in typically developing and struggling readers across different alphabetic languages. Front. Psychol. 6, 1–10. https://doi.org/10.3389/fpsyg.2015.00191.

Price, C.J., 2012. A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. Neuroimage 62, 816–847. https://doi.org/10.1016/j.neuroimage.2012.04.062.

Price, C.J., Winterburn, D., Giraud, A.L., Moore, C.J., Noppeney, U., 2003. Cortical localisation of the visual and auditory word form areas: a reconsideration of the evidence. Brain Lang. 86, 272–286. https://doi.org/10.1016/S0093-934X(02)00544-8.

Ramus, F., 2003. Theories of developmental dyslexia: insights from a multiple case study of dyslexic adults. Brain 126, 841–865. https://doi.org/10.1093/brain/awg076.

Raschle, N.M., Chang, M., Gaab, N., 2011. Structural brain alterations associated with dyslexia predate reading onset. Neuroimage 57, 742–749. https://doi.org/10.1016/j.neuroimage.2010.09.055.

Richardson, U., Leppänen, P.H.T., Leiwo, M., Lyytinen, H., 2003. Speech perception of infants with high familial risk for dyslexia differ at the age of 6 months. Dev. Neuropsychol. 23, 385–397. https://doi.org/10.1207/S15326942DN2303_5.

Richlan, F., Kronbichler, M., Wimmer, H., 2011. Meta-analyzing brain dysfunctions in dyslexic children and adults. Neuroimage 56, 1735–1742. https://doi.org/10.1016/j.neuroimage.2011.02.040.

Richlan, F., Kronbichler, M., Wimmer, H., 2009a. Functional abnormalities in the dyslexic brain: a quantitative meta-analysis of neuroimaging studies. Hum. Brain Mapp. 30, 3299–3308. https://doi.org/10.1002/hbm.20752.

Richlan, F., Sturm, D., Schurz, M., Kronbichler, M., Ladurner, G., Wimmer, H., 2010. A common left occipito-temporal dysfunction in developmental dyslexia and acquired letter-by-letter reading? PloS One 5, e12073. https://doi.org/10.1371/journal.pone.0012073.

Romanovska, L., Janssen, R., Bonte, M., 2019. Reading-induced shifts in speech perception in dyslexic and typically reading children. Front. Psychol. 10 https://doi.org/10.3389/fpsyg.2019.00221. Article 221.

Rosen, S., Manganari, E., 2001. Is there a relationship between speech and nonspeech auditory processing in children with dyslexia? J. Speech Lang. Hear. Res. 44, 720–736.

Ruff, S., Marie, N., Celsis, P., Cardebat, D., Démonet, J.-F., 2003. Neural substrates of impaired categorical perception of phonemes in adult dyslexics: an fMRI study. Brain Cognit. 53, 331–334. https://doi.org/10.1016/S0278-2626(03)00137-4.

Russeler, J., Ye, Z., Gerth, I., Szycik, G.R., Munte, T.F., 2018. Audio-visual speech perception in adult readers with dyslexia: an fMRI study. Brain Imaging Behav 12, 357–368. https://doi.org/10.1007/s11682-017-9694-y.

Sandak, R., Mencl, W.E., Frost, S.J., Pugh, K.R., 2004. The neurobiological basis of skilled and impaired reading: recent findings and new directions. Sci. Stud. Read. 8, 273–292. https://doi.org/10.1207/s1532799xssr0803_6.

Saygin, Z.M., Osher, D.E., Norton, E.S., Youssoufian, D.A., Beach, S.D., Feather, J., Gaab, N., Gabrieli, J.D.E., Kanwisher, N., 2016. Connectivity precedes function in the development of the visual word form area. Nat. Neurosci. 19, 1250–1255. https://doi.org/10.1038/nn.4354.

Schumacher, J., Hoffmann, P., Schmäl, C., Schulte-Körne, G., Nöthen, M.M., 2007. Genetics of dyslexia: the evolving landscape. J. Med. Genet. 44, 289–297. https://doi.org/10.1136/jmg.2006.046516.

Semel, E., Wiig, E.H., Secord, W.A., 2003. Clinical Evaluation of Language Fundamentals, Fourth. The Psychological Corporation, San Antonio.

Serniclaes, W., Sprenger-charolles, L., Carré, R., Démonet, J.-F., 2001. Perceptual discrimination of speech sounds in dyslexics. J. Speech Lang. Hear. Res. 44, 384–399. https://doi.org/10.1044/1092-4388(2001/032).

Shaywitz, S.E., 1998. Dyslexia. N. Engl. J. Med. 338, 307–312. https://doi.org/10.1056/NEJM199801293380507.

Shenhav, A., Botvinick, M.M., Cohen, J.D., 2013. The expected value of control : an integrative theory of anterior cingulate cortex function. Neuron 79, 217–240. https://doi.org/10.1016/j.neuron.2013.07.007.

Skiba, T., Landi, N., Wagner, R., Grigorenko, E.L., 2011. In search of the perfect phenotype: an analysis of linkage and association studies of reading and reading-related processes. Behav. Genet. 41, 6–30. https://doi.org/10.1007/s10519-011-9444-7.

Steffens, M.L., Eilers, R.E., Gross-Glenn, K., Jallad, B., 1992. Speech perception in adult subjects with familial dyslexia. J. Speech Hear. Res. 35, 192–200. https://doi.org/10.1044/jshr.3501.192.

Stevens, W.D., Kravitz, D.J., Peng, C.S., Henry Tessler, M., Martin, A., 2017. Privileged functional connectivity between the visual word form area and the language system. J. Neurosci. 37 https://doi.org/10.1523/JNEUROSCI.0138-17.2017, 0138–17.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System : an Approach to Cerebral Imaging. Thieme, New York.

Torgesen, J.K., Wagner, R.K., Rashotte, C.A., 1999. Test of Word Reading Efficiency. PRO-ED, Inc., Austin.

van Bergen, E., van der Leij, A., de Jong, P.F., 2014. The intergenerational multiple deficit model and the case of dyslexia. Front. Hum. Neurosci. 8, 1–13. https://doi.org/10.3389/fnhum.2014.00346.

van Laarhoven, T., Keetels, M., Schakel, L., Vroomen, J., 2018. Audio-visual speech in noise perception in dyslexia. Dev. Sci. 21, e12504 https://doi.org/10.1111/desc.12504.

Vandermosten, M., Correia, J., Vanderauwera, J., Wouters, J., Ghesquière, P., Bonte, M., 2020. Brain activity patterns of phonemic representations are atypical in beginning readers with family risk for dyslexia. Dev. Sci. 23, e12857 https://doi.org/10.1111/desc.12857.

Varnet, L., Meunier, F., Trollé, G., Hoen, M., 2016. Direct viewing of dyslexics' compensatory strategies in speech in noise using Auditory Classification Images. PloS One 11, 1–17. https://doi.org/10.1371/journal.pone.0153781.

Veuillet, E., Magnan, A., Ecalle, J., Thai-Van, H., Collet, L., 2007. Auditory processing disorder in children with reading disabilities: effect of audiovisual training. Brain 130, 2915–2928. https://doi.org/10.1093/brain/awm235.

Wagner, R.K., Torgesen, J.K., Rashotte, C.I., 1999. The Comprehensive Test of Phonological Processing. PRO-ED, Inc., Austin.

Wechsler, D., 2008. Wechsler Adult Intelligence Scale - IV, fourth ed. The Psychological Corporation, San Antonio.

Wechsler, D., 2003. Wechsler Intelligence Scale for Children-IV, fourth ed. The Psychological Corporation, San Antonio.

Wiederholt, J.L., Bryant, B.R., 2001. Gray Oral Reading Tests, fourth ed. PRO-ED, Inc., Austin.

Woodcock, R.W., McGrew, K.S., Mather, N., 1999. Woodcock-Johnson III, third ed. ed. Riverside Publishing, Itasca, IL.

Yoncheva, Y.N., Zevin, J.D., Maurer, U., McCandliss, B.D., 2010. Auditory selective attention to speech modulates activity in the visual word form area. Cerebr. Cortex 20, 622–632. https://doi.org/10.1093/cercor/bhp129.

Zhang, Yajing, Zhang, L., Shu, H., Xi, J., Wu, H., Zhang, Yang, Li, P., 2012. Universality of categorical perception deficit in developmental dyslexia: an investigation of Mandarin Chinese tones. JCPP (J. Child Psychol. Psychiatry) 53, 874–882. https://doi.org/10.1111/j.1469-7610.2012.02528.x.

Ziegler, J.C., Pech-Georgel, C., George, F., Lorenzi, C., 2009. Speech-perception-in-noise deficits in dyslexia. Dev. Sci. 12, 732–745. https://doi.org/10.1111/j.1467-7687.2009.00817.x.

Zoubrinetzky, R., Collet, G., Serniclaes, W., Nguyen-Morel, M.A., Valdois, S., 2016. Relationships between categorical perception of phonemes, phoneme awareness, and visual attention span in developmental dyslexia. PloS One 11, 1–26. https://doi.org/10.1371/journal.pone.0151015.