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Role of the superior parietal lobules in letter-identity processing within strings: FMRI evidence from skilled and dyslexic readers

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ABSTRACT

Traditionally, the ventral occipito-temporal (vOT) area, but not the superior parietal lobules (SPLs), is thought as belonging to the neural system of visual word recognition. However, some dyslexic children who exhibit a visual attention span disorder – i.e. poor multi-element parallel processing – further show reduced SPLs activation when engaged in visual multi-element categorization tasks. We investigated whether these parietal regions further contribute to letter-identity processing within strings. Adult skilled readers and dyslexic participants with a visual attention span disorder were administered a letter-string comparison task under fMRI. Dyslexic adults were less accurate than skilled readers to detect letter identity substitutions within strings. In skilled readers, letter identity differs related to enhanced activation of the left vOT. However, specific neural responses were further found in the superior and inferior parietal regions, including the SPLs bilaterally. Two brain regions that are specifically related to substituted letter detection, the left SPL and the left vOT, were less activated in dyslexic participants. These findings suggest that the left SPL, like the left vOT, may contribute to letter string processing.

1. Introduction

A large body of research has supported difficulties with phonological processing as the core disorder in developmental dyslexia (Bishop & Snowling, 2004; Ramus, 2003; Vellutino, Fletcher, Snowling, & Scanlon, 2004). Accordingly, a number of left hemisphere language-related regions have been described as showing atypical function in individuals with dyslexia (Démonet, Taylor, & Chaix, 2004, for a review). Involvement of the left inferior frontal gyrus (for phonological short-term memory and phonological processing; Dufor, Serniclaes, Sprenger-Charolles, & Démonet, 2007; Heim, Eulitz, & Elbert, 2003), the left superior temporal gyrus (for speech sound analysis and letter-sound mapping; Blau et al., 2010; Brambati et al., 2006; Paulesu et al., 2001) and the left temporo-parietal areas (for letter-to-sound conversion; Aylward et al., 2003; Price & Mechelli, 2005; Temple et al., 2003) is well in line with the phonological theory of developmental dyslexia (Snowling, 2000). A further brain region, the left inferior temporal area that more specifically relates to visual recognition of letter strings (Dehaene & Cohen, 2011) has also been reported as consistently impaired in developmental dyslexia (Richlan, Kronbichler, & Wimmer, 2011). However, there is now strong evidence that not all dyslexic children have a phonological disorder (Vidyasagar & Pammer, 2010). A visual attention span disorder – a parallel letter string processing impairment due to reduced visual attention capacity – has been found to account for the poor reading outcome of a subgroup of dyslexic individuals (Bosse, Tainturier, & Valdois, 2007). Some studies have identified the superior parietal lobules (SPLs) as visual attention (VA) span brain correlates (Peyrin, Démonet, N'Guyen-Morel, Le Bas, & Valdois, 2011; Peyrin et al., 2012). These regions are specifically activated when the task requires multi-element processing, regardless of the alphanumeric or non-alphanumeric nature of the stimuli to be processed (Lobier, Zoubrinetzky, & Valdois, 2012c). However, evidence for SPL involvement in developmental dyslexia derives from tasks that did not directly relate to reading but required multi-element visual categorization. Thus, no direct evidence was provided for this region to be involved in letter identification within strings. Moreover, typically this brain region is not recognized as part of the reading network, although being involved in reading under some specific conditions (Cohen, Dehaene, Vinckier, Jobert, & Montavont, 2008; Valdois et al. 2006). As letter string

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identification is a necessary component process of word recognition, the current study aimed at exploring whether the SPLs are involved in letter identity encoding within strings thus contributing to the early phase of the reading process.

1.1. Role of the left ventral occipito-temporal (vOT) cortex in word recognition

The report of cases of pure alexia showed that some regions of the neural system are dedicated to visual word recognition. Pure alexia is an acquired deficit of reading that results from lesions of the left vOT (Binder & Mohr, 1992; Cohen et al., 2003; Gaillard et al., 2006; Leff et al., 2001; Leff, Spitsyna, Plant, & Wise, 2006). Numerous neuroimaging studies of reading have identified part of this cortical region – namely the 'Visual Word Form Area' (VWFA) – as playing an important role in visual word recognition (Cohen et al., 2000; Cohen et al., 2002; Dehaene & Cohen, 2011). Its activity is strictly visual (Dehaene, Le Clec, Poline, Le Bihan, & Cohen, 2002), yet invariant for spatial location (right or left visual field) (Cohen et al., 2000), or typographical characteristics (Dehaene et al., 2001). Left vOT activity increases with word visibility and this perceptual sensitivity to word visibility correlates with the ability to quickly read words by sight (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011). Further, this brain region is sensitive to word frequency (Bruno, Zumberge, Manis, Lu, & Goldman, 2008). Thus, it is widely accepted that the left vOT encodes the abstract identity of strings of visual letters on the basis of fast and parallel processing of letter identification (Cohen et al., 2000; Szwed et al., 2011; Tagamets, Novick, Chalmers, & Friedman, 2000; Vigneau, Jobard, Mazoyer, & Tzourio-Mazoyer, 2005). However considerable literature argues for a domain-general role of the left vOT cortex that is not strictly specialized for recognition of written words (Hellyer, Woodhead, Leech, & Wise, 2011; Price & Devlin, 2003, 2011; Starrfelt & Gerlach, 2007; Twomey, Kawabata Duncan, Price, & Devlin, 2011). Indeed in line with the recycling hypothesis (Dehaene & Cohen, 2007), the left vOT cortex is not exclusively activated by words but further responds to pseudowords, consonant strings or even objects' line drawings or false font strings, thus suggesting a more general involvement in the identification of multi-element "objects" (Inhoff & Tousman, 1990). Thanks to its general property in multipart object processing, the vOT area plays a crucial role in the perceptual expertise required for reading.

The vOT area further belongs to the network of brain areas involved in developmental dyslexia (Wandell, Rauschecker, & Yeatman, 2012). Reading skills in children with dyslexia correlates with the magnitude of vOT cortex activation (Shaywitz et al. 2002). In their meta-analysis of 18 studies, Richlan et al. (2011) found support for a dysfunction of the vOT cortex in both children and adults with developmental dyslexia. They reported age modulated activations within this region and located the peak of age difference within the VWFA. In a longitudinal study of children with familial risk of dyslexia, Maurer et al. (2007) found reduced electrophysiological tuning in vOT area for those kindergarten children who showed a specific reading disorder two years later. This result clarifies that in dyslexia visual tuning for print is reduced from the early phase of reading acquisition. A similar reduction was reported for adults with developmental dyslexia (Helenius, Tarkiainen, Cornelissen, Hansen, & Salmelin, 1999). Thus there is strong evidence that the vOT region develops into a fast word recognition system over time and that a failure to recruit the vOT cortex characterizes developmental dyslexia. Specialization of this region in word identification may be due to its dense interconnection with language regions, so that reduced activation in developmental dyslexia may relate to the poor phonological skills and language disorder typically reported in dyslexic children (Price & Devlin, 2011; Wandell, et al., 2012). However, a growing body of evidence suggests that a subset of dyslexic children exhibit a multi-element string processing disorder in the absence of any phonological disorder.

1.2. A multi-element string processing disorder in developmental dyslexia

There is strong evidence that dyslexic children exhibit a multi-element parallel processing disorder that reflects poor visual attention processes (Hawelka & Wimmer, 2005; Jones, Branigan, & Kelly, 2008; Pammer, Lavis, Hansen, & Cornelissen, 2004; Pammer & Vidyasagar, 2005; Valdois et al., 2003). Several studies have explored multi-element visual processing in dyslexic children using 5-consonant report tasks (Bosse et al., 2007; Bosse & Valdois, 2009; Valdois, et al., 2003; Valdois, Bosse, & Tainturier, 2004). These tasks require identifying as many letters as possible or a single cued letter within 5-consonant letter strings that are briefly displayed. Impaired performance on these tasks was interpreted as reflecting a simultaneous processing disorder, known as a visual attention (VA) span deficit (Valdois et al., 2004). This disorder prevents dyslexic children from processing as many letters in parallel as non-dyslexic children do. There is evidence that the VA span disorder is strictly visual since it is not affected by concurrent phonological processing (Valdois, Lassus-Sangosse, & Lobier, 2012) and further extends to non-verbal tasks and non-verbal material (Lobier et al., 2012c; Pammer et al., 2004; Pammer & Vidyasagar, 2005). Furthermore, both group studies and single case studies have shown that the VA span disorder typically dissociates from phonological problems in developmental dyslexia (Bosse et al., 2007; Lallier, Donnadieu, Berger, & Valdois, 2010; Valdois et al., 2011; Valdois et al., 2003). Research on typical development further showed that VA span abilities contribute to reading performance independently of the child's phonological skills (Bosse & Valdois, 2009). They suggest a more specific involvement of VA span abilities in irregular word processing and reading speed, even if the VA span further contributes to pseudo-word reading. This is consistent with report of VA span disorders in children with a selective irregular word reading disorder (Dubois et al., 2010; Valdois et al., 2003) and in cases of mixed dyslexia (Valdois et al., 2011). This disorder is interpreted as a reduction in the amount of visual attention that can be distributed over the letter string, so that the attentional load allocated to each letter within the string is not sufficient to allow accurate identification of the whole letters simultaneously. A reduced visual attention span would prevent normal processing of the whole word sequence, thus affecting words' fast recognition in reading. In preventing identification of their whole constitutive letters, such a reduction would further impact normal processing of relevant multi-letter sub-lexical units, thus leading to impaired pseudo-word reading. A VA span disorder was expected to relate to lower activity in those brain regions specifically dedicated to attentional processing.

1.3. Role of superior parietal lobules (SPLs) in letter string processing

The neural underpinnings of the VA span have been investigated in dyslexic individuals and skilled readers. Using categorization tasks under fMRI, Peyrin et al. (2011, 2008) identified the superior parietal lobules bilaterally (SPLs) as the neural correlates of VA span. Peyrin et al. (2011) investigated the VA span cerebral substrates in normal reading children and in a group of dyslexic children chosen to have a VA span disorder at the behavioral level (i.e. poor performance on the letter report tasks). In this study, two flanked and isolated letter categorization tasks were designed which differently taxed visual attention. In typical readers, the

more taxing flanked condition activated a broad parietal network including the SPLs while the less attention-demanding task of isolated stimuli did not. No significant activation in this area was found in dyslexic children suggesting a difficulty to recruit brain regions involved in attention demanding multi-element processing tasks. A second brain imaging study was conducted on two contrasted cases of developmental dyslexia to demonstrate that under-activation of the SPLs was not just a correlate of poor reading outcome but specifically related to the VA span disorder (Peyrin et al., 2012). This later study showed that lower SPLs activation was only found in the participant with a VA span disorder but not in the dyslexic participant who showed good VA span abilities but poor phonological processing skills. The SPLs may thus play a specific role in reading-related visual processing skills. To demonstrate SPLs specific involvement in multi-element processing efficiency, Lobier, Peyrin, Le Bas, and Valdois (2012a) explored skilled readers' brain activation while performing multiple and single element visual categorization tasks with alphanumeric (letters and digits) and non-alphanumeric (Hiragana and pseudo-letters) characters under fMRI. Results showed higher activation of the SPLs for multiple than single element processing and similar activity regardless of character type. These findings suggest a specific role of the superior parietal regions in multi-character processing. However, available evidence for atypical SPLs activation in developmental dyslexia derives from categorization tasks that did not require identification of the stimuli to be processed.

1.4. Purpose of the current study

The present study aims to reveal the neurobiological underpinnings of letter-identity encoding and compare brain activation in healthy skilled readers and dyslexic adults. We used a visual letter-string comparison task in which letter identity was manipulated through the substitution of two letters within strings. From a methodological perspective, one particularly useful approach to such issues is to examine the process of letter perception in unreadable consonant strings (i.e. non-words). In this way, one can record responses relating to letter-level (pre-lexical) processes while minimizing the influence of higher-level phonological and semantic processes or word-specific orthographic knowledge. A second issue was to limit presentation time to avoid useful ocular saccades and constrain parallel processing of letter strings in preventing serial processing of letters within strings. Thus, the neurobiological counterparts of letter identity encoding during multi-letter string parallel processing were assessed. In healthy skilled readers, the letter string comparison task was expected to elicit activation within both the left vOT area and the SPLs bilaterally. Dyslexic individuals were expected to show lower SPL and vOT activations during letter-identity processing within strings.

2. Materials and method

2.1. Participants

Twenty-four native French speakers participated to the study: 12 adults with developmental dyslexia (four males; mean age ± S.D. = 24.9 ± 3.7 years) and 12 skilled readers (seven males; mean age ± S.D. = 26.2 ± 4.8 years). All participants were right-handed as assessed by the Edinburgh Inventory (Oldfield, 1971). They had normal or corrected-to-normal visual acuity and no history of neurological or psychiatric disorders. All dyslexic participants had a documented history of reading difficulties. They received a formal diagnosis of developmental dyslexia during childhood and reported persistent problems with reading and spelling. From a previously established procedure, four behavioral tests were used to further ascertain the diagnosis of developmental dyslexia: reading regular words (cut-off latency between stimulus appearance on a computer screen and onset of subject's oral response 660 ms), reading legal pseudo-words (cut-off latency 940 ms), reading aloud 50 digits (mean time cut-off 18 s), spelling on dictation of 15 irregular frequent words (cut-off > 4 errors). Cut-offs were defined following a pre-experimental study (Dufor, Serniclaes, Sprenger-Charolles, & Demonet, 2007) involving a separate group of 18 adult dyslexics and 65 controls; similar criteria were initially used in the European Dyslexia Study in Paulesu et al. (2001) and later in Ruff, Cardebat, Marie, and Démonet (2002), Ruff, Marie, Celsis, Cardebat, and Démonet (2003)'s and Silani et al. (2005)'s studies. Subjects were considered dyslexic when they scored out of cut-off on at least two of the four tests. They were further administered phonological (i.e. phoneme deletion, syllable deletion and spoonerisms) and letter report tasks to estimate their phoneme awareness and visual attention span abilities. Characteristics of the dyslexic participants are provided in Table 1.

Table 1
Characteristics of the dyslexic participants. *Z*-scores were calculated based on control data taken from the European Dyslexia Study in Paulesu et al. (2001). Exception for the *Z*-score obtained on visual attention span, which were calculated based on control data taken from another study (not yet published).

Tasks	DYS (SD)	CON (SD)	*Z*-score
Reading			
Words (*n*=40)			
Accuracy	38.33 (1.72)	39.85 (0.44)	−3.4***
Speed (s)	0.77 (0.14)	0.56 (0.52)	−4.1***
Pseudo-Words (*n*=40)			
Accuracy	30.92 (5.21)	38.65 (1.58)	−4.6***
Speed (s)	1.00 (0.21)	0.70 (0.12)	−2.5**
Phoneme awareness			
Phoneme deletion (*n*=40)			
Error rates	7.58 (4.76)	2.30 (2.6)	−2.0*
Speed (s)	159.83 (68.69)	98.70 (18.8)	−3.2***
Syllable deletion (*n*=20)			
Error rates	3 (3.22)	1.26 (1.25)	−1.4
Speed (s)	136.75 (68.89)	74.6 (17.84)	−3.5***
Spoonerisms (*n*=12)			
Error rates	4.33 (2.06)	0.86 (1.27)	−2.7**
Speed (s)	211.25 (75.58)	96.4 (32.27)	−3.6***
Visual rhymes (*n*=40)			
Error rates	7.8 (3.1)	5.02 (3.21)	−0.9
Speed (s)	1.64 (0.16)	1.22 (0.26)	−1.6*
Spelling			
Irregular words (*n*=15)			
Error rates	7.42 (2.74)	2.72 (20.2)	−2.3**
Pseudo-words (*n*=15)			
Error rates	2.92 (1.78)	1.67 (1.33)	−0.9
Visual attention span			
Global report (*n*=100)	89.50 (7.52)	97.43 (3.32)	−2.4**

Abbreviations: DYS = dyslexic participants.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

All the dyslexic participants had a normal verbal IQ (score > 85 on Wechsler Adult Intelligence Scale, WAIS III) but an unexpectedly low reading level (mean reading age ± S.D. = 10.3 ± 1.7), as established using the Alouette Reading Test (Lefavrais, 1965). They showed a phonological disorder with significantly lower performance and/or slower speed than expected on all four phonological tasks. They further exhibited a VA span disorder using the global report paradigm in which they had to report as many letter names as possible from a briefly displayed 5 consonants string. The dyslexic participants reported significantly fewer letters than controls (mean = 89.5, $t = -3.45$, $p = 0.002$) on this task, thus showing reduced VA span abilities. None of the skilled readers reported any learning impairment for reading or spelling. They showed an expert reading level on the Alouette Reading Test. All participants gave their informed written consent before participating in the study which was approved by the local ethic committee (CPP Sud Est V, France).

2.2. Stimuli

Stimuli were random 5-letter strings built up from 10 upper-case consonant letters (B, G, T, F, L, M, D, S, R and H). Stimuli were framed, embedded in hashes (e.g., # L F T D R #) and immediately followed by a pattern mask of

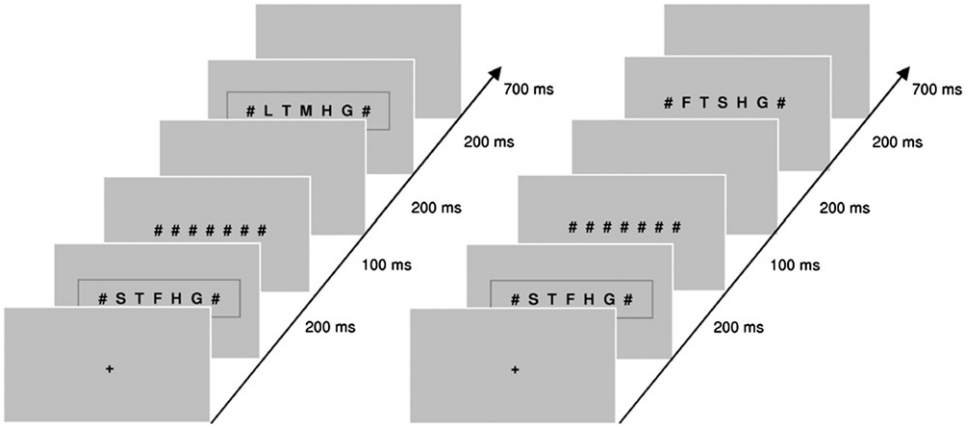

Fig. 1. Schematic illustration of the experimental paradigm. In the substitution condition (left side), participants had to judge whether two successively presented consonant strings were strictly identical or not. In the control frame condition (right side), they had to judge whether the two successively displayed identical strings were both framed or not.

7 hashes (# # # # # # #). The framework was added for comparison with the control condition. The distance between adjacent letters/hash was 1.2° to minimize lateral masking. The stimuli consisted of two successive letter strings made up of either two identical letter strings (identical pairs) or of two different letter strings (different pairs). The strings were displayed at the center of the screen for 200 ms in order to avoid useful ocular saccades and prevent serial processing of letters within strings. The array subtended an angle of approximately 6.8°. Fig. 1 provides a schematic representation of the experimental design.

All stimuli were written in black and displayed on a gray background (RGB: 160, 160, 160) to avoid eyestrain. Stimuli were delivered with Presentation® software (Neurobehavioral system®) on an ACER laptop computer connected via optic fibers (NordicNeuroLab®) to MRI-compatible devices (an adjustable visual system coil mounted display for the visual stimulus presentation and 2-button response box).

2.3. Experimental task

Participants had to perform a perceptual matching task in two substitution and frame conditions. The substitution condition is a letter string comparison task in which we manipulated the substitution of two letters within strings. They were instructed to fixate the central fixation cross and had to judge whether the two successively presented strings were strictly identical (condition SUB-Id; e.g., FBSHM, FBSHM) or not. Half of the pairs were made of identical strings, the other half pairs differed by two letters that were substituted (condition SUB-Dif; e.g., TSHFL, TGHML). Note that letter identity was explicitly manipulated in the SUB-Dif condition alone. This condition thus constitutes our main experimental condition. In the control condition (frame condition), the two strings of the pair were identical and participants were asked to focus on the frame, not the letters. They had to judge whether the frame was present for the two strings (condition Frame-Id) or not (condition Frame-Dif). The participants had to give their responses by pressing two buttons with the forefinger and the middle finger of their dominant hand (right hand). Half of the participants had to press the forefinger button if the two successively presented strings were identical, the middle finger button otherwise, while the other half participants had to press the middle finger button for the identical pairs, the forefinger button otherwise. The substitution and frame conditions were presented in two different sessions. There were 40 trials for each session, half with identical pairs (i.e. two framed strings) and half with different pairs (i.e. one framed letter-string, the other not). Trial order was pseudo-randomized within sessions.

2.4. Event-related fMRI experimental design

Pseudo-randomized ER-fMRI paradigms were used to optimize the onset of each type of stimuli (Friston, Zarahn, Josephs, Henson, & Dale, 1999). Each participant performed 2ER-fMRI consecutive sessions corresponding to the substitution and frame conditions. The order of the fMRI sessions was counterbalanced across participants. For each session, 40 pairs of stimuli were displayed: 20 identical letter-string pairs, 20 different letter-string pairs. In addition, 25 null-events (five of them at the end of the session) were included in each session in order to provide an appropriate baseline measure (Friston et al., 1999). Null-events were composed of a gray screen and a black fixation cross sized 0.3° of visual angle displayed at the center of the screen. This central fixation cross was also displayed between stimuli in order to encourage participants to fixate the center of the screen. For each functional session, three initial dummy scans were performed in order to stabilize the magnetic field. After dummies, 78 functional volumes were acquired during each session of the string comparison experiment. The inter-stimulus interval was 4 s on average (ISI = 1 s, 4 s or 7 s). The total duration of each functional session was 3 min 25 s. Response accuracy and reaction times in milliseconds were recorded. Before the experiments, participants underwent a training session outside the scanner, with stimuli that differed from those used in functional sessions.

2.5. MR acquisition

Event-related data acquisition was performed with a Philips Achieva® (3T) MRI system equipped for echo-planar imaging (EPI). Prior to the functional runs, 3D T1-weighted images (field of view = 256 × 256 × 190 mm, matrix size = 256 × 175 mm, spatial resolution = 1 mm3/voxel) were collected for each participant. For functional scans, the manufacturer-provided gradient-echo/T2* weighted EPI method was used. Each volume consisted of 41 continuous slices (thickness = 3.5 mm) parallel to the AC–PC line, to cover the entire brain, including the cerebellum (AC–PC line on the 20th slice) in an interleaved acquisition order. The in-plane voxel size was 2.38 × 2.4 mm (230 × 230 mm field of view acquired with a 96 × 96 pixel data matrix). The time interval between two successive acquisitions of the same slice (TR) was 2500 ms with a flip angle of 90° and 35 ms echo time.

2.6. Data processing

Data analysis was performed by using the general linear model (Friston, 1995) as implemented in SPM8 (Welcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm) where each event is modeled using a hemodynamic function model. Data analysis started by applying several spatial pre-processing steps. First, functional volumes were time-corrected with the 21st slice as reference, in order to correct effects caused by the different acquisition time of each slice. Subsequently, all volumes were realigned to correct head motion using rigid body transformations. The first volume of the first ER-fMRI session was taken as reference volume. The T1-weighted anatomical volume was co-registered to mean images created by the realignment procedure and was normalized to the MNI space using a trilinear interpolation. The anatomical normalization parameters were subsequently used for the normalization of functional volumes. Finally, each functional volume was smoothed by an 8 mm FWHM (Full Width at Half Maximum) Gaussian kernel. Time series for each voxel were high-pass filtered (1/128 Hz cutoff) to remove low-frequency noise and signal drift.

After these pre-processing steps, statistical analyses were performed on functional images. Four conditions (identical and different pairs for the substitution and frame conditions) were modeled as four regressors convolved with a canonical hemodynamic response function (HRF): Sub-Id, Sub-Dif, Frame-Id, Frame-Dif. Movement parameters derived from realignment corrections (three translations and three rotations) were also entered in the design matrix of each experiment as additional factors. The general linear model was then used to generate parameter estimates of activity at each voxel, for each condition, and each participant. Statistical parametric maps were generated from linear contrasts between the HRF parameter estimates for the different experimental conditions.

At the individual level, we first assessed the whole network of cerebral areas involved in each condition (substitution and frame) by contrasting interest condition (identical and different pairs for the substitution and frame) to the baseline (crosshair fixation). Then, we identified the cerebral areas specifically involved in letter identity processing by contrasting substitution to frame

conditions ([Sub-Id > Frame-Id] and ([Sub-Dif > Frame-Dif] contrasts). We then performed a separate random-effect group analysis for controls and dyslexics on the contrast images from the individual analyses (Friston et al. 1998), using one-sample *t*-tests. Finally, two-sample *t*-tests were performed to statistically compare brain activity between controls and dyslexics on the relevant contrasts. Clusters of activated voxels were then identified, based on the intensity of the individual responses ($p < 0.001$ uncorrected for multiple comparisons, $T > 4.02$, extended threshold of 15 voxels).

While this uncorrected threshold may seem liberal, it is in line with those of previous papers reporting significant activations to identify pre-orthographic character string neural correlates (Lobier et al., 2012a) as well as activation differences between skilled and dyslexic readers within the parietal (Peyrin, Demonet, N'Guyen-Morel, Le Bas, & Valdois, 2011; Peyrin et al., 2008) or occipito-temporal areas (Van Der Mark et al., 2009). To facilitate comparisons with other studies, a transformation of MNI into Talairach and Tournoux (1988) coordinates was performed using the MNI2TAL function (created by Matthew Brett, available at http://www.mrc-cbu.cam.ac.uk/Imaging).

Analysis was finally completed by statistically comparing activity for skilled and dyslexic readers within regions of interest (ROIs). A set of a priori ROIs were defined using predefined masks from the Wake Forest University (WFU) PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). ROI masks were created with the automated anatomical labeling atlas, which uses an anatomical parcellation of the MNI MRI single-subject brain and sulcal boundaries to define each anatomical volume. All ROIs were constructed using the SPM Marsbar toolbox (http://marsbar.sourceforge.net). Parameter estimates (% signal change relative to the global mean intensity of signal) of event-related responses were then extracted from these ROIs for each participant. The average parameter of activity was calculated for each skilled and dyslexic reader and each ROI and ROIs' activity was compared between groups. Previous research has linked behavioral deficits in simultaneous visual processing in dyslexia to lower activation in parietal brain areas, and more specifically in the superior parietal lobule bilaterally and the left inferior parietal lobule lobule (Peyrin et al., 2011; Peyrin et al., 2012). Atypical activation patterns in dyslexia have been also observed in the left inferior frontal areas – including Broca's area – implicated in output phonology and articulatory processing (Paulesu et al., 1996; Shaywitz et al., 1998; Wimmer et al., 2010). Other research showed a deficit in activation in ventral pathway of reading centered in the left middle and inferior temporal gyrus (Démonet et al., 2004; Paulesu et al., 2001). Thus, six a priori defined cortical ROIs were investigated: left SPL, BA 7; right SPL, BA7; left IPL; BA 40; right IPL, BA 40; left IFG, BA 44; left ITG, BA 37.

3. Results

3.1. Behavioral results

As shown in Fig. 2, both dyslexic and skilled readers showed high accuracy performance on both the identical and the different pairs. Data were corrected with Arcsinus transformation and log transformation for the percentage of correct responses (CRs) and median reaction times (RTs) respectively, so that variables had normal distribution.

ANOVAs were performed on the mean percentage of correct responses and mean median correct reaction times with the two Experimental conditions (substitution vs. frame) and Similarity of pairs (identical vs. different) as within-subject factors and Groups (controls vs. dyslexics) as between-subjects factor. Tukey HSD test were used for post-hoc comparisons.

The ANOVA on mean CRs showed a significant main effect of Group [$F_{1,\ 22} = 9.36$, $p < 0.01$] and Task [$F_{1,22} = 79.52$, $p < 0.0001$]. Dyslexic adults were less accurate than controls and the frame condition easier than the substitution condition. The 'Task × Group' interaction was not significant [$F_{1,22} < 1$] suggesting similar effects of the task for both skilled readers and dyslexic participants. Similarly, the 'Task × Similarity', 'Similarity × Task' and 'Task × Similarity × Group' interactions were not significant [$F_{1,22} = 1.24$, $p = 0.28$ and $F_{1,22} < 1$, respectively]. Planned comparisons between groups were performed because of our a priori hypothesis of disturbed processing in letter identity encoding in the dyslexic group. Dyslexics were significantly less accurate than skilled readers in the substitution task ($88\% \pm 8$ vs. $81\% \pm 11$; $F_{1,22} = 6.30$, $p < 0.05$). Their performance was similar on the identical and different pairs of the substitution condition ($79.2\% \pm 11.2$ vs. $83.3\% \pm 10.5$, $F_{1,22} = 1.09$, $p = 0.31$).

The ANOVA on mean RTs showed that dyslexics responded as fast as skilled readers [$F_{1,22} < 1$]. RTs were as fast for the frame as the substitution condition, in the whole population [$F_{1,22} = 3.27$; $p = 0.08$]. Results showed a significant 'Task × Group' interaction [$F_{1,22} = 8.98$, $p < 0.01$]. This interaction was due to faster reaction times for the frame than the Substitution condition for the dyslexic participants only ($F_{1,\ 22} = 11.54$, $p < 0.01$; Skilled readers: $F_{1,22} < 1$). However, planned comparisons showed no significant difference between skilled readers and dyslexic participants for either the substitution (594 ± 128 ms vs. 715 ± 241 ms, $F_{1,\ 22} = 2.35$, $p = 0.14$) or the frame condition (612 ± 109 ms vs. 604 ± 134 ms, $F_{1,22} < 1$). The 'Similarity × Group' interaction was not significant for either task (both tasks: $F_{1,22} < 1$). Finally, the 'Task × Similarity × Group' interaction was not significant ($F_{1,22} < 1$).

Overall, dyslexic adults performed lower on the substitution than the frame condition and took more time to respond. They were significantly less accurate than controls on the substitution condition but showed no accuracy-speed trade-off on this condition.

3.2. FMRI results

FMRI data from skilled readers showed that the substitution condition on different pairs ([SUB-Dif > baseline] contrast, see

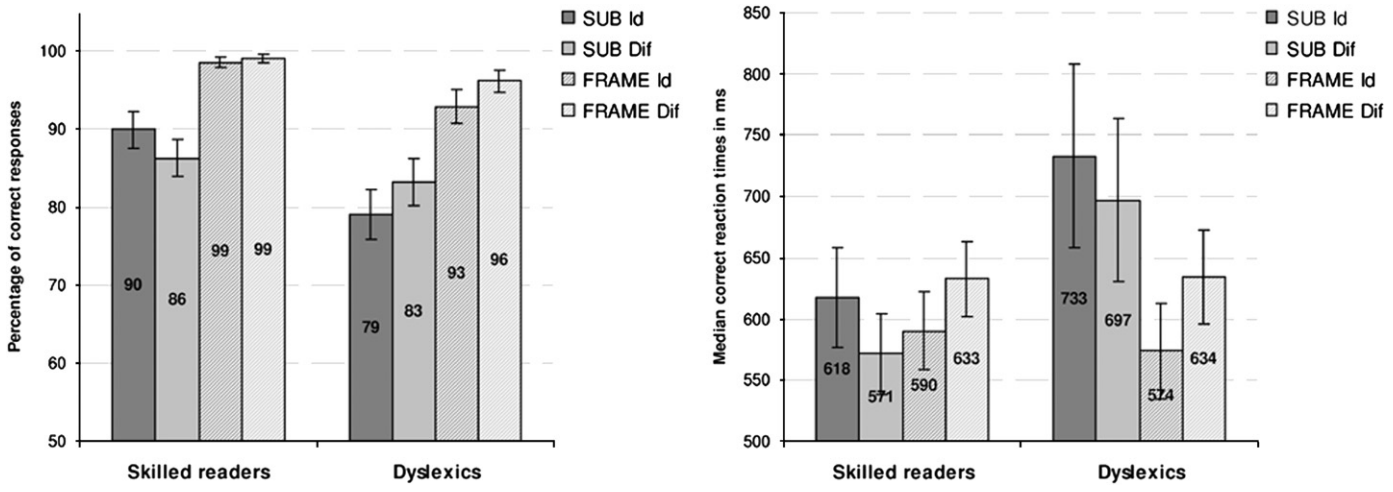

Fig. 2. Mean percentage of correct responses and mean correct reaction times in ms for the identical and different pairs of the substitution (SUB Id and SUB Dif) and frame (FRAME Id and FRAME dif) conditions for the two groups of skilled and dyslexic readers.

Table 2
Cerebral regions activated during the letter string comparison task for the substitution condition relative to baseline ([Sub-Id > baseline] and ([Sub-Dif > baseline] contrasts) and relative to the frame condition ([Sub-Id > Frame-Id] and [Sub-Dif > Frame-Dif] contrasts) for the healthy skilled and dyslexic readers considering the identical and different pairs. The statistical significance threshold for individual voxels was set an uncorrected $p < 0.001$ ($T > 4.02$). For each cluster, the Talairach coordinates (x, y, z) of the peak and the spatial extent (k) are indicated.

	Skilled readers		**Dyslexic adults**	
	x, y, z	*k*	*x, y, z*	*k*
[Sub-Id > baseline]				
Parietal cortex				
Left inferior parietal lobule (BA 40)	−44, −41, 30*	66*	−46, −46, 45	18
Left superior parietal lobule (BA 7)	−40, −50, 54*	15*	–	
Right superior parietal lobule (BA 7)			32, −65, 51	47
Frontal cortex				
Left inferior frontal gyrus (BA 44)	−48, 25, 1	15		
[Sub-Dif > baseline]				
Parietal cortex				
Left superior parietal lobule/precuneus (BA 7)	−22, −63, 53	669	–	
[Left inferior parietal lobule (BA 40)]	−50, −35, 48		−42, −52, 54*	82*
Left supramarginal gyrus (BA 40)	30, −47, 32	76	–	
Right superior parietal lobule (BA 7)	30, −48, 50	317	39, −59, 58*	81*
[Right precuneus (BA 7)]	26, −71, 50		–	
[Right inferior parietal lobule (BA 40)]	38, −38, 48		53, −37, 46*	38*
Left postcentral gyrus (BA 1/2/3)	−63, −18, 23	20		
Temporal cortex				
Left superior temporal gyrus (BA 22)	51, 5, −9	115	–	
Right superior temporal gyrus (BA 22)	−46, 13, −6	185	–	
Left inferior temporal gyrus (BA 20)	−48, −22, −16	28	–	
Left middle temporal gyrus (BA 21/37)	−48, −37, −2	65	–	
Left fusiform gyrus (BA 37)	−55, −49, −16	23	–	
Frontal cortex				
Right middle frontal gyrus (BA 9, 46, 10)	53, 18, 40	87	44, 50, −6	50
	53, 32, 15	57		
	42, 55, 8	55		
Left middle frontal gyrus (BA 9, 10)	−51, 12, 40	114		
	−36, 36, 13	134		
Left inferior frontal gyrus (BA 44)	−59, 16, 18	52		
Left precentral gyrus (BA 4/6)	36, −2, 44	32		
Cerebellum	34, −63, −19	662	–	
	−38, −63, −19	242		
[Sub-Id > Frame-Id]				
No significant voxel	–		–	
[Sub-Dif > Frame-Dif]				
Parietal cortex				
Right superior parietal lobule/precuneus (BA 7)	24, −71, 48	137	–	
	32, −60, 49	29		
Right inferior parietal lobule (BA 40)	63, −32, 20	22		
Left superior parietal lobule/precuneus (BA 7)	−20, −64, 49	56	–	
Left inferior parietal lobule (BA 40)	−30, −47, 32	18	−42, −32, 26*	57*
Left supramarginal gyrus (BA 40)	−40, −55, 34	31	–	
Left angular gyrus (BA 39)	−22, −62, 34	71	–	
Temporal cortex				
Left fusiform gyrus (BA 21)	−36, −11, −21	18	–	
Frontal cortex				
Left inferior/middle frontal gyrus (BA 46/10)	−38, 32, 11	158	–	
	−36, 47, −2	31		
Right middle frontal gyrus (BA 47, 10, 9)	22, 35, 0	74	–	
	48, 47, 7	69		
	53, 19, 38	15		
Cerebellum	−26, −38, −32	18	–	

All peaks $p < 0.001$ uncorrected (random-effect analysis), except $p < 0.005$*.
Abbreviations: BA=Brodmann area; k=number of voxels in the cluster.

Table 2 and Fig. 3) specifically activated a large fronto–parietal–temporal network including the left and right superior and inferior parietal lobules (SPLs and IPLs), the left supramarginal gyrus (SMG), the left and right superior temporal gyri, the left inferior and middle temporal gyrus (ITG) extending to the fusiform gyrus (FG), the right and left middle frontal gyrus, and the left inferior frontal gyrus (IFG). Other areas were also activated (left precentral gyrus, left postcentral gyrus and the cerebellum), possibly in relation with other processes involved in the task (e.g., motor response). Dyslexic adults only showed an activation of the right middle frontal gyrus at the statistical threshold used to identify clusters of activated voxels in skilled readers ($p < 0.001$ uncorrected). Contrary to skilled readers, they did not show any activation of either the parietal or temporal cortex when processing letter strings that differed by two substituted letters. Three further regions – the right SPL, right and left IPL – were found

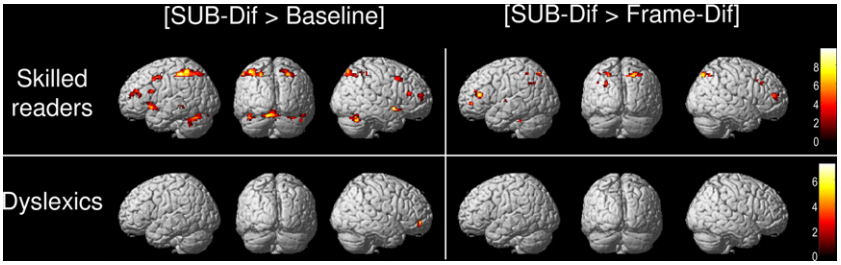

Fig. 3. Cerebral regions activated by skilled readers and dyslexic participants during the substitution condition considering the different pairs relative to baseline ([SUB-Dif > Baseline] contrast) or relative to the control condition ([SUB-Dif > FRAME-Dif] contrast). Relative to controls, dyslexic participants showed no significant activation within the parietal cortex (BA 7 and BA 40) bilaterally, the left inferior gyrus (BA 44) and the left inferior temporal (BA 37) areas when processing substituted letter strings.

Table 3
Brain activity comparison between skilled and dyslexic readers ([Controls > Dyslexics] contrast and [Dyslexics > Controls] contrast) for the substitution condition relative to the baseline considering the identical and different pairs ([Sub-Id > baseline] and [Sub-Dif > baseline] contrasts). The statistical significance threshold for individual voxels was set an uncorrected $p < 0.001$ ($T > 4.02$). For each cluster, the Talairach coordinates (x, y, z) of the peak and the spatial extent (k) are indicated.

	Controls > Dyslexics		**Dyslexics > Controls**	
	x, y, z	*k*	*x, y, z*	*k*
[Sub-Id > baseline]				
Frontal cortex				
Left superior frontal gyrus (BA 10)	−28, 52, −4	19	–	
Occipital cortex				
Left inferior occipital gyrus (BA 18)	−26, −84, −4	24	–	
Right middle occipital gyrus (BA18/19)	30, −93, 6	20	–	
Cerebellum	−18, −50, −31	21	–	
	20, −77, −16	39		
	32, −81, −20	20		
[Sub-Dif > baseline]				
Parietal cortex				
Left superior parietal lobule (BA 7)	−20, −66, 49	25	–	
Temporal cortex				
Left superior temporal gyrus (BA 22)	−44, 7, -5	34	–	
Right superior temporal gyrus (BA 22)	53, 3, −9	51	–	
Left inferior/middle temporal gyrus (BA 37)	−46, −66, 2	851	–	
Occipital cortex				
Left inferior occipital gyrus (BA 18)	−26, −80, −9	204	–	
Right middle occipital gyrus (BA18)	28, −91, 1	104	–	
Frontal cortex				
Left inferior frontal gyrus (BA 44)	−57, 18, 19	70	–	
Left inferior/middle frontal gyrus (BA 46/10)	−40, 40, 18	178	–	
Left precentral gyrus (BA 4/6)	−38, −1, 50	22	–	
Right inferior frontal gyrus (BA 44)	44, 11, 22	15	–	

All peaks $p < 0.001$ uncorrected (random-effect analysis).
Abbreviations: BA=Brodmann area; k=number of voxels in the cluster.

activated at a less restrictive threshold ($p < 0.005$ uncorrected). It is however noteworthy that none of the two regions (left SPL and left ITG) that were more specifically involved in the substitution condition in skilled readers were found activated in dyslexic participants, even at this less restrictive threshold.

When focusing on the identical pairs of the substitution condition ([SUB-Id > baseline] contrast), activation was globally weaker. Skilled readers only activated the left IFG, and the left SPL and IPL at a less restrictive threshold ($p < 0.005$ uncorrected). Dyslexic adults, like controls, showed significant activation of the left IPL. Further activity was observed in the right SPL, instead of the left SPL in controls.

Those brain regions specifically involved in letter string processing were identified by contrasting the substitution and control frame conditions, for the identical and different pair trials. For skilled readers, the [SUB-Dif > Frame-Dif] contrast revealed that the substitution condition elicited greater neural activity than the frame condition within the parietal cortex (including the left and right SPL, the left and right IPL, the left SMG, the left angular gyrus), the middle frontal gyrus bilaterally and the left fusiform gyrus. For dyslexic participants, only the left IPL was more activated in the substitution condition and evidence for SPL activation was only found when using a less restricted threshold ($p < 0.005$ uncorrected). Finally, for both groups, no significant activation was obtained by contrasting the substitution condition to the frame condition on the identical pairs.

A two-sample t-test was performed to statistically compare brain activation in dyslexic and skilled readers on the relevant contrasts (see Table 3 and Fig. 4). For the substitution task on different pairs, the left SPL, the bilateral superior temporal gyrus, the left ITG, the occipital cortex, the bilateral IFG and left middle frontal gyrus were more activated in skilled readers than dyslexics. On identical pairs, the left superior frontal gyrus, the occipital cortex and the cerebellum were more activated in skilled

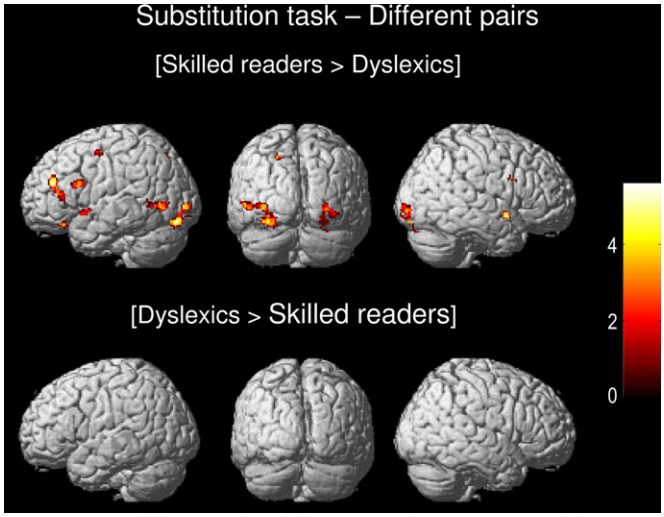

Fig. 4. Cerebral regions differentially activated by skilled readers and dyslexic participants during different pairs processing in the substitution condition. Skilled readers exhibit stronger activation of the left superior parietal lobule, left inferior frontal gyrus and left inferior temporal gyrus.

readers than dyslexics. No significant activation was obtained for the opposite contrasts (Dyslexics > Skilled readers).

The analysis was completed by statistically comparing dyslexic and skilled readers irrespective of normal brain activation by performing a region of interest (ROIs) analysis on predefined and standardized neuroanatomical areas using predefined masks from the "WFU Pickatlas" (Maldjian et al., 2003). Based on skilled readers' data on the [SUB-Id > baseline] and [SUB-Dif > baseline] contrasts and our a priori hypotheses of decreased activation within particular brain regions for the dyslexic participants, the six following a priori cortical ROIs were investigated: left SPL, BA 7; right SPL, BA7; left IPL; BA 40; right IPL, BA 40; left IFG, BA 44; left ITG and FG, BA 37 (Fig. 5). Brain activity in these regions was submitted to separate repeated-measures ANOVAs with Groups (Dyslexics vs. Controls) as between-subjects factor, the Experimental conditions (Substitution vs. Frame) and Similarity of pairs (Identical vs. Different) as within-subjects factors. Skilled readers showed stronger activation of the left SPL ($F_{1,22}=9.95$, $p<0.01$), the right SPL ($F_{1,22}=7.19$, $p<0.05$), the left IPL ($F_{1,22}=7.55$, $p<0.05$) and the left ITG/FG ($F_{1,22}=5.86$, $p<0.05$) for the SUB-Dif than FRAME-Dif condition. Not any brain region was more activated for the SUB-Id than the FRAME-Id condition in either skilled or dyslexic readers. Compared to skilled readers, dyslexic adults showed lower activation for the SUB-Dif condition in the left SPL ($F_{1,22}=10.20$, $p<0.01$), left ITG/FG ($F_{1,22}=6.88$, $p<0.05$) and left IFG ($F_{1,22}=6.48$, $p<0.05$). Note that only the left IFG ($F_{1,22}=6.58$, $p<0.05$) was also more activated for skilled readers than dyslexics for the SUB-Id condition.

4. Discussion

The current study aimed at exploring the neurobiological correlates of letter identity encoding within strings in skilled and dyslexic adult participants. The dyslexic participants were a priori selected to have a parallel letter string processing dysfunction, thus a VA span disorder (Bosse et al., 2007). They were administered a perceptual matching task in which they had to judge whether two successively and briefly displayed letter strings were identical or not. They further performed a control condition that required deciding whether two identical letter strings displayed in turn were both framed or not. The control condition involved similar visual processing and motor responses as the experimental condition but attention was focused on the frame and letters had not to be processed.

As expected, the dyslexic participants were less accurate than adult skilled readers to compare letter strings. They responded as fast as the controls as a whole but contrary to the controls, they took more time to judge whether two letter strings were identical or not than deciding whether the two strings were both framed or not. At the neurobiological level, three brain regions were found to respond more specifically to letter-identity differences within strings than frame differences, namely the right and left SPL (BA7), the left IPL (BA 40) and the left ITG (BA 37). However, only two of these regions, the left SPL and the left ITG showed significant activation enhancement for the different pairs' comparison together with being less activated in dyslexic than control readers. Thus, the left SPL and left ITG more specifically relate to poor letter-identity encoding within strings in dyslexic individuals. Although it was activated during different pairs processing, the left IPL (SMG) does not distinguish dyslexic from control participants. This region is known as responding to letters but does not specifically relate to letter-strings and similarly responds during single-letter processing (Lobier et al., 2012c). Normal activation of the left IPL during different pairs processing but impaired activation of the left SPL and left ITG suggest a specific letter-identity within strings encoding disorder. Higher activation of the right SPL in the dyslexic group when the two letter strings differ may reflect higher right SPL sensitivity to attention demanding tasks (Lobier, Peyrin, Pichat, Le Bas, & Valdois, 2012b). Similar activation of this region in the dyslexic and control participants suggests that the two groups of participants were similarly engaged in the task. A large number of prior studies has emphasized the implication of the left IFG in subvocal articulation (Démonet et al., 1992; Démonet, Price, Wise, & Frackowiak, 1994) and orthography to phonology mapping (Fiez, Balota, Raichle, & Petersen, 1999; Heim et al., 2005). Activation of this region by control participants in the two substitution conditions (identical AND different pairs) may reflect covert articulation of letter names during processing. Lower activation of this region in dyslexic than control participants may be a consequence of their poor visual letter-string processing abilities or the consequence of their additional phonological disorder. Lastly, weaker brain activation when processing identical pairs in the substitution condition may be the consequence of a repetition effect (Penney, Mecklinger, & Nessler, 2001; Rugg, Doyle, & Wells, 1995).

Lower activation of the left inferior temporal cortex in dyslexic participants is a very robust finding (Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Richlan, Kronbichler, & Wimmer, 2009). The comparison of underactivation maps in adults and children with dyslexia identified the left ITG, with more underactivation in the adult studies (Richlan et al., 2011). Indeed although some evidence suggests that this region is recruited from the beginning of reading acquisition (Brem et al., 2010; Church, Coalson, Lugar, Petersen, & Schlaggar, 2008), it is well established that the left ITG, more specifically the portion of this region known as the VWFA develops visual tuning for print with expertise (Dehaene et al., 2010). It is however noteworthy that failure to activate the left ITG was here observed in a population of dyslexic individuals chosen to have a VA span disorder. Evidence that even baboons can learn orthographic regularities suggests that information about letter identity within strings can be processed independently of any prior language knowledge (Grainger, Dufau, Montant, Ziegler, & Fagot, 2012). This suggests that a failure to encode orthographic knowledge may not be necessarily driven by poor phonological abilities. Prototypical cases of developmental surface dyslexia provide further evidence of independent development of orthographic and phonological skills (Brunsdon, Coltheart, & Nickels, 2005; Castles & Coltheart, 1996; Dubois, De Micheaux, Noel, & Valdois, 2007; Valdois et al.,

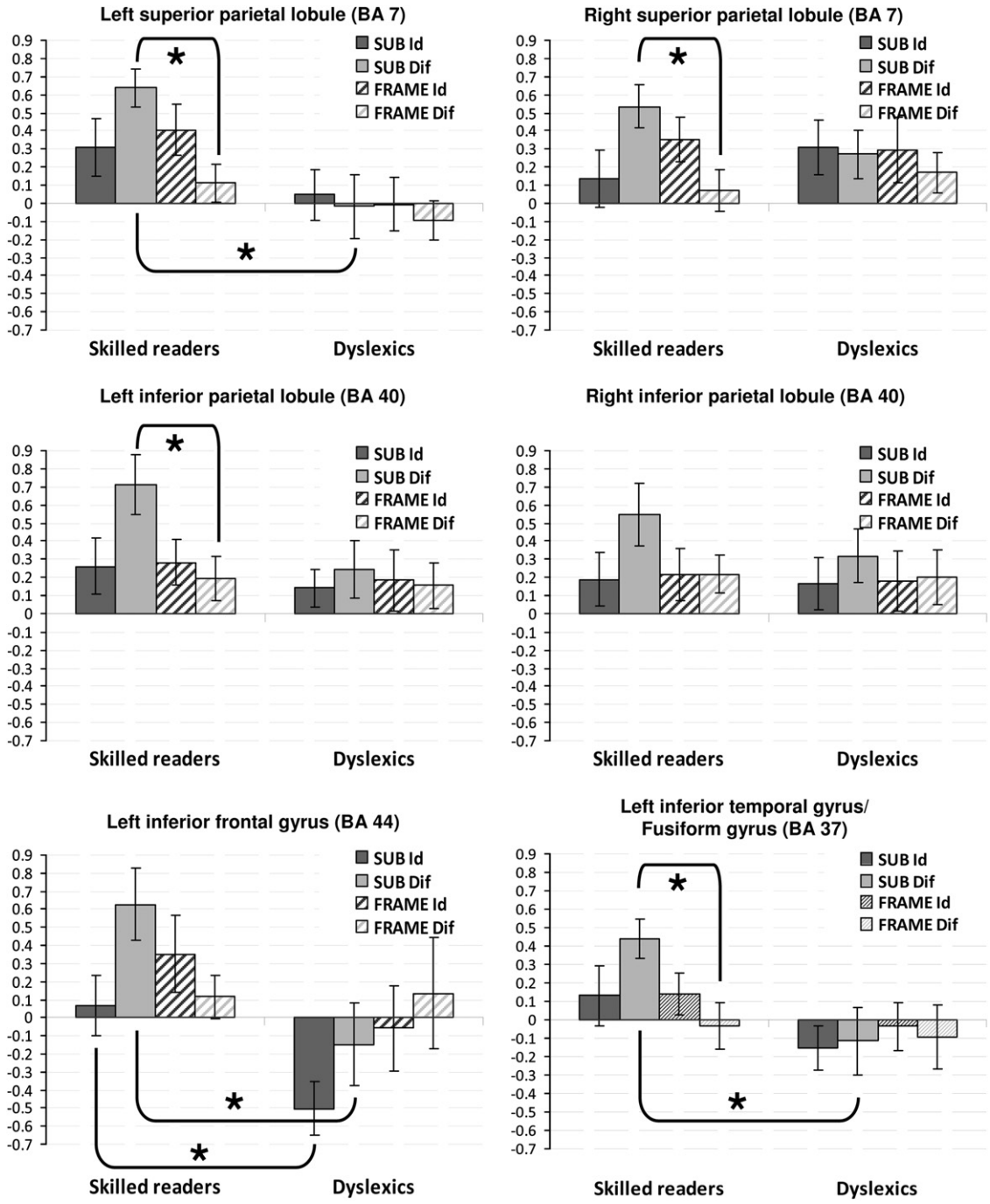

Fig. 5. Comparison of ROIs neural activity in skilled readers and dyslexic participants as a function of condition (substitution vs. frame) and similarity of pairs (identical vs. different pairs). Difference between the average parameter of activity (% change relative to the global mean intensity of signal) calculated for skilled and dyslexic readers shows that the left superior parietal lobule, left inferior frontal gyrus and left inferior temporal gyrus were less activated for the dyslexic than normal readers. The asterisk (*) indicates significant differences.

2003). However, our dyslexic participants further exhibited a phonological disorder. A phonological disorder is rather unlikely to affect performance on a perceptual matching task that did not require naming, however an impact of poor phonological skills on ITG tuning for orthographic information cannot be a priori discarded.

A key finding of the current study is to show that in addition to the left ITG another brain region, the left SPL, further contributes to letter-identity processing within strings. The left SPL has been already identified as specifically involved in orthographic and letter string processing in skilled readers (Joseph, Cerullo, Farley, Steinmetz, & Mier, 2006; Levy et al., 2009; Pernet, Celsis, & Démonet, 2005). In typical readers, the SPLs bilaterally were found activated in visual categorization tasks that required multi-element processing but no identity processing (Peyrin et al., 2011; Peyrin et al., 2012). These brain regions more specifically respond to letter strings than single letters (Lobier et al., 2012a). However, this is not to say that the SPLs are specialized for letter-string processing. To the contrary, they have been found activated by non-alphabetic multi-element strings, such as strings mixing geometrical shapes, pseudo-letters or Hiragana characters (Lobier et al., 2012a) thus suggesting their

more general involvement in multi-character visual parallel processing. The current findings however show that these regions further contribute to multiple letter identity processing. Previous involvement of the SPLs in string processing was mainly observed in categorization tasks that did not require stimuli identification. Evidence for SPLs involvement in a perceptual matching task that requires letter identification is more direct evidence that this region may be involved in the earlier stages of visual word processing.

Traditionally, it is believed that the posterior parietal cortex that belongs to the dorsal visual processing stream codes for spatial location (the "where" system) whereas the ventral system codes for letter (or object) identity (the "what" system). The current findings suggest that letter identity processing within strings is not confined to the ventral pathway but further involves the dorsal visual pathway, more specifically the left SPL. Such findings are compatible with current knowledge on object visual processing, showing that the two dorsal and ventral visual neural systems process very similar visual information (Konen & Kastner, 2008; Xu & Chun, 2007, 2009).

In the current study, VA span impaired dyslexic children under-activated both the left inferior temporal cortex and the left superior parietal lobule during letter-identity processing within strings. Cooperation of the dorsal and ventral visual pathways during visual word recognition has already been emphasized (Rosazza, Cai, Minati, Paulignan, & Nazir, 2009) and reading-related connectivity between the posterior parietal cortex and the inferior temporal cortex has been identified. Through resting-state connectivity investigation, Vogel, Miezin, Petersen, and Schlaggar (2012) identified SPLs as belonging to the network associated with the VWFA. Significant connectivity between VWFA and SPLs was reported in typical readers but not found in dyslexic individuals (Van Der Mark et al., 2009). Available data thus suggests involvement of the dorsal attention network in reading. While our data does not directly bear on the question of how the VWFA and SPLs contribute to reading acquisition, we speculate that these two regions may play a complementary role in perceptual learning and visual specialization. Although most reading models ignore the role of visual attention (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Harm & Seidenberg, 1999), the computational Multi-Trace Memory (MTM) model of reading (Ans, Carbonnel, & Valdois, 1998) to the contrary postulates that visual attention plays a key role in both skilled reading and reading acquisition (Valdois et al., 2004). Indeed, the implemented network includes a visual attention component that delineates the amount of orthographic information that is processed at each step of reading. After individuation of the orthographic information to be processed, this attentional component further identifies and encodes visual information on the input letter string under focus to match previously learned information about orthographic regularities in long-term memory. We speculate that the superior parietal lobules hold the attentional network that subserves individuation and early visual processing of letter-strings in reading. In support of this hypothesis, disrupted activation of this dorsal attentional region was specifically reported in dyslexic individuals who showed a VA span disorder, thus a reduction of the number of letters they could simultaneously process in reading (Peyrin et al., 2011; Peyrin et al., 2012). Further studies are required to determine how the two ventral (ITG and VWFA) and dorsal (SPLs) brain regions interact to ensure perceptual learning.

Acknowledgments

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