

Evidence for a dysfunction of left posterior reading areas in German dyslexic readers

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Abstract

The brain activity during a sentence reading task and a visual control task was examined with fMRI in 13 German dyslexic readers and 15 age-matched fluent readers (age: 14–16 years). These participants came from a longitudinal study and the dyslexic readers exhibited a persistent reading fluency deficit from early on. For the first time with German dyslexic readers, and in correspondence with the majority of functional imaging studies, we found reduced dyslexic activation in the left occipitotemporal cortex and in a small region of the left supramarginal gyrus. Enhanced activation was found in left inferior frontal and subcortical regions.

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1. Introduction

Difficulties in learning to read despite adequate intelligence and schooling are observed in substantial numbers of children. The predominant explanation of this difficulty refers to a verbal-phonological disorder, which is assumed to precede and underlie the difficulty in learning to read (e.g., Snowling, 2000). In its dominant version, this explanation assumes that the main stumbling block in the early phase of learning to read is the acquisition of phonological decoding, that is, the transformation of the letters of an unfamiliar printed word into phonemes and the assembly of these segments into pronunciations. A problem with phonological decoding hinders the young reader to decode in a self-reliant manner the many words which are new in the early phase of learning to read. An important side effect is that this decoding deficit reduces orthographic “self-teaching” (Share, 1995), that is, the formation of memory traces repre-

senting the letter sequences of successfully decoded words. On further encounters, such memory traces (termed orthographic recognition units) allow fast visual word recognition (or of letter strings within words) and, thereby, relieve the system from slow effortful decoding.

This developmental version of the well known dual-route conception of word reading (e.g. Castles & Coltheart, 1993) is commonly used as framework for integrating neuroimaging findings on abnormal brain activation in dyslexic readers (Demonet, Taylor, & Chaix, 2004; McCandliss & Noble, 2003; Pugh et al., 2000; Shaywitz & Shaywitz, 2005; Temple, 2002). A frequent finding is underactivation of left temporoparietal regions, including posterior superior temporal, supramarginal and angular gyrus areas during reading related phonological tasks (e.g., Rumsey et al., 1997; Shaywitz et al., 2002; Temple et al., 2001; Temple, 2002). A further frequent finding is underactivation of the left occipitotemporal cortex, including the fusiform gyrus and posterior parts of the middle and inferior temporal gyri (e.g., Brunswick, McCrory, Price, Frith, & Frith, 1999; McCrory, Mechelli, Frith, & Price, 2005; Paulesu et al., 2001; Salmelin, Service, Kiesila, Uutela, & Salonen, 1996; Shaywitz et al., 2002). In line with the dual-route conception of visual

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word processing, the temporoparietal underactivation is interpreted as reflecting a phonological decoding deficit, and the occipitotemporal underactivation is interpreted as a failure with fast visual word recognition (e.g., McCandliss & Noble, 2003; Pugh et al., 2000). However, there are alternative interpretations. The temporoparietal underactivation is alternatively interpreted as reflecting erroneous performance or performance failures of dyslexic readers (McCrory, 2003) and the occipitotemporal underactivation is alternatively interpreted as reflecting a general impairment of phonological name retrieval (Brunswick et al., 1999; McCrory et al., 2005). In support of this latter interpretation, a PET study found occipitotemporal underactivation in dyslexic readers both for reading aloud visual words and for naming pictures of objects (McCrory et al., 2005). However, inconsistent with a general occipitotemporal dysfunction in dyslexia is the finding of a MEG study which found normal left occipitotemporal activation during face processing in dyslexic readers (Tarkiainen, Helenius, & Salmelin, 2003). Based on findings showing that activation in this region increases with reading skill (Shaywitz et al., 2002), a neutral characterization refers to the left occipitotemporal cortex as reading skill zone which is dysfunctional in dyslexia (Sandak, Mencl, Frost, & Pugh, 2004; Shaywitz & Shaywitz, 2005). In contrast to these posterior underactivations, increased activation during reading and reading related tasks in participants with dyslexia has been reported for the left inferior frontal cortex (e.g., Brunswick et al., 1999; Georgiewa et al., 2002; Grünling et al., 2004; Rumsey et al., 1997; Salmelin et al., 1996; Shaywitz et al., 1998, 2002). This increased activation is commonly interpreted as reflecting stronger reliance of dyslexic readers on phonological decoding, pronunciation assembly and subvocal articulatory activity in attempts to compensate for impaired visual orthographic word recognition (e.g., McCandliss & Noble, 2003; Pugh et al., 2000; Salmelin & Helenius, 2004).

Both the behavioral and the neuroimaging evidence on developmental dyslexia to a large extent comes from participants with difficulties in learning to read English, who indeed suffer from marked difficulties with the acquisition of phonological decoding. This raises the question whether the primacy of the phonological decoding deficit also applies when orthographies, different from English, exhibit regular “easy” grapheme–phoneme correspondences and when teaching directly induces children to phonological word decoding. Indeed, normally progressing children in a substantial number of regular orthographies acquire phonological decoding much faster than English children (Aro & Wimmer, 2003; Seymour, Aro, & Erskine, 2003), and this decoding accuracy advantage was also found in direct comparisons of German and English dyslexic children (Landerl, Wimmer, & Frith, 1997; Ziegler, Perry, Ma-Wyatt, Ladner, & Schulte-Körne, 2003). Extensive research with German and Italian dyslexic children found reduced reading fluency as main dyslexic impairment (De Luca, Borrelli, Judica, Spinelli, & Zoccolotti, 2002; Hutzler & Wimmer, 2004; Wimmer, 1993; Wimmer & Mayringer, 2002; Zoccolotti, De Luca, Di Pace, Judica, & Orlandi, 1999). In terms of the dual-route conception, this fluency deficit can be interpreted as a failure of visual-orthographic word recognition and

on reliance on slow serial decoding instead. Support for this interpretation is provided by an abnormal word length effect on reading time (Landerl et al., 1997; Ziegler et al., 2003). Similarly, eye movement studies found an abnormal increase in number of fixation with increasing word length (De Luca et al., 2002; Hutzler & Wimmer, 2004).

If acquisition of phonological decoding is less of a problem in regular orthographies, then one would expect that not a dysfunction of the “phonological” temporoparietal, but of the “visual” occipitotemporal reading circuit may be the origin of a persistent impairment of fast fluent reading. A primary dysfunction of the occipitotemporal reading circuit is indeed suggested by a series of MEG studies with Finnish dyslexic adults (reviewed by Salmelin & Helenius, 2004). Finnish is one of the most regular alphabetic orthographies and dyslexia primarily means slow dysfluent reading. Finnish dysfluent readers exhibited normal early low level visual processing in occipital regions, but, different from the controls, no activation of left occipitotemporal reading areas during the first 200 ms of word presentation (Helenius, Tarkiainen, Cornelissen, Hansen, & Salmelin, 1999; Salmelin et al., 1996). A dysfunction of left occipitotemporal reading areas was also found in the cross-linguistic PET study by Paulesu et al. (2001) which included dyslexic adult readers from the regular Italian orthography and from less regular orthographies (French and English). Different from these results, suggesting a left occipitotemporal dysfunction in dyslexic readers in regular orthographies, fMRI studies with German dyslexic children surprisingly did not find such an occipitotemporal underactivation (Georgiewa et al., 1999, 2002; Grünling et al., 2004; Ligges et al., 2003). However, Georgiewa et al. (2002) examined only one slice (around $z = +7$) and cannot be informative on occipitotemporal brain activation abnormalities. Three studies with German dysfluent readers found enhanced, presumably compensatory activation in left inferior frontal regions as the main abnormality (Georgiewa et al., 2002; Grünling et al., 2004; Ligges et al., 2003), whereas one found the opposite pattern (Georgiewa et al., 1999).

The present fMRI study is a further attempt to examine functional brain abnormalities in German dyslexic readers who suffer primarily from slow dysfluent reading. As stimuli we used short sentences with all words of a sentence presented simultaneously. Participants had to verify whether the sentence makes sense in relation to world knowledge (e.g., true: “A flower needs water”, false: “Cows eat only honey”). The idea was to examine brain activation with a task, which is close to natural reading in the sense that it requires reading for meaning. However, the short sentences were syntactically simple and meaningful or not in an obvious way. Therefore, it can be assumed that differences between fluent and dysfluent readers are mainly due to the difference in efficiency of word processing and may have comparatively little to do with differences in syntactic and semantic skills. The present dysfluent readers came from a longitudinal study, which started at the beginning of Grade 1. This allowed to ascertain the persistence of the reading fluency problem as even at the beginning of school the later dysfluent readers exhibited a serial rapid naming deficit when confronted with a sequence of pictured objects. In contrast, our dysfluent participants had little

difficulty with the acquisition of accurate decoding so that the fluency problem cannot be attributed to a prolonged difficulty with phonological decoding.

Our fMRI study used a block design and contrasted brain activation during sentence reading with brain activation during a visual processing task using strings of false fonts. The use of a block design was motivated by its increased sensitivity to detect activation (Friston, Zarahn, Josephs, Henson, & Dale, 1999). A first analysis of dyslexic abnormalities in reading specific brain activation used regions of interest (ROIs) suggested by the above-mentioned functional imaging studies. The specific expectation was that our dysfluent readers will exhibit underactivation of the left occipitotemporal region presumably engaged by fast visual word recognition. Reliance on phonological decoding may be reflected in increased activation of the left inferior frontal cortex engaged by pronunciation assembly and subvocal articulatory activity. From reliance on phonological decoding one may also expect enhanced activation of left temporoparietal regions. However, as already mentioned, contrary to this expectation a number of studies found underactivation of this region in dyslexic readers. This ROI-based analysis was supplemented by a voxel-based analysis to obtain a more complete characterization of abnormal brain activation during reading in dysfluent readers.

2. Methods

2.1. Participants

Thirteen German-speaking adolescents with a severe reading fluency impairment and 15 nonimpaired readers were recruited from a large longitudinal sample. All participants were male and at the time of the present study they were in the final year (Grade 9) of obligatory schooling (age range: 14–16 years). The study was approved by the ethical committee of the University of Salzburg and written informed consent was obtained from all participants and one of their parents. The initial selection of candidates from the longitudinal sample relied on reading fluency percentiles (dysfluent readers: <11, fluent readers: >20) from a preceding assessment in Grade 7. In addition, all boys had to have a nonverbal IQ of at least 85 at the end of Grade 1 based on three subtests of the Primary Test of Cognitive Skills (Huttenlocher & Cohen-Levine, 1990) and they had to show consistent right hand preference at the school entrance assessment. The final selection of participants relied on reading fluency percentiles of below 11 and above 20 for dysfluent and fluent readers, respectively, at the time of the present assessment (Grade 9). The Grade 9 fluency test (paper and pencil) consisted of a list of sentences, and participants were asked to mark as correct or incorrect as many sentences as possible within 1 min. The percentiles corresponding to the number of correctly marked sentences are based on preliminary norm data from 213 Grade 9 students. A similar fluency test, but with a 3 min time limit, was used for the preceding Grade 7 reading fluency assessment (Auer, Gruber, Mayringer, & Wimmer, 2005). As these paper and pencil tests should allow a quick screening for a reading fluency impairment, the sentences are of rather simple syntax and content with the effect that erroneous judgements are very infrequent.

Table 1 (upper section) shows that the dysfluent readers evaluated only about half of the number of sentences of the fluent readers, but similar to the fluent readers, committed very few errors. Furthermore, Table 1 presents reading fluency data from an additional assessment (see Hawelka & Wimmer, 2005) which was done at the time of the present fMRI study and consisted of reading aloud three lists of unrelated words and three lists of pseudo-words. Accuracy was close to ceiling even for the dysfluent readers. As evident from Table 1, the reading rate of the dysfluent readers on the word and pseudo-word list reading tasks – similar to the sentence verification rate – was only about half the rate of the controls. Combined over both groups, the correlations between performance on the paper and

Table 1
Descriptive measures and early reading performance

	Fluent readers (<i>n</i> = 15)		Dysfluent readers (<i>n</i> = 13)		<i>t</i> (26)
	M	S.D.	M	S.D.	
Age (years)	15.46	0.58	15.89	0.75	0.43
Nonverbal IQ	106	14.31	106.6	11.34	0.12
Sentence reading					
Fluency (N/min)	21.33	3.77	10.54	2.18	−9.41***
Accuracy (% correct)	98.23	3.21	94.76	7.98	−1.34
List reading fluency (syl/min)					
Words	189.45	24.20	99.78	30.59	−8.48***
Pseudo-words	137.66	18.54	72.37	24.32	−7.89***
Spelling (% correct)	68.8	19.43	27.69	14.28	−6.43***
Early measures					
Serial visual naming (school entrance)					
Fluency (syl/min)	50.18	10.98	39.18	7.24	−3.07**
Reading fluency (syl/min)					
1st Grade	63.61	27.38	24.87	9.76	−4.83***
3rd Grade	110.42	15.10	54.98	16.51	−9.29***
Reading accuracy (% correct)					
1st Grade	93.33	9.57	73.85	34.41	−1.98*
3rd Grade	91.12	8.18	86.54	17.61	−0.90

Notes: *t*-Values refer to group comparisons and are pooled in such a way that negative values indicate lower performance of dyslexic readers.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

pencil sentence verification task and reading rate for words and pseudo-words were very high with $r(21) = 0.81$ and $.88$, $ps < 0.001$, respectively. Table 1 also shows that dyslexic readers exhibited an massive orthographic spelling deficit. However, nearly all misspellings were phonemically acceptable. With respect to spelling, it is important to note that German exhibits high regularity in the reading direction (resulting in few misreadings), but low regularity in the writing direction (resulting in many misspellings).

The lower section of Table 1 shows that the dysfluent readers from the very beginning of reading development exhibited a fluency deficit. At the beginning of Grade 1, serial rapid picture naming was part of a school entrance assessment and required to name quickly a sequence of pictured object. On this task, the later dysfluent readers exhibited substantially reduced naming fluency. At the end of Grade 1, the longitudinal participants were instructed to read aloud quickly and accurately a list of 10 words and a list of 10 pseudo-words, and in Grade 3 with the same instruction a list of 24 pseudo-words was presented. Table 1 shows that both in Grade 1 and in Grade 3 the reading rate of the dysfluent group was only about half the rate of the fluent group. At the end of Grade 1, the dysfluent group also exhibited reduced reading accuracy. However, this lower accuracy (still 74% correct) is mainly due to two very poor readers who were unable to synthesize phonemes into pronunciations and uttered isolated phonemes instead. This failure with synthesis could be characterized as an extreme form of a fluency impairment (see Wimmer, 1996, for a detailed analysis of early difficulties of German dyslexic readers). Without these two cases of synthesis failure, the mean accuracy (87% correct) of the dyslexic group in Grade 1 would have been close to that (93% correct) of the fluent readers. At the end of Grade 3 the present dysfluent readers no longer differed from fluent readers in reading accuracy for pseudo-words in a list reading task with speed instruction. In summary, the fluency deficit at the time of the fMRI study in the final year of schooling was already present in the early phase of learning to read and was preceded by a deficit in rapid picture naming at school entrance. In contrast, reading accuracy was less of a problem with the majority of the dysfluent readers exhibiting high accuracy already after about 8 months of instruction.

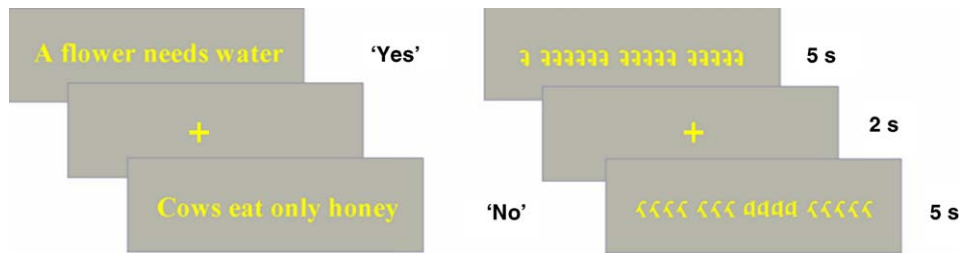


Fig. 1. Example stimuli and stimulus timing for the sentence verification and the false fonts visual control task.

2.2. fMRI Procedure

Functional MR images were acquired during sentence verification and a corresponding visual control task. All sentences were short (3–6 words, $M = 4.27$; 16–27 letters, $M = 23.61$), syntactically simple and of simple content. The nouns, verbs and adjectives of the sentences had a median frequency according to the CELEX Database (Baayen, Piepenbrock, & van Rijn, 1993) of 161 per million. All sentences were in the active voice and contained no negations or subordinate clauses. Examples are “A flower needs water” or “Cows eat only honey”. Each of the 28 sentences was presented for 5 s and had to be evaluated as correct (“making sense”) or incorrect by a button press response. Presentation of whole sentences was preferred to word-by-word presentation as it corresponds more closely to the natural reading situation and reduces memory load. The presentation time of 5 s per sentence was based on a pretest showing that this presentation time allowed poor readers to correctly evaluate sentences similar to the present ones. The fixed presentation rate compared to self-paced presentation prevents that fluent readers process more sentences within a block than dysfluent readers. More sentences within a block may lead to increased reading brain activation in fluent readers simply because of higher number of processed sentences. Increasing the number of words within a block was found to lead to increased activation in several regions including the left occipitotemporal cortex (Mechelli, Friston, & Price, 2000).

For the visual control task, the letters of each test sentence were replaced by false fonts. The sentences and false font stimuli subtended a mean visual angle of approximately 19.5° (range 15.8° – 24.4°). The task was to evaluate whether all “words” of the “sentence” consisted of one and the same false font or whether one “word” differed from the rest by a different false font. The “false fonts” strings shared with the sentences basic visual characteristics and the visual control task shared with sentence verification the decision component and the motor response. Fig. 1 illustrates stimuli and time course for both sentence reading and false font processing.

No resting (or fixation) baseline was included. A resting baseline may lead to spontaneous semantic processes (e.g., Binder et al., 1999) and may therefore hinder the detection of areas involved in semantic sentence processing. The present low-level visual control task reduces such uncontrolled activity. A further advantage is that the majority of functional neuroimaging studies on dyslexia also used low-level visual control conditions and not resting baseline. Obviously, equivalent control conditions enable a better comparison across studies (see Newman, Twieg, & Carpenter, 2001).

Participants were familiarized with the tasks outside the scanner. Each participant completed a functional imaging run which consisted of seven reading epochs and eight visual control epochs. The reading and control epochs alternated, but the first and last epoch for each participant was a control epoch. Each reading epoch presented four sentences. To ensure attention to all sentences of an epoch, the number of incorrect sentences in one epoch varied between one and two. Altogether, 12 of the 28 sentences were incorrect. The sequencing of the stimuli in the visual control epoch corresponded to that of the sentence processing epochs. The sentence processing and visual control epochs followed each other in immediate succession. The whole run lasted 420 s.

The stimuli were projected by a video beamer (located outside the MR-scanner room) on a semi-transparent screen and viewed by the participants via a mirror mounted above their heads. A MR-compatible response box with two buttons in the right hand allowed responding “yes” with the index finger and “no” with the middle finger. Projection and timing of the stimuli as

well as recording of responses were controlled by “Presentation” (Neurobehavioral Systems Inc.). Foam pillows and a strap over the forehead reduced head movements.

2.3. Image acquisition

First, a low resolution T1-weighted MPRAGE structural scan was acquired from each participant (TR 12 ms, FA 12° , TE 4 ms, FOV 220 mm, matrix 64×64 , twenty-one 6 mm thick axial slices). During the functional imaging run 177 T2*-weighted gradient-echo EPI images with a TR of 2400 ms (TE 40 ms, FA 86° , FOV 220 mm, matrix 64×64 , twenty-one 6 mm thick axial slices sensitive to BOLD contrast) were acquired. After functional imaging a high resolution T1-weighted MPRAGE structural scan was acquired (TR 13 ms, FA 12° , TE 4 ms, matrix 256×256 , 130 1.3 mm thick axial slices). During the pauses between each scan communication was initiated with participants to inform them of the remaining scans and check their well-being. For functional and structural imaging a Philips Intera 1.5 Tesla MR-scanner (Philips Medical Systems Inc., Best, The Netherlands) was used.

2.4. Image analysis

SPM 2 (<http://www.fil.ion.ucl.ac.uk/spm>) was used for data preprocessing and statistical analysis. Functional images were realigned to correct for head movements and unwarped to reduce variance due to interactions between head movements and EPI distortions (Andersson, Hutton, Ashburner, Turner, & Friston, 2001). Afterwards, the low-resolution structural scan was coregistered to the mean functional image to facilitate the following coregistration of the functional images to the high-resolution structural scan. For these processing steps mutual information coregistration was used. For warping into standard stereotactic space, the high-resolution T1-weighted scan was normalized to the MNI T1 brain template by using affine registration and $4 \times 5 \times 4$ nonlinear basis functions. The resulting normalization parameters were then applied to the functional images, which were resampled to 3 mm isotropic voxels. To compensate for residual differences between subjects after normalization and to enhance activation detection the normalized functional images were smoothed with an isotropic 9 mm FWHM Gaussian Kernel.

The functional data were high-pass filtered with a cut-off of 128 s. Removing frequencies below 1/128 Hz reduces low frequency drifts. For correction of temporal autocorrelations an AR (1) model (Friston et al., 2002) as implemented in SPM 2 was used. Statistical analysis was performed within a two stage mixed effects model. First, for each participant a contrast image between activation in sentence processing versus control epochs was calculated by fitting a statistical model to the data, which consisted of a boxcar function convolved with a synthetic hemodynamic response function for each reading epoch. Second, these subject-specific contrast images were used for the second level (random effects) analysis, which allows generalization to the population.

For the ROI analysis, three left hemisphere regions based on previous published findings in functional neuroimaging studies were used. For the left occipitotemporal region a box-shaped ROI was centred at $x = -51$, $y = -51$, $z = -6$ with an extension of ± 8.5 mm along the x -, ± 10 mm along the y -, and ± 10 mm along the z -axis. This ROI includes posterior parts of the middle and inferior temporal gyrus and a region of the fusiform gyrus and is based on coordinates from previous studies showing reduced activation of the left occipitotemporal cortex in dyslexic readers (Brunswick et al., 1999; McCrory et al., 2005; Paulesu

et al., 2001; Shaywitz et al., 2002). For the left temporoparietal region a ROI was centred at $x = -51$, $y = -48$ and $z = 21$ and extended ± 5.5 mm along the x -, 18.5 mm along the y -, and ± 11 mm along the z -axis. It covers segments of the posterior superior temporal, the angular and the supramarginal gyrus. It is based on coordinates of neuroimaging studies reviewed by Temple (2002). The left frontal region involved in phonological output processes was based on coordinates from three studies which found higher reliance on left inferior frontal and precentral regions in dyslexic readers (Brunswick et al., 1999; Rumsey et al., 1997; Shaywitz et al., 2002) and includes parts of the inferior frontal and the precentral gyrus. Its centre was at $x = -51$, $y = 10$, and $z = 26$ and it extended ± 13 mm along the x -, ± 14 mm along the y -, and ± 14 mm along the z -axis. For each of these left hemisphere ROIs a homologue right hemisphere was identified by changing the sign of the x coordinate.

For the voxel-based analysis t -test comparisons identified voxels with higher reading than control activation within each group. A threshold of $p < 0.05$ corrected for multiple comparisons using the false discovery rate (Genovese, Lazar, & Nichols, 2002) was applied. An additional criterion was that at least four neighbouring voxels had to exhibit higher reading than control activation. In a second step, two sample t -tests were performed to identify voxels, which exhibit group differences during reading. These comparisons were limited to voxels in clusters, which in the preceding analysis were identified as showing higher reading than control activation in at least one group. For the two sample t -tests a threshold of $p < 0.05$ based on the false discovery rate (FDR) was used. Regions with a minimum extent of four voxels and surviving a liberal threshold of $p < 0.1$, FDR-corrected, are also reported for exploratory purposes.

3. Results

3.1. Behavioural measures during scanning

Table 2 shows reaction times and number of errors for sentence verification and false font processing. As expected, dysfluent readers exhibited longer sentence processing time than fluent readers, but made almost no errors. On the visual control task, dysfluent and fluent readers exhibited rather similar performance both with respect to speed and accuracy.

3.2. Regions of interest analysis

Fig. 2 shows brain activation elicited by sentence processing relative to false font processing with the positive values of left hemisphere ROIs indicating higher activation for sentence verification and the negative values of the right hemisphere ROIs indicating the opposite. Based on previous studies, dysfluent

Table 2
Behavioural performance on the fMRI tasks

	Fluent readers ($n = 15$)		Dysfluent readers ($n = 13$)		$t(26)$
	M	S.D.	M	S.D.	
Reaction time (ms)					
Sentence reading	2270	938	3329	854	-3.13***
Visual control task	1667	1098	1712	1118	-0.11
Accuracy (N errors)					
Sentence reading (max = 28)	0.53	0.74	1.23	1.79	-1.38
Visual control task (max = 32)	1.80	1.15	1.62	1.20	0.42

Notes: t -Values refer to group comparisons and are pooled in such a way that negative values indicate lower performance of dyslexic readers.

*** $p < 0.001$.

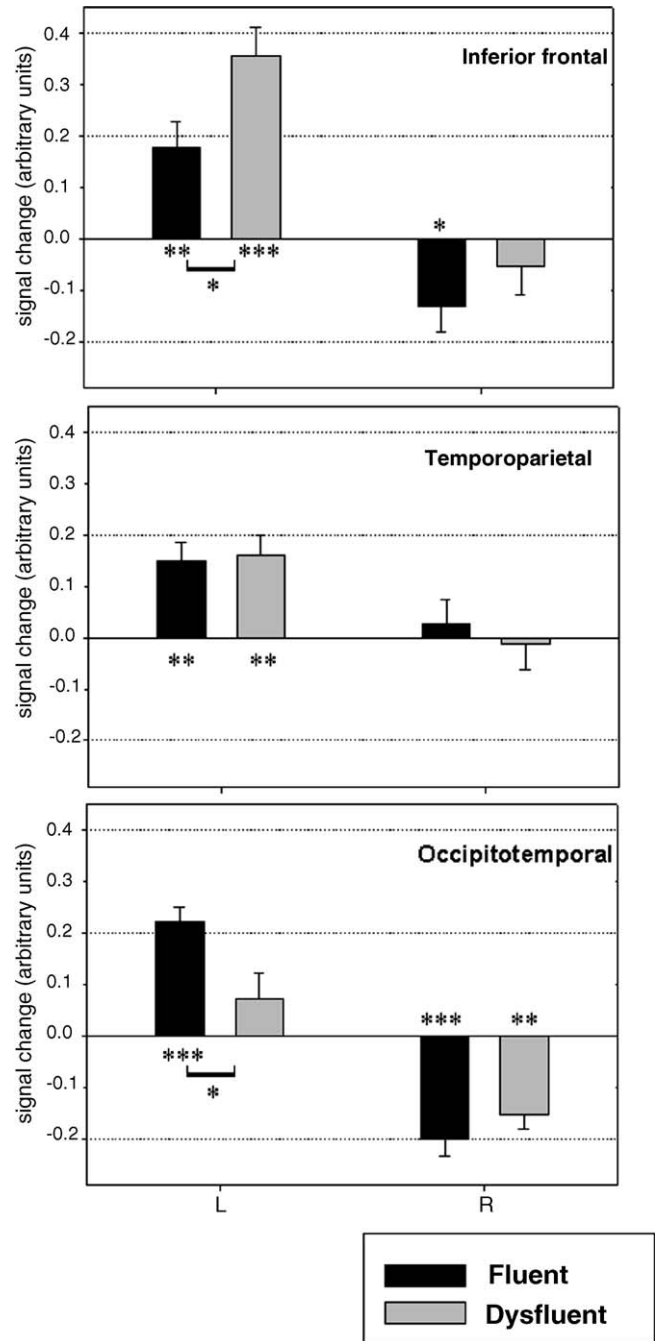


Fig. 2. Mean (\pm S.E.M.) reading specific signal changes (compared to the visual control task) for fluent (black) and dysfluent (gray) readers in regions of interest (ROIs) in the left and right hemisphere occipitotemporal, temporoparietal and inferior frontal/precentral cortex. Asterisks below bars indicate significant reading specific signal change (one sample t -test). Asterisks below brackets indicate significant group differences (independent samples t -test). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

ent readers were expected to exhibit underactivation of the left occipitotemporal ROI (engaged by fast visual word processing) and increased activation of the left inferior frontal ROI (engaged by phonological decoding). As evident from results of the group comparisons in Fig. 2, these expectations found support. The left temporoparietal ROI also exhibited reliable higher activation for sentence than false font processing but the groups did

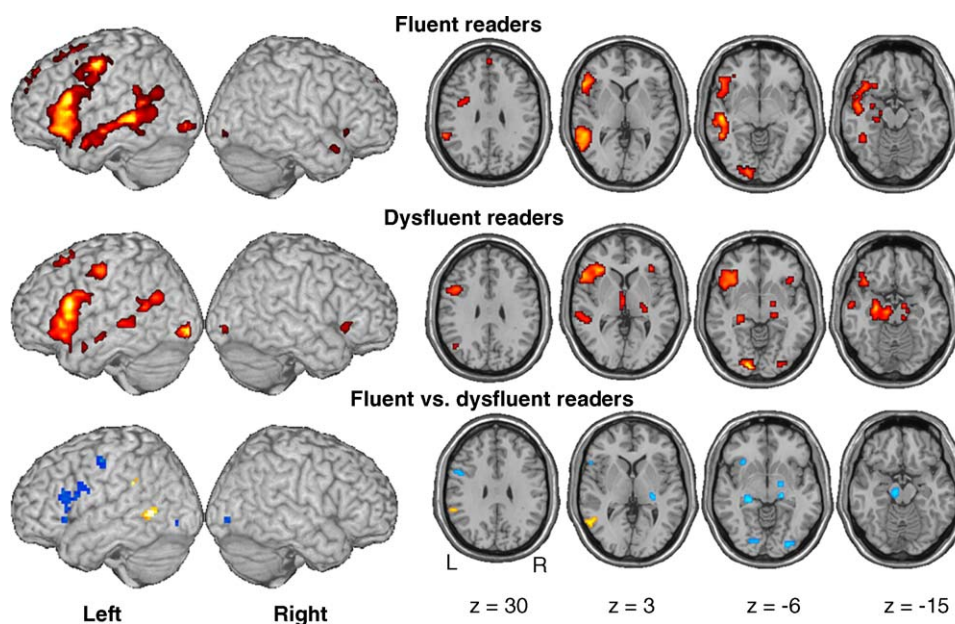


Fig. 3. Surface renders (render depth = 25 mm) and axial slices displaying regions exhibiting reliable sentence reading specific activation shown in red/yellow for fluent (upper row) and dysfluent readers (middle row), thresholded at $p < 0.05$ (FDR-corrected). Regions with reliable group differences are shown in the last section (warm colours: fluent > dysfluent readers, cold colours: dysfluent > fluent readers, $p < 0.1$, FDR-corrected).

not differ. Fig. 2 shows that only at left hemisphere ROIs did sentence processing lead to higher activation than false font processing. At the right hemisphere ROIs, activation in response to sentences either did not differ from activation in response to false font strings (temporoparietal ROI) or was reduced compared to false font processing and this was reliably so for both groups for the right occipitotemporal ROI. The hemisphere difference in activation was reliable for each of the three left–right ROI pairs, $F_s(1,26) > 11.2$, $p_s < 0.01$. The hemisphere by group interaction was only reliable for the occipitotemporal region, $F(1,26) = 7.08$, $p = 0.01$, and resulted mainly from the reduced sentence verification activation of the dysfluent readers for the left occipitotemporal ROI.

3.3. Voxel-based analysis

The surface renders and axial slices in Fig. 3 show brain regions where sentence reading led to reliably higher activation than the false fonts visual control task. For fluent readers (first row), extended activations were found in the left temporal cortex mainly along the superior temporal sulcus and in left inferior frontal and precentral regions. The left temporal activation extended into the supramarginal gyrus and the inferior occipitotemporal cortex. The later activation is evident from the axial slice at $z = -15$. Small clusters were also identified in a left and right occipital region, a right temporal region and a right inferior frontal region. The dysfluent readers (second row) exhibited a similar activation pattern, but the left temporal cluster was reduced in extent and specifically the posterior extension into the inferior occipitotemporal cortex was missing (see axial slice at $z = -15$). In dysfluent readers, additional activation clusters were found in the left medial temporal cortex and in a number of subcortical regions. The third row of Fig. 3 shows the results

of the group comparisons, which are presented in more detail in Table 3. Higher activation in fluent than dysfluent readers was found for a left occipitotemporal cluster centered in the posterior middle temporal gyrus and for a smaller cluster centered in the supramarginal gyrus. In contrast, higher activation in dysfluent than fluent readers was found in a substantial number of cortical clusters (left and right lingual gyri, left medial temporal cortex, left inferior frontal, precentral, and motor region and the left anterior insula). Furthermore, a number of subcortical regions with higher activation in dysfluent than fluent readers were identified (bilateral thalamic regions, right caudate, left brainstem). The mean signal change values in Table 3 show that with the exception of the left anterior frontal region where both fluent and dysfluent exhibited activation, all group differences resulted from one group exhibiting substantial sentence specific activation (relative to false fonts) and the other exhibiting no such activation.

As already noted the occipitotemporal cluster with reading specific activation in fluent readers extended into the inferior occipitotemporal cortex, which contains the so-called visual word form area (VWFA) of Cohen et al. (2000, 2002). This was not the case for the dysfluent readers. However, the voxel-based analysis did not identify this group difference as reliable. Therefore, an additional, more sensitive ROI analysis was performed. We extracted sentence processing activity from a spherical ROI with a 5 mm radius centered on previously published coordinates of the VWFA ($x = -43$, $y = -54$, $z = -12$), which could be localized within this region in the majority of cases (see McCandliss, Cohen, & Dehaene, 2003). In this sensitive ROI analysis, fluent readers exhibited more reading specific activation ($M = 0.177$, $SE = 0.054$) than dysfluent readers ($M = 0.051$, $SE = 0.046$), $t(26)$, $p = 0.045$, one-sided. As no imaging study to date has reported increased activation of left occipitotemporal

Table 3
Brain regions with group differences in reading specific brain activation

	Coordinates			<i>t</i>	Extent (mm ³)	Signal change				
	<i>x</i>	<i>y</i>	<i>z</i>			Fluent		Dyslexic		
						M	S.E.	M	S.E.	
Left hemisphere										
Fluent readers > dysfluent readers										
Posterior middle temporal	-57	-60	3	4.68	702	0.35	0.05	-0.05	0.07	
Supramarginal	-60	-42	30	4.21	108	0.21	0.04	-0.05	0.05	
Dysfluent readers > fluent readers										
Lingual	-15	-84	-9	2.95	270	0.06	0.03	0.20	0.03	
Medial temporal	-27	-27	-6	4.07	1053	0.05	0.04	0.29	0.05	
Motor	-54	-12	48	3.82	729	0.14	0.03	0.37	0.05	
Inferior frontal/precentral	-54	21	18	4.74	2214	0.23	0.04	0.57	0.06	
Anterior insula	-33	21	-6	3.45	162	0.07	0.04	0.27	0.05	
Thalamus	-9	-15	15	2.65	135	0.01	0.05	0.32	0.07	
Brain stem	-9	-18	-18	3.76	513	0.01	0.05	0.26	0.04	
Right hemisphere										
Dysfluent readers > fluent readers										
Lingual	27	-87	-6	3.69	216	-0.01	0.04	0.20	0.04	
Thalamus	27	-27	6	3.69	162	-0.04	0.04	0.18	0.04	
	18	-21	-6	4.72	216	-0.10	0.05	0.22	0.04	
	15	-9	-6	3.19	189	-0.04	0.07	0.21	0.04	
Caudate	18	12	18	3.35	135	0.04	0.04	0.23	0.05	
	21	-18	21	3.25	405	0.04	0.03	0.20	0.04	

Notes: analysis of group differences was restricted to regions showing significant reading specific activation in at least one of the two groups. Regions showing significant group differences at $p < 0.05$ (FDR-corrected) are printed in bold. Regions not in bold showed group differences at $p < 0.1$ (FDR-corrected). Signal change is in arbitrary units.

regions in dyslexic readers, we consider an one-sided significance level appropriate.

4. Discussion

In summary, the present functional neuroimaging study contrasted brain activity during a sentence reading task and a visual control task in dysfluent and fluent readers of German and found reduced dyslexic activation in the left occipitotemporal cortex and in a small region of the left supramarginal gyrus. Enhanced activation was found in left inferior frontal and subcortical regions. These results add to the pattern of findings showing reduced activation in left temporoparietal and left occipitotemporal regions and enhanced activation in left frontal regions as the universal signature of developmental dyslexia in alphabetic orthographies (see McCandliss & Noble, 2003; Pugh et al., 2000; Shaywitz & Shaywitz, 2005). In the following, we discuss in detail the main activation results and specific methodological aspects of the present study.

4.1. Brain regions with less activation in dysfluent readers

The voxel-based analysis identified not only a cluster in the left occipitotemporal cortex, but also a small cluster in the left supramarginal gyrus where dysfluent readers, different from fluent readers, exhibited no activation in response to sentences (compared to false fonts). This finding is in correspondence with several studies which found left temporoparietal underac-

tivation in dyslexic readers (e.g., Rumsey et al., 1997; Shaywitz et al., 2002; Temple et al., 2001; Temple, 2002). However, different from the voxel-based analysis, the ROI-based analysis did not provide evidence for left temporoparietal underactivation in dysfluent readers—actually there was a tendency to the opposite and both groups exhibited reliable reading specific activation. The ROI-based analysis was based on coordinates from previous findings (see Section 2) and included the posterior superior temporal gyrus and the angular gyrus, in addition to the supramarginal gyrus. The difference between the voxel-based and the ROI-based analysis implies that the absent supramarginal activation of the dysfluent readers was accompanied by increased activation in neighbouring temporoparietal regions. This focal underactivation of the left supramarginal gyrus is difficult to interpret. The common assumption is that the left temporoparietal region is engaged by orthographic–phonological transcoding and underactivation in this region reflects phonological decoding deficits in dyslexic readers (McCandliss & Noble, 2003; Pugh et al., 2000; Temple, 2002). It must remain open whether this explanation applies to the presently found focal left supramarginal underactivation, as our dysfluent readers apparently did not suffer from an impairment in phonological decoding, but an impairment in reading fluency.

A main finding of the present study is that dysfluent readers different from fluent readers exhibited no activation during sentence processing (relative to false font processing) in the left occipitotemporal cortex. This group difference in occipitotemporal activation was found in the voxel-based analysis and in

the ROI analysis based on previous neuroimaging studies (see Section 2). This group difference – absence of reading specific activation in dysfluent and presence of such activation in fluent readers – was also found for a smaller region of interest in the ventral occipitotemporal cortex centered at the visual word form area of Cohen et al. (2000, 2002). The peak voxel of the present cluster, exhibiting a group difference in the left occipitotemporal cortex, was located in the posterior middle temporal gyrus at $x = -57$, $y = -60$, $z = 3$. This corresponds closely to the cross-linguistic dyslexia study of Paulesu et al. (2001) which found the most reliable group difference centered at $x = -60$, $y = -56$, $z = 0$. As outlined in Section 1, underactivation of the left occipitotemporal cortex is one of the most common findings of functional neuroanatomical studies of dyslexia (see McCandliss & Noble, 2003; Pugh et al., 2000; Shaywitz & Shaywitz, 2005). The new contribution here is that this underactivation was for the first time demonstrated in a sample of German dyslexic readers. Previous functional neuroimaging studies with German dyslexic children surprisingly failed to find occipitotemporal underactivation (Georgiewa et al., 1999; Grünling et al., 2004; Ligges et al., 2003). The reasons for this discrepancy cannot be definitely determined. One may speculate that the letter strings used as base-line control in these previous German studies led to relatively high activation in left occipitotemporal regions so that a further increase by word processing could not be detected. This interpretation finds support in a finding of Cohen et al. (2003). The present study apparently is the first one which found occipitotemporal underactivation in non-adult dysfluent readers of a regular orthography as the Finnish MEG studies (see Salmelin & Helenius, 2004) and the cross-linguist PET study by Paulesu et al. (2001), which included Italian dyslexic readers, investigated adult dysfluent readers.

The present evidence for left occipitotemporal underactivation in dysfluent readers was found in a relatively natural sentence reading task. There are only two other studies which used a sentence reading paradigm. A MEG study by Helenius, Salmelin, Service, and Connolly (1999) with Finnish dyslexic readers found only a tendency toward reduced early activation in the left occipitotemporal region. A small-scale fMRI study with Japanese dyslexic readers described the main result as rather vague middle temporal activation in dyslexic readers, but this study is hard to interpret since groups were not directly compared (Seki et al., 2001). All other studies, which documented left occipitotemporal underactivation in dyslexic readers used word processing tasks so that a recent review of research explicitly recommended an extension to the sentence level (Sandak et al., 2004).

A possible concern is that the occipitotemporal underactivation of our dysfluent readers may have less to do with sentence processing than with false font processing. The argument would be that false font processing may have led to enhanced left occipitotemporal activation in dysfluent readers with the result of a reduced difference compared to sentence processing activity. Although this cannot be ruled out definitively, it is rather unlikely. First, there was no difference in accuracy and speed with which fluent and dysfluent readers performed on the visual control task. Furthermore, the underactivation of left occipi-

totemporal regions was also found in neuroimaging studies, which contrasted reading activation with a fixation baseline (e.g., Brunswick et al., 1999).

The left occipitotemporal underactivation exhibited by dyslexic readers is commonly interpreted as reflection of a dysfunction of fast operating processes of visual word recognition (McCandliss & Noble, 2003; Pugh et al., 2000). However, there are rival hypotheses. For example, it was suggested that the occipitotemporal underactivation of dyslexic readers may reflect a dysfunction of fast prelexical letter string processing (Salmelin & Helenius, 2004) or a deficiency of fast phonological name retrieval in response to visual stimuli (Brunswick et al., 1999; McCrory et al., 2005). The present study using a sentence verification task relative to false font processing obviously cannot provide evidence relevant for an evaluation of these alternative hypotheses. Due to the nature of the present task, we have to consider the possibility that the supramarginal and occipitotemporal underactivations of our dyslexic readers reflect semantic and syntactic processing deficits. However, this explanation seems rather unlikely as such underactivations were also found during pseudo-word processing tasks in which syntactic and semantic processing should be absent or minimized (e.g., Brunswick et al., 1999; Paulesu et al., 2001; Shaywitz et al., 2002).

Interestingly, our dysfluent readers did not exhibit reduced brain activation in regions, which are assumed to be engaged in syntactic and semantic sentence comprehension. These include the anterior part of the left temporal lobe (e.g., Vandenberghe, Nobre, & Price, 2002), areas in the superior temporal gyrus (e.g., Constable et al., 2004; Helenius & Salmelin et al., 1999) and regions in the left inferior frontal cortex (e.g., Dapretto & Bookheimer, 1999; Fiebach, Vos, & Friederici, 2004; Hagoort, Hald, Bastiaansen, & Petersson, 2004). However, as the present sentences were syntactically and semantically simple, one cannot exclude that more complex sentences might lead to imaging results reflecting syntactic and/or semantic dysfunctions in dyslexic readers.

4.2. Brain regions with increased activation in dysfluent readers

The voxel-based analysis identified a substantial number of left and right brain regions with higher activation for dysfluent than fluent readers in response to sentence verification (contrasted with false font processing). The largest cluster with increased activation was found in the left inferior frontal and precentral cortex where both groups exhibited reading specific activation. The ROI-based analysis also found substantially increased activation for dysfluent readers in the left inferior frontal region. The present finding of left inferior frontal overactivation corresponds to those of several studies with dyslexic readers (e.g., Brunswick et al., 1999; Georgiewa et al., 2002; Rumsey et al., 1997; Salmelin et al., 1996; Shaywitz et al., 1998, 2002). Importantly, these studies - different from the present one - presented single words or word pairs and interpreted the left inferior frontal overactivation as reliance of dyslexic readers on slow phonological articulatory word decoding in order to compensate for a deficiency with fast visual word processing

(see recent reviews by Salmelin & Helenius, 2004; Sandak et al., 2004; Pugh et al., 2000; Shaywitz & Shaywitz, 2005). In the present study, the left inferior frontal overactivation of the dysfluent readers may not solely result from slow phonological word decoding, but may also reflect a cascading effect of slow word decoding on syntactic and semantic processing with a higher demand on working memory. This possibility is suggested by MEG studies which found early abnormalities of visual word processing in a left occipitotemporal region to be followed by a delayed N400 response in dyslexic readers which reflects delayed semantic processes (Helenius & Salmelin et al., 1999; Salmelin & Helenius, 2004).

One may further reason that slow effortful word decoding and a resulting prolongation of linguistic and semantic sentence processing may be responsible for our finding that a substantial number of brain regions exhibited reading specific activation in dysfluent but not in fluent readers. Phonological articulatory word decoding may not only be responsible for the left frontal and precentral activation, but also for the activation in the left anterior insula, the left motor cortex and the right caudate (e.g., Wise, Greene, Buchel, & Scott, 1999). The increased visual attention and visual processing demands required by focus on letters or short letter strings within words may be reflected in the increased activation of the bilateral lingual gyri (e.g., Büchel et al., 1998; Indefrey et al., 1997) and generally high demands on attention and effort may be reflected in activation of the thalamus and the brain-stem (e.g., Kinomura, Larsson, Gulyas, & Roland, 1996; Sturm et al., 1999). We also found enhanced activation of the left medial temporal cortex in dyslexic readers. This may reflect stronger reliance on semantic knowledge during sentence verification (e.g., Daselaar et al., 2002) or, alternatively, increased demands on working memory (e.g., Cabeza, Dolcos, Graham, & Nyberg, 2002).

4.3. Methodological issues

For interpretation of the present brain activation results it is important to note that the performance of the dysfluent readers on the sentence verification task used for measuring brain activation corresponded to their general reading profile with hardly any errors but a massive speed problem. As the sentences were syntactically and semantically very simple, the reduced speed of sentence verification can be assumed to reflect reduced speed of word recognition processes to a major extent.

A specific feature of the present study is that all words (i.e., between 3 and 6) of a sentence were presented simultaneously whereas neuroimaging studies of sentence processing typically rely on word by word presentation of sentences (e.g., Constable et al., 2004; Cutting et al., 2005; Ferstl & von Cramon, 2001; Noppeney, Price, Duncan, & Koeppe, 2005; Noppeney & Price, 2004; Stowe et al., 1999; Vandenberghe et al., 2002). Presentation of the whole sentence was preferred as it corresponds to the natural reading situation and reduces the demands on working memory. Obviously, presentation of the whole sentence, compared to word by word presentation, leads to increased eye movement activity and, certainly, dysfluent readers will have exhibited a higher number of eye movements than fluent read-

ers (Hutzler & Wimmer, 2004). The methodological problem is that the effect of eye movement activity on brain activation may not be fully controlled for by the present visual control task. The longer reaction times for sentence verification than false font processing suggest more eye movement activity for the former task. Furthermore, this reaction time difference between sentence verification and false font processing was larger for dysfluent than fluent readers.

There are two reactions to these potential problems for interpreting the present brain activation findings. With respect to sentence presentation mode and control task it is important to note that the presently found brain regions with increased activation in response to sentences (in contrast to false fonts strings) correspond remarkably well to those found in the mentioned studies which used word by word presentation of sentences and a variety of control conditions. These studies found sentence processing activations mainly in extended regions of the left temporal lobe (specifically along the superior temporal sulcus up to anterior temporal regions) and in the left inferior frontal cortex. Such activations were also found when all visual factors were excluded and sentences were presented in auditory mode (Constable et al., 2004). In the present study, we also found that sentence processing (in contrast to false fonts) activated a large left temporal region along the superior sulcus and a large area of the left inferior frontal cortex. This correspondence suggests that the present mode of sentence presentation and the present visual control task led to a pattern of brain activation which is typical for sentence processing. We also have to consider methodological implications of the fact that fluent and dysfluent readers exhibited similar reaction times for evaluating the false fonts strings of the control task, but differed on the sentence processing task with dysfluent readers exhibiting sentence processing times about 1000 ms prolonged compared to fluent readers. As each sentence was presented for 5 s, this group difference implies that dysfluent readers were still engaged for further 1000 ms in sentence verification when fluent readers had already responded. One may reason that this much prolonged sentence processing of the dysfluent readers should be reflected in enhanced activation of brain regions which are engaged by visual word processing and sentence comprehension processes. Actually, a substantial number of such brain regions with enhanced activations in dysfluent readers were found (see previous section). However, despite this bias towards increased activation of brain regions engaged by sentence processing, brain regions with reduced activation in dysfluent readers were identified and these brain regions correspond to those typically reported in the imaging literature on dyslexia (see McCandliss & Noble, 2003; Pugh et al., 2000; Salmelin & Helenius, 2004). From a methodological point of view, the underactivation of the left occipitotemporal cortex exhibited by the dysfluent readers despite prolonged sentence processing time is of specific interest. We recently found for skilled adult readers that activation of the left occipitotemporal cortex was inversely related to word familiarity, that is, high frequency words led to lower activation than low frequency words or pseudo-words (Kronbichler et al., 2004). Furthermore, activation of the left occipitotemporal cortex was found to be associated with reading time for words and pseudo-words, that

is, the longer the reading time the higher the activation (Binder, Medler, Desai, Conant, & Liebenthal, 2005). A simple transfer of these findings to the present dysfluent readers would predict enhanced occipitotemporal activation as the words of our sentences presumably were less familiar for the dysfluent than for the fluent readers and definitively the sentences led to prolonged reading time. Contrary to this expectation and consistent with the majority of other studies, reduced occipitotemporal activation was found.

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