Cognitive levels of performance account for hemispheric lateralisation effects in dyslexic and normally reading children

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Abstract
Recent theories of developmental dyslexia explain reading deficits in terms of deficient phonological awareness, attention, visual and auditory processing, or automaticity. Since dyslexia has a neurobiological basis, the question arises how the reader’s proficiency in these cognitive variables affects the brain regions involved in visual word recognition. This question was addressed in two fMRI experiments with 19 normally reading children (Experiment 1) and 19 children with dyslexia (Experiment 2). First, reading-specific brain activation was assessed by contrasting the BOLD signal for reading aloud words vs. overtly naming pictures of real objects. Next, ANCOVAs with brain activation during reading the individuals’ scores for all five cognitive variables assessed outside the scanner as covariates were performed. Whereas the normal readers’ brain activation during reading showed co-variation effects predominantly in the right hemisphere, the reverse pattern was observed for the dyslexics. In particular, middle frontal gyrus, inferior parietal cortex, and precuneus showed contralateral effects for controls as compared to dyslexics. In line with earlier findings in the literature, these data hint at a global change in hemispheric asymmetry during cognitive processing in dyslexic readers, which, in turn, might affect reading proficiency.

Introduction
Developmental dyslexia is a frequent hereditary reading disability (Olson, 2002; Schulte-Körne et al., 2007; Shaywitz, 1998) which is encountered despite normal intelligence and adequate schooling. It is thought to be related to deficits in either phonological (e.g. Snowling, 2000), auditory (e.g. Tallal, 1980; Groth et al., 2009; but see Blomert and Mitterer, 2004), or visuo-magnocellular (e.g. Stein and Walsh, 1997) processing, attention (e.g. Facoetti et al., 2001), or cerebellar automaticity abilities (e.g. Nicolson et al., 2001). Recent evidence suggests that these cognitive variables individually differ in their impact on reading (dis-) ability (e.g. Heim et al., 2008; King et al., 2007; Ramus et al., 2003; Valdois et al., 2003). Whereas some children have primarily an attention deficit, others reveal a phonological deficit either in isolation or together with e.g. auditory and visuo-magnocellular impairment (Heim et al., 2008; for a review cf. Ramus, 2003).

The reading network – comprising inferior frontal, inferior temporal and fusiform, inferior parietal, occipital, motor cortex, and cerebellum – has extensively been investigated using functional magnetic resonance imaging (e.g. Devlin et al., 2006; Mechelli et al., 2003; Price, 2000; Schlagger and McCandliss, 2007). In addition, brain activation differences between dyslexic and normal readers have been examined (e.g. Paulesu et al., 2001; Temple et al., 2001; see Shaywitz et al., 2006). With respect to brain activation differences during reading, a seminal paper by Paulesu et al. (2001) investigated subjects with English, French, or Italian as their first language. Independent of language, dyslexics tended to show reduced activation in left posterior inferior temporal and middle occipital regions including the visual word form area in the left fusiform gyrus (cf. e.g. Cohen et al., 2000, 2004; but see also Price and Devlin, 2003, and Devlin et al., 2006). Although this difference was largely comparable over languages, activation during reading was strongest here for the English speaking normal readers. Similar results were reported e.g. by Brambati et al. (2006), Brunswick et al. (1999), and Kronbichler et al. (2006). A comparable pattern with focus on the left temporoparietal cortex was also observed for phonological processing in English dyslexics and normal readers (e.g. Booth et al., 2007; Cao et al., 2006; Hoef et al., 2006; Temple et al., 2001; but see Richards et al., 2007, for contradictory results from a study investigating phonological training...
effects in dyslexia). Moreover, reduced activation was sometimes observed in left inferior frontal gyrus (Cao et al., 2006; but see Temple et al., 2001, for no such difference; and Hoef a et al., 2007, for a reversed effect).

Since neuroimaging studies investigating activation differences between dyslexics and normal readers mostly relied on tasks related to reading and phonological processing, findings for other cognitive variables potentially relevant for reading and dyslexia are not as frequent (see the review by Richlan et al., 2009). With respect to auditory (non-phonological) processing, some studies found that rapid vs. slow transitions caused activation differences in left prefrontal cortex in normal but not in dyslexics (e.g. Gaab et al., 2007; Temple et al., 2000), whereas data from magnetoencephalography suggest a change in hemispheric asymmetry of auditory cortex (e.g. Heim and Keil, 2004) and planum temporale (e.g. Foster et al., 2002) involvement. Moreover, bilateral anterior insula was observed to be involved in the processing in human speech and non-speech sounds in dyslexia (Steinbrink et al., 2009a). Brain function differences between dyslexic and normally reading persons were also reported for visual processing and visual attention, but data mostly come from electrophysiological studies (e.g. Schulte-Körne et al., 2004). Overall, right parietal cortex is assumed to play an important role, in particular since some dyslexics present with “mini-neglect” (for a review see Jaskowski and Rusiak, 2005). The central role of right parietal cortex is in line with neuroimaging studies of normally reading subjects performing attentional shifting tasks (see e.g. Raz and Buhle, 2006). Others (e.g. Arrington et al., 2000) additionally stress the role of the right inferior and middle frontal cortex. Moreover, the temporo-occipital cortex (Area V5/MT), which is part of the magnocellular processing stream, seems to be of particular relevance in the domain of reorienting of attention (Gitelman et al., 1999) as well as visuo–magnocellular processing of motion (Wilms et al., 2005).

Despite the reported diversity of brain regions showing differential activation between proficient and non-proficient readers, there is relatively strong evidence for changes in hemispheric (a-)symmetry in dyslexics during both visual and auditory processing of speech and non-speech stimuli. Behavioural studies investigating dichotic listening or visual processing in left vs. right visual field as well as neuroimaging studies using event-related potentials, magnetoencephalography, or functional magnetic resonance imaging (fMRI) in a number of paradigms unequivocally report that laterality of processing in the left or right hemisphere is altered in dyslexia (e.g. Abrams et al., 2009; Boles and Turan, 2003; Cao et al., 2008; Facoetti et al., 2001; Heim et al., 2003a,b; Henderson et al., 2007; Iliadou et al., 2010; Kobus et al., 1986; Leisman, 2002; Maisog et al., 2008; Milne et al., 2002; Penolazzi et al., 2006; Richlan et al., 2009; Rutherford, 2006; Spironelli et al., 2008; Temple et al., 2003).

This brief literature survey demonstrates that a number of brain regions are specifically or more generally associated with dyslexia when functions such as visual attention, phonological awareness etc. are investigated with fMRI, and that potential hemispheric processing differences between dyslexic and unimpaired readers exist. As an alternative approach, more recent studies investigated the influence of reading-related functions on brain activation during a reading task in dyslexic and control children. So far, the main focus has been on phonological abilities (Bolger et al., 2008; Frost et al., 2009; Pekkola et al., 2006; Turkeltaub et al., 2003). Pekkola et al. (2006) could demonstrate that dyslexic readers’ haemodynamic response co-varied with their phonological processing abilities in visual cortex and in left inferior frontal cortex, thus replicating the seminal results reported by Turkeltaub et al. (2003). These latter authors also observed a negative correlation of right hemispheric brain regions (including inferior temporal and fusiform gyrus and precuneus) with increasing reading ability, while positive correlations were found in the left hemisphere in middle temporal, inferior frontal, and superior frontal regions. Other more recent imaging studies (e.g. Bolger et al., 2008; Frost et al., 2009) observed a correlation of brain activation during English pseudo-word reading and phonological awareness in a number of brain regions including left (Frost et al., 2009) and right (Bolger et al., 2008) occipito-temporal areas, precuneus, and also parahippocampal complex.

Whereas the role phonological awareness as the most prominent factor is thus understood at least to some degree, it remains to be seen which parts of the reading network show some relationship with visuo-magnocellular processing, attention, auditory processing, and automaticity. Consequently, we conducted a functional magnetic resonance imaging (fMRI) study elucidating how scores for phonological awareness, auditory and visual processing, attention, and automaticity co-vary with brain activation during reading. In Experiment 1, we investigated which part of the reading network in the brain showed co-variation effects in normally reading German primary school children. In Experiment 2, the same rationale was applied to children with developmental dyslexia in order to investigate the deviant mechanisms in the dyslexic brain that result in impaired reading. This issue is important because the importance of phonological awareness, visuo-magnocellular processing, auditory processing, attention, and automaticity was identified in samples of dyslexics rather than controls, and today form the bases of influential theories of dyslexia. The two experiments in the present study thus reveal first of all how these five variables relate to the reading network in the brain in principle, i.e. in the normal case. On the basis of these findings, their role for disturbed reading mechanisms in the brain of dyslexics is potentially better understood.

**Experiment 1**

**Materials and methods**

**Participants**

Nineteen German primary school children (mean age 9.4 years; 7 girls) and their parents gave informed consent to participate in the fMRI study according to legal requirements as approved by the ethics committee of the Medical Faculty, RWTH Aachen University (for details cf. Table 1). According to the research guidelines of the International Classification of Diseases (ICD-10; WHO, 2006) children were considered as normal readers if their reading score in the Würzburger Leise Leseprobe (WLLP; Küspert and Schneider, 1998), a standard German reading test, was above the 25th percentile, and non-verbal IQ (short form of the CFT-20; Weiß, 1998) was at least in the range of 1 standard deviation around the average, or better (>85).

**Behavioural tests**

The children were tested with respect to phonological awareness (phoneme deletion and discrimination of vowel length), auditory

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal readers (n = 19; 9-9; 7 girls)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
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<tr>
<td>READING (Percentile)</td>
<td>66.7</td>
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</tr>
<tr>
<td>IQ</td>
<td>115.1</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>AUDIO (T value)</td>
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<td>6.7</td>
<td></td>
</tr>
<tr>
<td>ATTENTION (ms)</td>
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<td>88.4</td>
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</tr>
<tr>
<td>PHON (T value)</td>
<td>51.8</td>
<td>6.6</td>
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<tr>
<td>AUTO (number)</td>
<td>4.0</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>VISUAL (ms)</td>
<td>650.7</td>
<td>198.3</td>
<td></td>
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</tbody>
</table>
sound discrimination (same-different judgements on minimal pairs), visuo-magnocellular processing (detection of changes in a moving starfield scenario), visual attention (Posner paradigm for attention shifts), and automaticity (imitation of rhythmic sequences). The tests were either standardised psychometric tests or computerised paradigms that had previously been applied for the cognitive assessment of dyslexics and controls (Heim et al., 2008). The presentation of the stimuli during the computerised tests and the registration of the button presses were performed with Presentation™ software (version 0.70; Neurobehavioral Systems, Albany, CA, USA).

Reading ability was assessed with the Würzburger Leise Leseprobe (WLLP) (Küspert and Schneider, 1998), a standard German test for reading speed. Participants read words at the beginning of a row and mark with a pencil the one out of four pictures displayed in the same row that is denoted by the word. The names of the three distractor pictures may be semantically related, phonologically related, or semantically and phonologically related to the target word (e.g., “Blatt” [leaf]; BLATT [target], BETT [bed – phonologically related], AST [branch – semantically related], BAUM [tree – semantically and phonologically related]). Separate norms (of 1997) are available for boys and girls in the first, second, third, and fourth grade. According to the research criteria of the International Classification of Diseases (WHO, 2006) children performing on or below the 10th percentile were considered as dyslexic if the subsequent non-verbal intelligence test yielded an average or above-average IQ. Children performing above the 25th percentile and with comparable IQ were included into the control group.

Non-verbal IQ was assessed with the German version of the Cattell Culture Fair Test 20 (CFT 20) (Weiß, 1998). In this test participants are shown series of pictures generated according to a particular logic. In subtest 1 “Series” subjects have to complete a series of pictures (e.g., white squares containing increasingly long black bars) by marking the one out of five alternatives that is the correct continuation. Subtest 2 “Classifications” requires the participants to indicate which out of five pictures had not been generated after the same principle as the others (e.g., a white square with a vertical black bar among four white squares with horizontal black bars). In subtest 3 “Matrices” participants have to identify which out of five alternative pictures completes a set of three pictures (e.g., find a white square with two horizontally oriented black circles). Subtest 4 “Topologies” is supposed to assess logic reasoning. Subjects have to identify the one out of four alternatives that was created according to the same principle as a sample stimulus (e.g., where a dot can be inserted in a circle without placing it in a square). The performance in each subtest was assessed as the number of items that were correctly marked in a pre-defined time period (4 min for subtests 1 and 2, and 3 min for subtests 3 and 4). The CFT-20 was administered individually in its short form (Part 1) for reasons of time economy. Norms for the short form are available for different age-groups (8–70 years), grades (5th to 10th), or school types (primary school grade 3 and 4; vocational school years 1 and 2) as IQ scores, T values, and percentiles. In the present study age-related IQ scores were used. Children were only included in the study if their non-verbal intelligence was at least in the range of one standard deviation below average (i.e. IQ ≥ 85) in order to ensure that no children with learning disabilities participated.

Phonological awareness was tested with the German “Basiskompetenzen für Lese-Rechtschreibleistungen” (BAKO 1–4; Stock et al., 2003). From the seven subtests included in the BAKO one productive (Test 4: Phoneme Exchange) and one receptive test (Test 6: Vowel Length Discrimination) were selected, for which separate norms (of 2002; T values and percentiles) for grades 1–4 are available. In the productive test subjects heard spoken stimulus words played from a CD and had to utter the pseudo-word that results from exchanging the first two phonemes (e.g., Masse → “amse”). In the receptive test, they had to identify the one out of four auditorily presented pseudo-words in which the vowel was of a different length (vowel length is a contrastive feature in German, e.g. “Bann”/curse vs. “Bahn”/railway; see Groth et al., 2009; Steinbrink et al., 2009b). For each child, the average T value was calculated as the measure for phonological awareness, since the scores of both tests are highly correlated (cf. Heim et al., 2008). The higher the T values were, the better was phonological awareness.

Speech sound discrimination was assessed with subtest 1 of the Heidelberger Lautdifferenzierungstest (H-LAD) (Brunner et al., 1998). The children indicated if minimal sound pairs (e.g., /ba/ → /pa/) were identical or different. Stimulus materials included both non-lexicalised syllables (Test 1B) and words (Tests 1A and 1C). The stimuli were played from a CD at 60 dB. The higher the T score was, the better was the auditory discrimination.

Automaticity ability was assessed with a rhythm imitation paradigm (Tiffin-Richards et al., 2004). In this paradigm the children had to click a button synchronously to an auditorily presented rhythm consisting of 5–6 beats with stimulus-onset asynchronies of 300 or 600 ms. For the present study we chose the complex rhythms #1, #4, and #5 from Tiffin-Richards et al. (2004) which had best differentiated between dyslexic and normally reading children in that study. Each rhythm was first presented once in order to familiarise the child with it. Then, each rhythm was repeated five times while the subjects had to imitate it by synchronously clicking the left mouse button with the right index finger. The total number of correct rhythms was used as the indicator for automaticity ability. Only those rhythms were judged as correct for which (i) the number of mouse clicks equalled the number of beats and (ii) a required click was made before the next beat was played. Thus, the higher the number of correctly imitated rhythms, the better the performance.

Visuo-magnocellular processing was tested with a motion detection paradigm previously shown to activate area V5/MT+ as part of the magnocellular system (Wilms et al., 2005; see also Heim et al., 2008). In this paradigm the participants are presented with a radially expanding, static, or contracting random dot pattern which is well controlled for visual properties (for details see Wilms et al., 2005). It has been demonstrated that such moving stimuli are processed differently by dyslexics and by normal controls: Dyslexics have attenuated motion-onset related visual evoked potentials (Schulte-Körne et al., 2004). Therefore, in the present study the paradigm of Wilms et al. (2005) was adopted. The random dot pattern changed its type of motion (e.g., expand→static, static→contract, static→expand, etc.) after a variable time interval of 1 s, 1.5 s, 2 s, 2.5 s, or 3 s. The time intervals and motion direction changes were pseudo-randomised. The transition probabilities were equal for all types of motion changes. The participants had to indicate the changes in motion by clicking the left mouse button as quickly as possible. The average reaction times for correct responses were taken as measures for magnocellular functioning, with longer reaction times indicating worse performance.

Visual attention was assessed with the Posner paradigm (Posner, 1980). Subjects had to indicate by clicking the left or right mouse button as quickly as possible at which of two positions in the left and right periphery of the computer screen a target stimulus occurred. A target stimulus could be preceded by a cue which was either informative (“valid”), neutral, or misleading (“invalid”). In case of a valid cue the participant could correctly prepare the reaction. In the neutral condition he or she was alerted that a stimulus would be presented soon but could not prepare a left or right button click. In the invalid condition attention to the shadowed position had to be redirected to the correct position of the target in order to perform the required reaction. The “cue validity effect” which is the reaction time difference between invalid and valid trials is taken to reflect how quickly attention can be shifted to a new location. Smaller effects indicate better performance. The Posner paradigm has been successfully applied for the identification of attentional deficits in dyslexic children (Heiervang and Hudahl, 2003). In the present study we used a realisation of the Posner paradigm that was previously applied by...
Vossel et al. (2006) with central cues and a ratio of 80:20 for valid vs. invalid cues. Only correct trials were analysed. The average cue validity effect was calculated for each participant and entered in the subsequent analyses.

**Interpretation of the behavioural effects**

To summarise, the following scores indicate higher performance in the behavioural tasks:

- **High scores**
  - Phonological awareness: High scores indicate high performance
  - Auditory discrimination: High scores indicate high performance
  - Rhythm imitation: High scores indicate high performance

- **Low scores**
  - Visual motion detection: Low scores indicate high performance
  - Attention shifting: Low scores indicate high performance

**fMRI procedures**

The fMRI experiment was carried out on a 1.5 T Siemens Avanto scanner (Siemens, Erlangen, Germany) with a standard birdcage head coil. Foam paddings were used to reduce head motion. Echo-planar images (repetition time 4 s; field of view 200 mm; flip angle 90°; echo time 60 ms) were acquired from 31 sagittal slices covering the entire brain (slice thickness 3 mm; gap 1.35 mm).

The study consisted of two task blocks. In one task block, children saw 60 written mono- and disyllabic words (mean lexical frequency according to the CELEX database [http://www.kun.nl/celex]: 440 per million; number of letters: 3–8; font: Helvetica; font size: 48), which should be read aloud. In the other task block, 60 black-and-white line drawings of real objects instead of words were presented and should be named overtly by the children. This second task block was used as a high-level baseline for later analysis, featuring visual processing and articulation as in the reading task but no grapheme-to-phoneme conversion. Thus, subtracting activation due to picture naming from activation due to reading reveals brain regions selectively involved in the processing of visual written font (cf. Seghier and Price, 2010). It should be noted here that word reading, unlike picture naming, may also be accomplished without semantic mediation. However, this potential difference between the tasks would only result in stronger deactivation in semantic regions when contrasting reading with picture naming as a high-level control task; since only positive activations are considered here, such effect is of no relevance to the subtraction logic and the choice of baseline in the present study.

Stimuli were presented by a projector on a translucent screen at the end of the magnetic bore and were viewed by the children via mirror glasses. At the beginning of each trial the screen was blank for 1000 ms. Then a stimulus was presented for 3000 ms. During the last 1000 ms of the presentation the scanning stopped, resulting in a silent pause with no gradient noise. The children were instructed to say aloud the picture name or read aloud the word during this silent period. Reading aloud was chosen instead of silent reading in order to ensure that the children actually attended the word presented on the screen. Speaking during this pause provided a clearer speech signal from the children, allowing the experimenter to assess whether the task was performed correctly. Moreover, speaking during scanning pauses prevents the induction of susceptibility artefacts in the fMRI signal (Gracco et al., 2005; for applications of such “bunched-early” sequences cf. De Zubicaray et al., 2001). After a series of five stimuli, one null event was included, resulting in a total of eleven null events that served as a resting baseline. The duration of one block of five contiguous stimuli was 20 s.

**fMRI data analysis**

Data analysis was performed using SPM5 (Wellcome Department of Cognitive Neurology, UK) running on MATLAB 7 (The Mathworks Inc., Natick, USA) in combination with the SPM Anatomy toolbox (Eickhoff et al., 2005) for the localisation of effects. Pre-processing involved the standard procedures of realignment to the mean image of the EPI time series, normalisation to the EPI template, and spatial smoothing using a Gaussian kernel of 8 mm FWHM, and a highpass filter of 1/128 Hz.

The first-level analyses employed block design in which the respective task (reading or picture naming) was modelled, whereas the implicit resting baseline (i.e. the null events) was not modelled. The haemodynamic response functions were convolved with a box-car function with duration of 20 s, equalling the block length in the experiment. The linear contrast of picture naming or of word reading against the implicit resting baseline was calculated and entered the second-level random-effects group analysis.

This second-level analysis was realised as a repeated-measures ANCOVA, with “task” (reading vs. picture naming) as a factor and the individual test scores for phonological awareness, reorienting of attention (i.e. visual attention), sound discrimination (i.e. auditory processing), motion detection (i.e. visuo-magnocellular processing), and rhythm imitation (i.e. automaticity) that had been obtained outside the scanner as covariates of interest. Before entering the vectors for the covariates into SPM, they were orthogonalised and z-transformed using the SPSS 15 software package (SPSS Inc., Chicago, Illinois, USA). This orthogonalisation was necessary in order to intercorrelations between variables, thus leaving only their unique variance for the ANCOVA. (Note that this method is recommended in order to assess the individual contribution of each variable to the signal but at the same time alters the natural relationship among the variables. As a consequence, the strong co-variance between phonological processing and reading, which was observed in other studies, may be somewhat reduced here because the contributions of other factors such as auditory processing are factored out in the present analysis). To this aim, a series of multiple regressions was carried out by regressing always one of the five variables upon the four others and saving the residuals as a new vector for the fMRI analysis.

In order to assess where reading-related brain activation co-varied with the scores for the five variables, the following steps were performed. First, the contrast READING->PICTURE NAMING was calculated in order to identify those regions that were particularly involved in the processing of graphemes but not in visual processing or articulation. The resulting map was used as a mask for the ANCOVA of the five cognitive variables (at a threshold of P<.05, uncorrected, with cluster extent k≥60 voxels).

Next, the “Effect of Interest” for the five orthogonalised covariates (i.e. the F contrast with one word for each variable) in the contrast READING->REST was calculated, which reveals all voxels showing a significant effect during reading in at least one of the five covariates. This effect was then masked inclusively with the contrast READING->PICTURE NAMING as described above. The effects for each single covariate (represented in this Effect of Interest) were then assessed individually.

**Results**

**Behavioural data**

The performance in the behavioural paradigms and tests is presented in Table 1. In the standardised tests, the group performance was within the normal range (T values: 40–60; percentile: 25–74).

**Activation specific for reading**

The contrast READING->PICTURE NAMING revealed a brain network including bilateral middle frontal gyrus, angular gyrus,
middle temporal gyrus, precuneus, fronto-orbital cortex (left superior orbital and right rectal gyrus), right inferior frontal gyrus, right hippocampus, and left cerebellum (Fig. 1, top).

Co-variation effects
The Effect of Interest for the covariates revealed that within this reading-specific network, activation in a number of regions co-varied with one or more of the cognitive variables (Table 2 and Fig. 1, bottom). These regions included middle frontal gyrus, angular gyrus, hippocampus, precuneus, and cerebellum. Except for the cerebellum, which was in the left hemisphere, all other regions revealing co-variation effects were located only in the right hemisphere.

Co-variation effects by regions. Right middle frontal gyrus and angular gyrus showed effects for phonological awareness, motion detection, sound discrimination, and rhythm imitation. Right hippocampus activation co-varied with reorienting of attention, motion detection, and rhythm imitation. For right precuneus and left cerebellum, co-variance with all five variables was observed.
### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Region</th>
<th>Coordinates</th>
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**Co-variation effects by variables.** Reorienting of attention was related to activation in right hippocampus, left cerebellum, and right precuneus. Phonological awareness and sound discrimination showed co-variation effects in all regions except right hippocampus. Finally, motion detection and rhythm imitation involved all five regions.

### Discussion

The present study investigated the co-variation of brain activation during reading with five cognitive variables representing potential causes for reading disability. Apart from phonological awareness which had been investigated in previous neuroimaging studies (e.g. Bolger et al., 2008; Frost et al., 2009; Turkeltaub et al., 2003), auditory sound discrimination, visual motion detection, reorienting of visual attention, and rhythm imitation as a measure of automaticity were included. In contrast to these other studies, which used processing of pseudo-words or false-font strings as a baseline, the present study involved a picture naming task sharing visual processing and articulation with the reading task under investigation. Importantly, picture naming also involves lexical access and phonological code retrieval; as a consequence, the reading task and the picture naming baseline did not differ with respect to lexical processing. This aspect will become important when interpreting the observed pattern of co-variation effects.

The main observation was that the five covariates elicited co-variation effects predominantly in the right hemispheric part of the reading-specific brain network, replicating findings from earlier studies. Co-variation effects of brain activation and phonological processing ability in the right precuneus region had been previously reported by Turkeltaub et al. (2003) and by Frost et al. (2009); the involvement of the right middle frontal gyrus was also found by Bolger et al. (2008), while Frost et al. (2009) also reported right inferior parietal lobule effects. Consequently, considering the phonological effects in the present study, the data reported here are well in line with the few studies currently available. Interestingly, however, it was only the right hemisphere that showed co-variation effects in the present study. This cannot be due to topography of the underlying reading-specific brain network serving as an inclusive mask, since this network comprised basically symmetrical effects in both hemispheres. A similar network was previously reported by Park and Rugg (2008; see also Price et al., 2006). Therefore, the reason for the difference between a bilateral network in the earlier studies and the predominantly right-lateralised network in the present study is potentially due to the choice of the high-level baseline task. As pointed out above, the studies by Bolger et al. (2008), Frost et al. (2009), and Turkeltaub et al. (2003) used stimuli in the baseline conditions that were either pseudo-words or false-font strings which did not have lexical entries. In contrast, in the present study, picture naming was used as a baseline, which did involve the retrieval of lexical entries. Lexical processing is associated in particular with left-hemispheric regions (see e.g. Vandenberge et al., 1996, who also compared word reading and picture naming), in particular left inferior frontal and left superior and inferior temporal/fusiform cortex. In the studies by Bolger et al. (2008), Frost et al. (2009), and Turkeltaub et al. (2003), it was exactly these regions which showed the co-variation effects. The choice of an appropriate baseline task in the present study which involved also lexical processing may explain why such left-lateralised effects cancel out here, but not in the above studies by Bolger, Frost, or Turkeltaub. As a consequence, the effects reported here can be attributed to co-variation of phonological awareness with orthographic, non-lexical processing.

Interestingly, effects comparable to those found for phonological awareness were also found for the other four cognitive variables. These effects were found in almost all regions involved, although to different degrees. In particular, visual motion detection as a measure of magnocellular processing and rhythm imitation as indicator for
automaticity both recruited the entire network, hinting at the relevance of this network for automatized visual processing which is crucial for reading. Likewise, among the regions within the network, it was the precuneus as a visual region and the left cerebellum related to automaticity (Nicolson et al., 1999) that showed co-variation effects with all five cognitive functions. Thus, there is converging evidence both from the behavioural covariates and from the neuroimaging data that automatized visual processing is a universally important aspect for successful reading. We will return to this issue in the General discussion after considering the pattern of results observed in Experiment 2 for dyslexic readers. To summarise, in children with normal reading ability, cognitive variables considered as potential causes of dyslexia have a repercussion in reading-related brain activation predominantly in the right hemisphere, indicating its role for automatized visual processing of grapheme stimuli.

Experiment 2

Materials and methods

Participants

Nineteen dyslexic primary school children (mean age 9.4 years; 7 girls) and their parents gave informed consent to participate in the fMRI study (for details cf. Table 3). According to the research guidelines of the International Classification of Diseases (ICD-10; WHO, 2006) children were considered as dyslexic if their WLLP reading score was below the 10th percentile, whereas non-verbal IQ was at least in the range of one standard deviation around average, or better (i.e. CFT-20 IQ > 85).

Procedure

The procedure was identical to that in Experiment 1. One data set from a dyslexic child was excluded due to problems with normalisation, resulting in a total sample size of n = 18.

Results

Behavioural data

The performance in the behavioural paradigms and tests is presented in Table 3. In the standardised tests, the group performance was within the normal range (T values: 40–60) except for the WLLP reading test in which, by definition, performance was below the 10th percentile.

Activation specific for reading

The contrast READING > PICTURE NAMING revealed a brain network including bilateral middle frontal gyrus, inferior parietal cortex, middle temporal gyrus, precuneus, fronto-ordinal cortex (left superior orbital and right middle orbital gyrus), supplementary motor area, inferior frontal gyrus, hippocampus, right middle cingulate, and left cerebellum (Fig. 2, top).

Co-variation effects

The Effect of Interest for the five covariates involved a predominantly left-lateralised network (Table 4 and Fig. 2, bottom). This network comprised left middle frontal gyrus, left inferior parietal cortex, left precuneus, supplementary motor area, and right mesial parietal cortex.

Co-variation effects by regions. Left inferior parietal and right mesial parietal cortex activation during reading co-varied with scores for all five variables. Effects in the supplementary motor area were present for all variables except reorienting of attention. Left middle frontal gyrus showed effects for reorienting of attention and for motion detection. Finally, left precuneus activation revealed co-variation with all variables except for sound discrimination.

Co-variation effects by variables. Scores for motion detection showed co-variation effects in all five regions. Phonological awareness and rhythm imitation yielded co-variation with reading-related brain activation in all regions except left middle frontal gyrus. For reorienting of attention, effects were observed in all regions with the exception of supplementary motor area. Finally, sound discrimination ability co-varied with reading activation in left inferior parietal and right mesial parietal cortex and in supplementary motor area.

Discussion

In order to do so, one basic methodological point must be addressed first. It would be possible that this deviant co-variation pattern was merely an effect of masking. If the contrast READING > PICTURE NAMING, which served as a mask for the ANCOVA, yielded different results for normally reading children and for dyslexics, this could explain the left vs. right-lateralised effects. However, as Fig. 2 shows, the overall reading-specific activation was largely comparable between dyslexics and controls. In particular, the pattern was rather symmetrical, involving homologue regions in left and right hemisphere. As a consequence, the explanation that the differential co-variation patterns are basically artefacts due to masking can be excluded.

General discussion

The present study investigated the influence of a number of cognitive variables regarded as potential causes of dyslexia on the reading-specific brain network in normal and dyslexic readers. The main finding was a differently lateralised co-variation effect in the right vs. left hemisphere in the normally reading vs. dyslexic sample. In particular, activation in homologue regions in middle frontal gyrus, inferior parietal lobule, and precuneus co-varied with the cognitive variables. As argued above, these effects are unlikely to relate to lexical processing since they occurred in regions specifically associated with the processing of written stimuli, which were identified by cancelling out regions commonly activated for reading and for picture naming.

This strikingly mirrored pattern of effects for dyslexics and controls will now be discussed in some depth, with focus both on variables and on regions, before putting it into a larger context. As
mentioned earlier, contralateral effects for dyslexics and for normal readers were observed in precuneus, inferior parietal cortex, and middle frontal gyrus. These regions are implicated in mapping orthography to phonology in normal readers (e.g. Bolger et al., 2008; Graves et al., 2009), with particular sensitivity of inferior parietal cortex to lexical variables such as word frequency (Graves et al., 2009; Kuo et al., 2003). Likewise, neuroimaging studies of dyslexic reading relatively consistently showed reduced activation in left inferior parietal cortex (for a review cf. e.g. Shaywitz and Shaywitz, 2008) but may increase after training (Meyler et al., 2008). The pattern of results observed here provides a potential explanation for this under-activation in dyslexia. In Experiment 2, left inferior parietal cortex activation co-varied systematically with the dyslexics’ performance in all variables, including phonological awareness, sound discrimination, visual motion detection, rhythm imitation, and reorienting of attention. In other words, activation in this region was overall variable. Independently of the individual deficit of a dyslexic child, be it phonological or other, activation in left inferior parietal cortex is thus altered in comparison to normal readers. In group analyses, the lesser degree of consistency of the activation in
this region in dyslexics may thus lead to an on average lower activation level and, as a consequence, to higher systematic activation in normal readers. However, at least the present data do not provide evidence for this notion, because for the main effect of reading, the standard error of mean at the local maximum showed, if at all, a trend in the opposite direction (SEM = .21 for the normal readers at MNI $x,y,z = -40,-50,31$; and SEM = .15 for the dyslexics at $-34,-42,27$). Therefore, future research is necessary here in order to systematically evaluate this hypothesis in a larger sample of children and adults.

Alternatively, one could assume that grapheme-to-phoneme conversion supported by left inferior parietal cortex is generally impaired in dyslexia, no matter by which cognitive deficit it is caused (see Heim et al., 2008; Menghini et al., 2010). This argument is supported by the fact that for the dyslexic children, activation in left inferior parietal cortex did co-vary with the individual degree of proficiency in every single cognitive variable tested here. More generally, the data show the overall importance of visual perception over and above other cognitive deficits: It was visual motion detection which showed an overall co-variation effect in all regions and in both groups. Visual motion detection is a test for magnocellular processing (e.g. Wilms et al., 2005). A magnocellular deficit, in turn, is taken by some authors (e.g. Stein, 2001) as the most basic of a reading deficit. This is because dyslexic children perceive the letters as moving or turning and thus encounter greater difficulties in successful grapheme-to-phoneme conversion. To conclude, the present study gives some indication that grapheme-to-phoneme conversion in left inferior parietal cortex is affected in dyslexia as a consequence of the individual magnocellular processing level as well as of other cognitive functions.

Further insight into the different mechanisms in the dyslexic vs. normally reading brains comes from a closer analysis of the commonalities and discrepancies in the patterns of co-variation in homologue areas. The first aspect is the size of the effect for phonological awareness and for visual motion detection in the angular gyrus. Note that these are the same two functions and the same brain region discussed in the paragraph above. Qualitatively, the pattern suggests that the activation in angular gyrus is the higher, the lower phonological awareness and visuo-magnocellular motion detection. These effects are smaller for the dyslexics than for the controls. The different amounts of co-variation indicate that there is a closer (inverse) link between performance levels and brain activation in controls than in dyslexics, hinting at the more efficient use of the right angular gyrus in controls than of the left angular gyrus in dyslexics. A similar effect can be observed for right vs. left precuneus, not so much for phonological awareness (which makes sense for this region) but for all other variables, in particular the visual ones. Likewise, the middle frontal gyrus shows a comparable pattern of co-variation, with one striking exception. Note that there is a negative co-variation between the cue validity effect (i.e., attention shifting) and brain activation in right middle frontal gyrus in controls, indicating that attention shifting can be accomplished the faster, the higher the activation is (remember that a high cue validity effect implies slow attention shifting). For dyslexics, the left middle frontal gyrus shows the reverse effect. For phonological awareness and auditory discrimination, the pattern is somewhat similar, with no significant effect in the dyslexics but strong effects in normal readers. This pattern suggests that the use of frontal cortex, here of the middle frontal gyrus (but see also Heim et al., 2010, for complementary findings in the inferior frontal gyrus), differs between dyslexics and controls, and that there is also an issue about the distinction between phonological processing and other processes such as attention shifting or visual motion detection which tend to be subsumed under the umbrella term of “magnocellular functions” by some authors (e.g. Stein, 2001; for a detailed discussion cf. Ramus, 2004; and our recent work by Heim et al., 2010).
Apart from the symmetrically mirrored effects in middle frontal gyrus, precuneus, and inferior parietal cortex, another interesting pattern emerges when comparing the co-variation effects for dyslexics and normal readers. Whereas normal readers showed an effect in left cerebellum, which was driven by all five covariates, no such effect was present for the dyslexics. In contrast, the dyslexic children revealed an effect in the supplementary motor area for all variables except shifting of attention. The cerebellum has since long been regarded as a core region for dyslexia (e.g., Nicolson et al., 1999) because of its role for the automatisation of cognitive and motor abilities. The study by Nicolson et al. (1999) demonstrated cerebellar under-activation for dyslexics when compared to controls, which was taken as the basis of a general procedural deficit in dyslexics (see Nicolson and Fawcett, 2007, for a comprehensive account). A recently published study by Brendel et al. (2010) related cerebellar activation to activation in supplementary motor area, demonstrating opposite temporal activation patterns during syllable production. Therefore, it is likely that cerebellum and supplementary motor area have related (and perhaps complementary) functions (see also Rubia and Smith, 2004). Weidner and colleagues (2009) demonstrated that supplementary motor area and cerebellum are part of a network for top-down visual search, which, however, is distinct from another network responsible for the reorienting of attention. The findings of the present study are partly in accordance with these results, because it was only reorienting of attention that did not co-vari with activation in supplementary motor area in the dyslexics. Although the present study was not designed to distinguish between the functions of cerebellum and supplementary motor area, the data might be taken as indication that a cerebellar dysfunction in dyslexics is (at least partly) compensated by involving the supplementary motor area. The exact nature of this mechanism is subject to further research; this research, however, should consider not only motor cognition and procedural learning but also, as suggested by the Weidner et al. (2009) study, top-down visual control.

So far, we have discussed the cognitive functions and components in the networks for normally reading and dyslexic children. However, the probably most striking observation in the present study was the strong laterality of effects, with a predominance for the right hemisphere in normally reading children and mostly left-hemispheric effects in dyslexic children. These findings relate to a long-lasting discussion in the literature about differences in hemispheric asymmetry in dyslexia (e.g. Abrams et al., 2009; Boles and Taran, 2003; Cao et al., 2008; Facetti et al., 2001; Heim et al., 2003a,b; Henderson et al., 2007; Illioud et al., 2010; Kobus et al., 1986; Leisman, 2002; Maisog et al., 2008; Milne et al., 2002; Penolazzi et al., 2006; Richlan et al., 2009; Rutherford, 2006; Spironelli et al., 2008; Temple et al., 2003). These studies investigated visual or auditory sensory processing but also covered a range of cognitive functions such as phonological processing, sound discrimination, or attention. Overall, there is no clear hint as to whether dyslexia is a left-hemisphere deficit, a right-hemisphere deficit, or both, or none. A meta-analysis by Maisog et al. (2008) suggested that dyslexics increasingly involve the right hemisphere instead of the left hemisphere during reading, which is in line with other findings by e.g. Spironelli et al. (2008), Richlan et al. (2009), or Cao et al. (2008). On the other hand, studies investigating bar graph recognition (Boles and Taran, 2003), attention (Facetti et al., 2001), or auditory processing (Abrams et al., 2009; Illioud et al., 2010) hint at a right-hemisphere deficit. Yet other studies reported reduced lateralisation effects (i.e. reduced hemispheric asymmetry) in dyslexics as compared to normal readers for auditory (Heim et al., 2003a,b; Leisman, 2002) but also phonological processing (Penolazzi et al., 2006). These effects could be due to the fact that asymmetries might be altered because of left-hemispheric increases induced by experience (Rutherford, 2006) or training (Temple et al., 2003).

This multitude of findings, which is at least partly due to the variety of modalities and paradigms, stems from studies investigating the neural mechanisms of cognitive functions which are regarded as potential causes of dyslexia, but mostly not from studies investigating the direct relationships of these functions on reading and reading-related brain activity. In contrast, the present study systematically focused on exactly this link, i.e. how the performance level in a potentially reading-related cognitive function influences the reading network in the brain. The data reveal that proficient readers have relatively stable left-hemispheric activation patterns related to orthographic processing and much larger variability in the (potentially supporting but not dominant) right hemisphere. In contrast, activation in the left, language-dominant hemisphere was much more variable for the dyslexic readers, revealing a strong dependency on levels of achievement in a variety of cognitive functions, and in particular visuo-magnocellular processing. These findings are in line with training studies (e.g. Meyler et al., 2008; Temple et al., 2003; for a recent review see also Gabrieli, 2009) showing the restitution of left-hemisphere regions after intervention and thus increasing comparability to normal readers with respect to both reading performance and brain activation. The findings of the two experiments presented here thus demonstrate potential mechanisms by which cognitive processing levels may be related to brain activation during reading, and how lateralisation differences between dyslexics and normal readers during reading may relate to variables discussed as potential causes of dyslexia.

Finally, the global interest of this study was to investigate how a larger set of cognitive variables gradually contributed to brain activation during dyslexic and normal reading. This research was motivated by the fact that earlier studies (e.g. Ramus et al., 2003; Heim et al., 2008; Menghini et al., 2010; Valdois et al., 2003) demonstrated the existence of cognitive subtype dyslexia, i.e. dyslexic reading was associated with different cognitive performance patterns when phonological awareness, visual attention, and other variables were considered. Apart from the distinct lateralisation of co-variation in left vs. right hemisphere discussed above, it is noteworthy that different cognitive variables showed co-variation with partly different brain regions, and that this effect was again different for dyslexics and controls. Since phonological awareness and visual attention were the most consistently observed variables to distinguish between cognitive subtypes of dyslexia in the previous studies, the last part of the discussion focuses in particular on them. When considering the co-variation effects for phonological awareness and reorienting of attention in the two groups, a double dissociation in the middle frontal gyrus is the most striking effect. For the normal readers, it is phonological awareness but not reorienting of attention that has an effect in (right) middle frontal gyrus. In contrast, for the dyslexic readers, it is reorienting of attention rather than phonological awareness that co-varies with (left) middle frontal activation. This pattern reveals that (at least for middle frontal gyrus) attention and phonological awareness are independent sources of co-variation in brain activation, as suggested by the previous studies that used only cognitive but no brain imaging measures (Heim et al., 2008; Valdois et al., 2003). Interestingly, the observed effects were contralateral to what is known from the literature about brain regions involved in phonological processing vs. attention (e.g. Arrington et al., 2000; Burton et al., 2000; Fan et al., 2005). However, it should be considered here that not proper phonological processing or reorienting of attention were investigated with fMRI, but rather co-variation of these cognitive variables with activation in brain regions involved in orthographic processing. When investigating proper phonological processing and reorienting of attention in the same dyslexic and control children, the expected lateralisation pattern in the prefrontal cortex emerges (Heim et al., 2010). Consequently, the double dissociation between variable (phonological/attention) and group observed in the present study reflects the interaction of the reading system with these variables. For the normal readers, left middle frontal cortex is involved in grapheme-to-phoneme conversion.
anyway; the role of its right homologue depends on the child's phonological abilities, but not on attention (the same also holds for right inferior parietal cortex, which is also involved in grapheme-to-phoneme conversion). Conversely, in dyslexic readers, and independ-ently of the individual level of phonological awareness, the middle frontal gyrus activation during grapheme processing depends on the child's ability to shift attention in order to support the reading process. In sum, this analysis tentatively describes a mechanism how two independent variables representing potential causes of dyslexia differentially affect the reading network in the brain, but do so in regions reciprocally related to these functions. Hereby, the present study thus complements earlier work by Shaywitz and Shaywitz (2008) who stressed the relevance of attention for reading and dyslexia and elucidated the underlying brain systems (with focus particularly on posterior, i.e. occipito-parietal regions). One central point put forth by Shaywitz and Shaywitz (2008) is that phonological processing may rely on intact attention. The authors thus establish a missing causal link from visual attention to phonology; the reverse relationship had been formulated earlier in the neurobiological model of dyslexia by Ramus (2004), who argued that attention (as a function of the magnocellular system) could be affected after (and perhaps sometimes as a consequence of) left-hemispheric perisylvian defects associated with phonological deficits. Future research will need to look more closely at the relationship of different aspects of attention on different aspects of phonological processing, and the function of this relationship for dyslexia. The present study sheds some light on different cognitive subtypes of dyslexia are necessary which corroborate or applies to children and to adults. In particular, more papers on must remain open at this point whether this discussion equally the prefrontal cortex of dyslexic and normally reading children. It modulate brain activation during orthographic processing in brain regions associated with the other of the two functions. Thus, whereas the cognitive variables are independent (achieved by orthogonalisation prior to fMRI analysis), they nonetheless affect related regions in the prefrontal cortex of dyslexic and normally reading children. It must remain open at this point whether this discussion equally applies to children and to adults. In particular, more papers on cognitive subtypes of dyslexia are necessary which corroborate or differentiate earlier behavioural findings. The available literature points at least at some continuity between children (Heim et al., 2008; Menghini et al., 2010) and adolescents (Valdois et al., 2003), whereas in adults (Ramus et al., 2003) interindividual variability but no clear subtypes were observable. A broader empirical basis with respect to cognition may then motivate developmental neuroimaging studies investigating brain–cognition relationships in dyslexia.

Conclusion

The present study investigated the role of cognitive levels of processing on brain activation during orthographic processing in normal and dyslexic readers. The findings revealed how a set of independent cognitive variables representing potential causes of developmental dyslexia co-vary with a right- vs. left-lateralised network in controls and dyslexics, respectively, thus providing a potential explanation for altered hemispheric asymmetry in dyslexia. The involvement of homologue regions by complementary variables demonstrate the intimate interrelation between distinct cognition cognitive variables in brain regions involved in translating script into sound during reading. Future research will need to focus on the developmental perspective, assessing the role of reading-relevant cognitive functions for visual word processing in adult dyslexic and normal readers.

Acknowledgments

Foremost thanks to Simone Vossel for providing us with the Posner paradigm and for her valuable discussions of the data. We wish to thank Cordula Kemper, Dorothee Krug, Barbara Elghahwagi, Petra Engels, Veronika Ermer, and Markus Ullisch for their assistance with the recording of behavioural and fMRI data. Furthermore, we are grateful to Peter Weiss-Blankenhorn for the neurobiological evaluation of the children’s anatomical brain scans. Thank you also to two anonymous reviewers, who provided valuable input for improving a first version of the paper. Finally, we thank all primary schools and in particular all parents and children who participated in this study.

This research was supported by the German Federal Ministry of Education and Research (BMBF 01GJ0613 to S.H. and BMBF 01GJ0614 to M.G.), the National Institute of Biomedical Imaging and Bioengineering, the National Institute of Neurological Disorders and Stroke, and the National Institute of Mental Health (K.A.).

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