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Distinct neural signatures of cognitive subtypes of dyslexia: Effects of lexicality during phonological processing

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The present study investigates the neurobiological basis of two subtypes of dyslexia with either a double deficit (concerning phonological awareness and rapid naming) or a single rapid naming deficit. We compared such groups of German dyslexic primary school children to each other and with good reading children in a phoneme deletion task performed during fMRI scanning. Children heard German words or pseudowords and repeated the remainder of the stimulus while deleting the initial phoneme (e.g. tear – _ear). In four conditions, the input stimulus (word or pseudoword) could either become another word or pseudoword as output. The word-word condition stuck out against all other conditions involving pseudowords: Dyslexics with a double deficit showed a strong response in left areas 44 and 45 in Boca's region, whereas dyslexics with rapid naming difficulties revealed a contralateral effect in right areas 44 and 45. These findings, which were obtained without presenting written or pictorial stimuli, reveal that a double deficit in dyslexia is not the sum of single deficits, but rather involves the interaction of lexical and phonological processing, making strong demands on the left inferior frontal cortex. In general, the results stress the importance of considering subtypes of dyslexia differentially in order to obtain better insights in the neurocognitive mechanisms of impaired and successful reading.

Key words: developmental dyslexia, phonological awareness, rapid naming, cognitive subtypes, lexicality effect, neuroimaging, inferior frontal gyrus

INTRODUCTION

With a prevalence of up to 17.5 percent (Shaywitz 1998) developmental dyslexia is a frequent neurobehavioral disorder in childhood. In relation to at least average non-verbal intelligence, cognitive ability, education or professional level, developmental dyslexia, is defined as an unexpected difficulty in reading (Critchley 1970, Lyon et al. 2003, Shaywitz 2005) and is characterized by poor spelling and decoding abilities. As a possible consequence dyslexia may include problems in reading comprehension and reduced reading experience inhibits growth of vocabulary and background knowledge (Shaywitz 2005; p. 3–12). Dyslexia is persistent in reading and writing and usually does not remit over age or time (Francis et al. 1994, Shaywitz et al. 1995). Several theoretical approaches have been developed to explain multifactorial phenotypes of dyslexia. One of the most influential theories is the phonological deficit hypothesis (Liberman 1973, Snowling 1995, Snowling 2000, Vellutino et al. 2004), which assumes dyslexia to be the result of language deficits in the phonological domain, which in turn are caused by deviant underlying neurofunctional processes (Ramus 2004). However, subsequent neurofunctional research with the common goal to analyze phonological processing showed a large heterogeneity of (de-)activation patterns in infe-

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rior frontal regions: A variety of studies consistently reported activation differences between good reading and dyslexic readers (Rumsey et al. 1997, Georgiewa et al. 1999, 2002, Temple et al. 2001, Cao et al. 2006, Hoeft et al. 2006, 2007, Heim et al. 2010a, Wimmer et al. 2010). However, the findings varied substantially with respect to the hemisphere (left/right/both) in which these differences occurred, and whether the dyslexic subjects showed a relative increase ("hyperactivation") or decrease ("hypoactivation") in comparison to good readers (for reviews see Richlan et al. 2009, 2011). A main declaration of these reviews is that developmental dyslexia is associated with underactivation in posterior regions of the left hemisphere and left frontal abnormalities with underactivation in the inferior frontal gyrus.

Ramus (2004) speculated that such heterogeneous findings might partly be due to the division of phonological processing into three main components: phonological awareness, rapid naming abilities, and phonological short term memory (Wagner and Torgesen 1987), each involving partially distinct cortical networks. In good readers Misra and coauthors (2004) showed that rapid naming tasks activate neural areas associated with eye movement control and attention as well as the network of structures previously implicated in reading tasks. In particular, rapid naming of letters caused greater activation in the angular gyrus of the superior parietal lobule. In dyslexia rapid naming is conducted with reduced activation in the posterior lobe (Lymberis et al. 2009)

The coexistence of phonological and rapid naming deficits rests on the double deficit hypothesis (Wolf and Bowers 1999) which distinguished phonological deficits from naming speed difficulties, the latter involving rapid-naming (RAN) processes such as visual coding of pictures to be named. Thus, rapid naming abilities contribute to reading beyond phonological awareness (Wagner et al. 1997).

In dyslexia, deficits in phonological awareness appear to account for reading difficulties in the majority of dyslexics (Ramus 2003, Ramus et al. 2003). However, recent studies revealed that they are not present in all dyslexics (e.g., Valdois et al. 2003, Bosse et al. 2007, Heim et al. 2008, Tholen et al. 2011), a finding which suggests that the individual cognitive deficit profile of a dyslexic reader may be relevant for his or her specific pattern of reading difficulties. Subsequent neuroimaging studies indeed revealed that different cognitive profiles in dyslexia are related to differential underlying neural networks (Heim et al. 2010a,b) during reading and phonological decisions, which involved areas 44 and 45 (i.e. Broca's region) in the left inferior frontal gyrus and the superiorly adjacent left middle frontal gyrus.

Interestingly, and in line with the double deficit theory of dyslexia, such activation differences in Broca's region between dyslexics and controls were not only observed for phonological processing, but also for lexical access. Building upon earlier findings of the sensitivity of areas 44 and 45 to lexical frequency as an indicator of the ease of lexical access (e.g. Fiebach et al. 2002, Kronbichler et al. 2004, Heim et al. 2005), Grande and colleagues (2011) demonstrated activation differences between dyslexic and good reading children in areas 44 and 45 for lexical access to written stimuli. This finding was extended to adults (Heim et al. 2013) for whom activation for lexical access differed as a function of reading ability. A recent fMRI study by Wimmer and coworkers (2010) sheds some more light onto these findings. These authors used a phonological lexical decision task on stimuli that were words (e.g. TAXI), pseudohomophones (TAKSI), or nonwords (TAZI). When comparing Nonwords (involving only phonological-orthographic processing) to pseudohomophones (involving additional access to the phonological output lexicon), Wimmer et al. observed a group difference between controls and dyslexics in the left IFG in approximately areas 45 (MNI coordinates −48 27 33) and 44 (at −45 6 36). Interestingly, the dyslexic participants were not only worse in different measures of reading, but also in rapid automatized naming (no scores for phonological processing abilities were reported). The fMRI activation difference in a contrast tapping into lexical access might therefore be interpreted as reflecting these differences in rapid lexical phonological access.

To summarize, the situation is as follows: (1) Dyslexic children with a phonological deficit show altered left inferior frontal responses for reading and phonological awareness tasks; (2) Left inferior frontal involvement is also observed for lexical access, in good readers as well as in dyslexia, with differences between these two groups. However, with respect to the double deficit hypothesis, it is yet unclear in how far this pattern reflects a double deficit in phonological and lexical access, or whether such differences are merely due to a deficit in either lexical access or phonological processing.

Consequently, we conducted a study that links phonological awareness to lexical status (i.e. processing of words or pseudowords) in two subgroups of dyslexic readers with RAN difficulties only vs. a double deficit in RAN and phonological awareness. In order to avoid confounding influences from orthographic stimuli, the study was conducted in the auditory domain, in which none of the children showed difficulties in a pre-study test (for the relevance of intact auditory processing cf. Steinbrink et al. 2009, 2012). We expected a specific left inferior frontal effect for dyslexics with a double deficit in both phonological awareness and lexical access, which would be different from both the dyslexics with only a RAN deficit and the good control readers.

METHODS

All procedures applied in this study were in accordance with the Declaration of Helsinki and were approved by the ethics committee of the Medical Faculty of RWTH Aachen University (Reference number EK 153/08).

Participants

There was an initial reading assessment with the Salzburger Lesescreening (SLS; Mayringer and Wimmer 2003) measuring reading speed and basic reading ability (automaticity, accuracy). Out of 785 German primary school children (grades 3 and 4), 42 children were included in this study. Additional written informed consent was obtained from their parents. The non-verbal IQ was assessed with the German version of the Cattel Culture Fair Test (CFT 20; Weiss 1998). Children were included in the study with an age-related IQ >80 in order to ensure that no children with general learning disabilities participated. In order to exclude that perceptual impairments influence the reading ability, the pre-test of auditory and visual perception of the Wiener Testsystem (WAF, Häussler and Sturm 2009) suitable from the age of eight years onwards was assessed. Children with a value of below 80 in at least one of the sub-tests were excluded from the study.

Depending on their reading performance, the children were assigned to one of the two groups of dyslexic (n=32; mean age = 9.8 years; range: 9.7–10.1; 15 girls) or good reading (n=10; mean age = 9.6 years; range: 9.3–9.9; 6 girls) children. Subjects (Table I) were monolingual speakers of German, physically healthy and free of neurological diseases.

In order to further divide the children into subjects with vs. without phonological deficits, their phonological awareness was tested with the standard German test "Basic Competences for Reading and Writing Abilities" (BAKO 1–4; Stock et al. 2003). This test consists of 7 subtests assessing receptive and expressive abilities of phonological synthesis and manipulation. Based on their average or below-average performance in the BAKO (i.e. T values above or below 40, respectively), the dyslexic group was further divided into 15 children with and 17 without phonological awareness deficits (Table I).

The least-significant differences Test (LSD-Test) showed that both the phonological dyslexics (P=0.005) and the dyslexics without phonological deficit (P=0.027) performed significantly worse in RAN (Mayer 2008, Verhalen 2011) than the controls. Therefore, the phonological dyslexics suffered from a double deficit (phonological and RAN deficit, henceforth called DoubleDys), whereas the dyslexics without phonological deficit exhibited only a deficit in RAN and will henceforth be named RanDys.

fMRI paradigm

Brain activation for phonological awareness was assessed in an event-related design, with a randomized sequence of stimuli. The phonological task was adapted from the phoneme deletion subtest of the standardized BAKO test of phonological awareness. The children heard a spoken word or a pseudoword and had to repeat this stimulus without its initial phoneme. The total number of 91 presented stimuli could be separated into words which remain words after omitting the initial phoneme (e.g. /tear/→/_ear/), words which become pseudowords (e.g. /tiger/→/_iger/), pseudowords which remain pseudowords (e.g. /lagon/→/_agon/) and pseudowords which become words (e.g. /topen/→/_open/). The children were instructed to produce their answers when a smiley appeared on the computer screen. During the smiley presentation the scanner noise turned off (sparse-sampling scanning sequence, cf. Grande et al. 2011). This enables an audio recording of the answers without interruption and subsequent analysis of each child's performance.

Table I

Subject characteristics of double deficit dyslexics (DoubleDys), rapid-naming dyslexics (RanDys) and controls (Con) for the total sample

	Con	DoubleDys	RanDys	*P* (ANOVA)
n (girls)	10 (6)	15 (7)	17 (8)	
Age (years ± SD)	9.6 ± 0.5	9.8 ± 0.5	9.7 ± 0.5	n. s.
IQ	123.7	103.9	112.1	<0.002
Reading (SLS score ± SD)	118.2 ± 13.4	72.6 ±11.1	79.5 ± 14.6	<0.001
Phon. Awareness (*T* score ± SD)	58.4 ± 9.6	32.8 ± 5.1	47.1 ± 5.1	<0.001
RAN (Items per second ± SD)	1.36 ± 0.17	1.12 ± 0.13	1.18 ± 0.25	0.016

The reading screening (Salzburger-Lese-Screening) contains the reading quotient which is scaled like the intelligence quotient [Reading quotient <90 is substandard (mean 100; SD 15)] ± the standard deviation (SD). The IQ refers to the age norms ± SD, whereas the results of the phonological awareness test ("Basic Competences for Reading and Writing Abilities" - BAKO) bears upon the total *T*-values (BAKO percentiles below 25 are clinically relevant). Performances in rapid-naming (Rapid automatized naming) are described items per second ± SD. There are no norms available for German population.

MRI data acquisition and analysis

The fMRI experiment was carried out on a 3T Siemens Trio scanner (Siemens, Erlangen, Germany) at the University Hospital Aachen. A standard bird-cage head coil was used and soft foam paddings were utilized to reduce head motion. Echo-planar images [repetition time (TR): 5 000 ms; gap in TR (sparse sampling) 1 000 ms at the end of the TR; field of view (FoV) 200 mm; flip angle 90°; echo time (TE): 30 ms] were acquired from 40 transversal slices covering the entire brain (slice thickness: 30 mm) in 95 measurements and a duration of 8 minutes.

In addition, anatomical images (orientation: sagittal; slice thickness: 1 mm; FOV = 250 mm, TR = 2 500 ms, TE = 30 ms) were obtained. Functional scans were analyzed with Statistic Parametric Mapping *SPM5* (Welcome Department of Cognitive Neurology, London) and Matlab 7 (The Mathworks Inc., Natick, USA). Pre-processing[1] involved the standard procedures of realignment to the first image, slice timing, normalization to standard MNI space, and smoothing with a Gaussian kernel of 8 mm FWHM. Event-related statistics at the first (single subject) level used separate stick functions (duration = 0 s), which were convolved with the canonical hemodynamic response function and its first temporal derivative. All conditions were contrasted separately against the resting state. These contrast images then entered the second level random effects group analysis. The second-level analysis was realized using a flexible factorial design for repeated measures, allowing the assessment of main effects for differences between the Word–Word condition involving lexical access for both stimulus and response and the other conditions involving at least one pseudoword stimulus without a lexical representation (Word–Pseudoword; Pseudoword–Pseudoword; Pseudoword–Word) as a function of Group. This interaction term between Lexicality (Word–Word vs. others) × Group is supposed to reveal brain regions that differentiate between the three groups in respect to lexicality effects.

First, the overall contrast for the lexicality effect was computed as a main effect over all groups and is expected to reveal brain regions showing a lexicality effect, i.e. activation differences for lexical vs. non-lexical stimuli. The present study focuses on bilateral areas 44 and 45 which are supposedly involved in phonological and lexical processing. Accordingly, regions of interest (ROIs) were defined bilaterally for these areas using the SPM Anatomy Toolbox (Eickhoff et al. 2005; see below). To show activation differences between the groups of DoubleDys, RanDys, and good readers (Con), the groups were contrasted against each

[1] In the present study, no artifact detection algorithms were applied to the fMRI data because the average head motion was comparatively low (mean[mean]: x = 0.07 mm; y = 0.01 mm; z = 0.03 mm) and because BOLD acquisition was temporally separated from phases of overt speech production (for details cf. Heim et al. 2006)

other. The contrast of DoubleDys against RanDys and Con is thus supposed to show brain areas specifically related to lexicality during a phonological awareness task for DoubleDys. Likewise, the reverse contrast was computed to assess specific lexicality patterns for the RanDys group.

Localization of effects using cytoarchitectonic maps

Cytoarchitectonic probability maps (Amunts et al. 2004) for the anatomical localization of the effects were obtained on the basis of mapping areas in histological sections based on an observer-independent approach for the definition of cortical borders (Zilles et al. 2002, Schleicher et al. 2005). The cytoarchitectonic probability maps allocate information about the position and variability of cortical regions within standard MNI reference space. The SPM Anatomy Toolbox (Eickhoff et al. 2005) facilitates the assignment of the MNI coordinates to the cytoarchitectonically defined regions and is receivable with all cytoarchitectonic probability maps and references from http://www2.fz-juelich.de/inm/inm-1/spm_anatomy_toolbox. The maps for left and right areas 44 and 45 (Amunts et al. 1999) were used as masks for the region of interest of the present analysis.

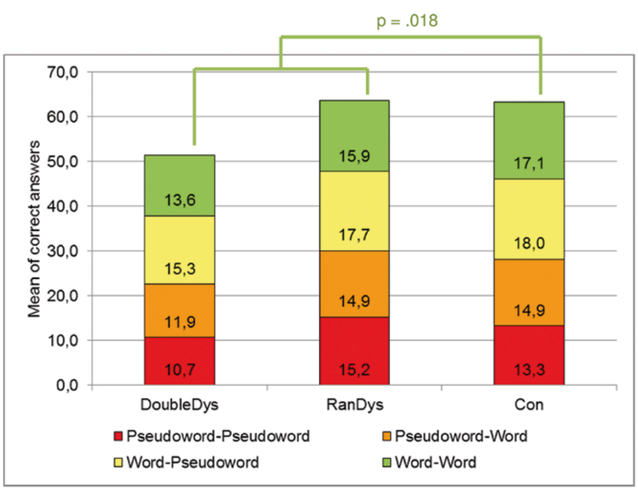

Fig. 1. Performance of double deficit dyslexics (DoubleDys; n=15), rapid-naming dyslexics (RanDys; n=17) and controls (Con; n=10) inside the scanner. Mean values describe the total number of correct answers for the conditions Word–Word (green), Word–Pseudoword (yellow), Pseudoword–Pseudoword (red); Pseudoword–Word (orange). There were only significant differences between dyslexics and controls in the Word–Word condition (green).

RESULTS

Behavioral data

The behavioral data set of the initial diagnostic session before the fMRI-Measurement is shown in Table I and was further analyzed with *SPSS* for Windows version 20.0 (SPSS, Inc., Chicago, Illinois).

The audio recording of the answers inside the scanner were transcribed and analyzed with SPSS Version 20.0 (Fig. 1). For all dyslexics together, the total number of correct answers did not differ significantly from the controls ($F_{1,40}$=1.910; P=0.175). A more detailed look at the data set revealed a significant effect for the Word-Word condition for all dyslexics versus controls ($F_{1,40}$=6.119; P=0.018). The other conditions did not differ significantly between these groups (Word–Pseudoword: P=0.602; Pseudoword–Word: P=0.648; Pseudoword–Pseudoword: P=0.497). Comparing the two dyslexic subgroups with each other and with the control group showed no significant differences.

In summary, the behavioral data conducted inside the scanner showed a discrepancy in the processing of the Word-Word condition between dyslexics and controls. There were no significant differences in the phonological processing between the two dyslexic subgroups.

Over all groups the behavioral data set showed significant correlation between phonological processing and reading ability (r=−703; P<0.001). The higher scores of the phonological test (BAKO), the better was the reading ability. Reading ability was only related to the number of correct answers when a word remained a word (r=0.411; P=0.008) and when the input of the stimuli was a word (e.g. Word–Word: Word–Pseudoword; r=0.354; P=0.023). Phonological awareness correlated with far more cognitive tasks: The better the phonological awareness, the higher was the number of correct answers of the phonological task inside the scanner (r=0.325; P=0.038). There were also significant correlations for two separate conditions of the phonological task: the higher the phonological awareness, the higher was the number of correct answers in the Word–Word (r=0.427; P=0.005) and Pseudoword–Pseudoword (r=0.314; P=0.046) condition. In summary better phonological awareness concur with higher scores in the phonological task when the out-

Table II

Pearson´s correlation coefficient (*r*) of cognitive abilities (phonological awareness; reading ability) and performance conducted inside the scanner

Performance	Phonological awareness	Reading ability
Phonological awareness (*T*-value)	–	*r*=0.406; *P*=0.008
Reading ability (Reading quotient)	*r*=0.703; *P*<0.001	–
Rapid naming (Items/second)	*r*=0.427; *P*=0.005	*r*=0.578; *P*<0.001
Number of correct answers „PP”	*r*=0.314; *P*=0.046	n. s.
Number of correct answers “WW”	*r*=0.427; *P*=0.005	*r*=0.411; *P*=0.008
Total Number of correct answers	*r*=0.325; *P*=0.038	n. s.
Output Word (Number of correct answers)	*r*=0.308; *P*=0.050	n. s.
Output Pseudoword (Number of correct answers)	*r*=0.325; *P*=0.038	n. s.
Input Word (Number of correct answers)	*r*=0.376; *P*=0.016	*r*=0.354; *P*=0.023
Input Pseudoword (Number of correct answers)	n. s.	n. s.

put of a word remained a word (*r*=0.308; *P*=0.050), or that of a pseudoword remained a pseudoword, respectively (*r*=0.325; *P*=0.038). The same applies when the input of the stimulus was a word (*r*=0.376; *P*=0.016) (Table II). There was no correlation between rapid naming (RAN) and any other cognitive tasks.

fMRI Data

Overall, there was a clear distinction between Word-Word trials and all other conditions involving pseudowords. This main effect for stimulus type covered areas 44 and 45 in both hemispheres (Table III and Fig. 2 top panel).

Controls *versus* dyslexics

Brain areas for the lexicality effect (X–Pseudo-X > Word–Word) revealing differences between good readers and dyslexics were identified within the inferior frontal gyrus (bilateral area 45 and left area 44) (Table III).[2]

To consider the question whether dyslexics with rapid naming deficits and dyslexics with a double deficit are differentiable in the lexicality effect bilateral in area 44 and 45, both subgroups were contrasted against each other and against controls (Table IV). RanDys and Con revealed increased activation in the left inferior frontal gyrus (area 44; 45) in contrast to DoubleDys (Table IV; Fig. 2 middle panel).[3] However, the rapid-naming dyslexics showed reduced activation contralateral in the right inferior frontal gyrus (area 44) (Table IV; Fig. 2 bottom panel).

Functional interaction of brain areas and performance

The present study found significant functional interaction of brain areas in bilateral area 44 (Table V). There were no significant correlations in area 45 in any hemisphere.

The higher the reading ability the stronger was the activation intensity bilaterally in area 44. Furthermore, only right area 44 showed significant correlations of brain activation patterns with characteristics of the stimulus set. In regard to the behavioral dataset conducted inside the scanner the present study showed that the higher the ratio of correct answers the stronger

[2] The group of dyslexics contains 32 subjects (RanDys: n=15; DoubleDys: n=17) and the control group 10 subjects. The groups sizes are thus in the range suggested as suitable for fMRI studies. Admittedly, the control group only comprised 10 subjects; however, good readers might be considered as more homogeneous than dyslexic readers. In fact, the error bars in Figure 2 support this point: The variability of activation in the control group was comparable to that in the two dyslexic groups.

[3] The lexicality effects only depends on relative indications

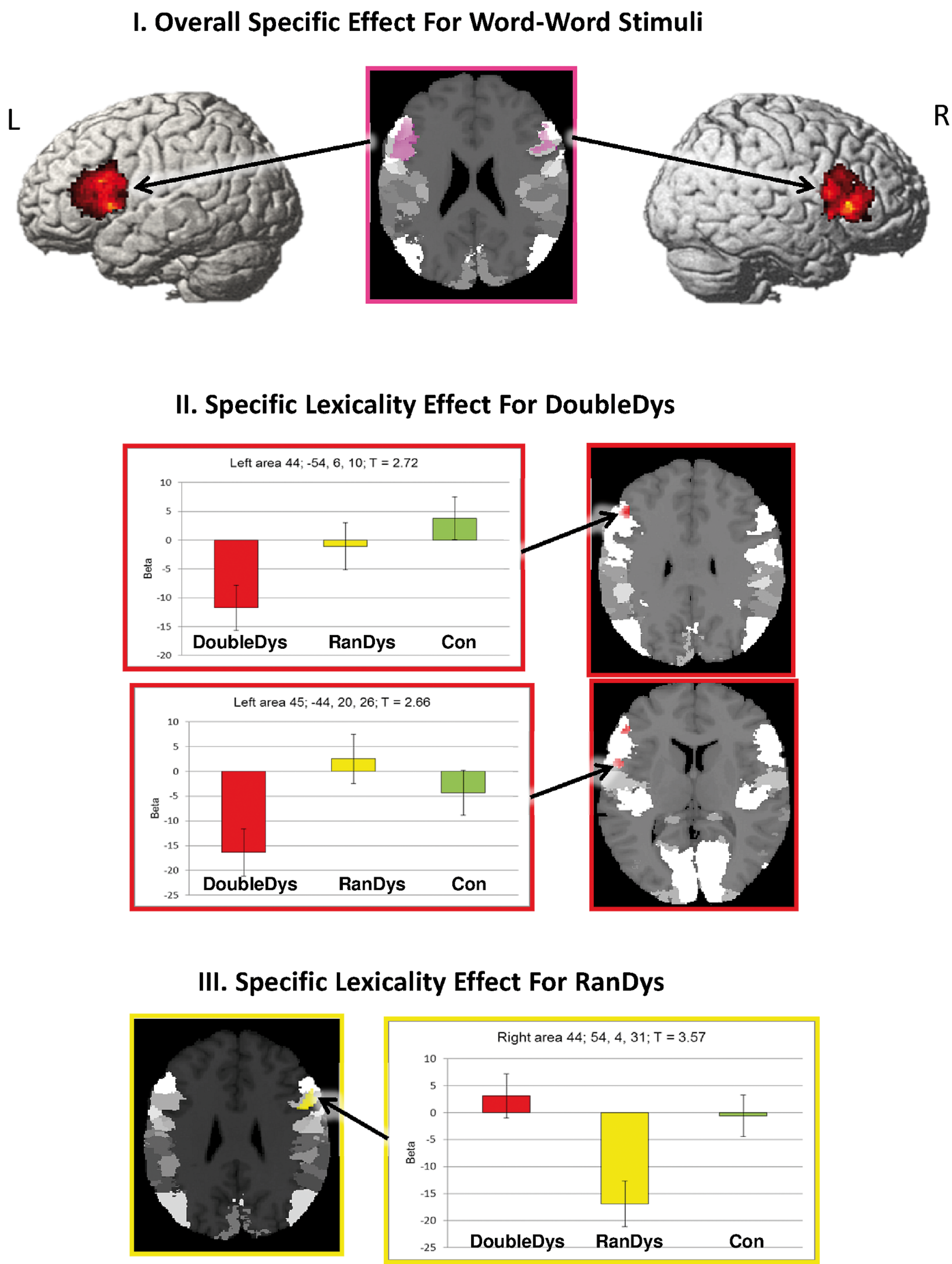

Fig. 2. Neuroimaging: (I) Areas 44 and 45 in Broca's region in the left hemisphere and also in its right-hemispheric homologue show specific effects for word stimuli that remain words after deleting the first phoneme (e.g., tear → _ear) in comparison to all other stimuli involving pseudowords as inputs or outputs (pink; negative lexicality effect, cf. body text). (II) Dyslexic children with double deficits in phonological awareness and rapid naming show a specifically larger negative lexicality effect than dyslexics with a single rapid naming deficit and good readers in Broca's region (areas 44 and 45). (III) Instead, dyslexic readers with problems only in rapid naming show a specifically increased negative lexicality effect in Broca's homologue particularly in area 44.

Table III

Neuroimaging results of lexicality effect revealing differences between normal readers and dyslexics within the mask of cytoarchitectonic areas 44 and 45

Cluster Size (Voxels)	Hemisphere	Cytoarchitectonic Area	x	y	z	T_{max}
Dys > Con						
1244	Left	55.4% Area 44	−40	20	22	4.72***
		35.1% Area 45				
1057	Right	46.0% Area 45	42	24	4	5.89***
		44.0% Area 44				
Con > Dys						
183	Right	71.0% Area 45	50	24	14	2.66**
		21.7% Area 44				
98	Left	82.1% Area 44	−58	10	4	2.55**

Effects are significant at $P<0.001$***, 0.01**, and 0.05*. Cluster size refers to $P<0.05$, extent $k=30$ voxels.

activation intensity in right area 44. There was a correlation between the number of correct answers and activation intensity in right area 44 when the output of the stimulus consisted of words and in the Word–Word condition. The higher the number of correct answers in the output word condition and in the Word–Word condition, the stronger was the activation intensity in right area 44. There was no correlation between RAN and activation of any brain region.

DISCUSSION

The present study demonstrated a differential neurofunctional organization of lexical access in two cognitive subtypes of dyslexia with either rapid naming (RAN) deficits alone or a double RAN and phonological awareness deficit. In a phoneme deletion task, there were unique activation differences between word stimuli and stimulus pairs involving pseudowords: The RanDys group showed clear effects in the right inferior frontal gyrus, i.e. a specifically reduced lexicality effect in right areas 44 and 45. In contrast, a different pattern emerged for the DoubleDys children, who had had a uniquely reduced lexicality effect in the left inferior frontal gyrus in areas 44 and 45. These results are indicative of two things: First, considering cognitive profiles or subtypes of dyslexia is advantageous because they differ both with respect to their cognitive and their neurofunctional architecture. Second, a double phonological awareness and RAN deficit in dyslexia does not merely imply a twice as restricted cognitive basis than an isolated RAN deficit. As becomes evident in the DoubleDys group, the two deficits are not simply additive in the sense that they produce two independent neurofunctional responses. Rather, when present in the same person, the two deficits seem to interact with each other, causing a unique extra charge on the left inferior frontal cortex with its neighboring regions for lexical selection (area 45) and phonological and lexical processing (area 44; cf. Heim et al. 2009b). These points will now be discussed in more detail.

Dyslexia and the inferior frontal gyrus

With respect to the whole dyslexic sample, controls showed increased activation bilaterally in the inferior frontal gyrus (area 44, 45). This stands in line with previous findings that controls show significantly greater activation clusters in the left (Georgiewa et al. 1999, Shaywitz et al. 2002, Bitan et al. 2006) or bilateral (Cao et al. 2006) inferior frontal gyrus. In the recent literature, the inferior

Table IV

Neuroimaging results of the lexicality effect revealing differences between dyslexics with a phonological and rapid naming deficit (DoubleDys), rapid-naming dyslexics (RanDys) and controls (Con) within the mask of cytoarchitectonic areas 44 and 45

Cluster Size (Voxels)	Hemisphere	Cytoarchitectonic Area	x	y	z	T_{max}
DoubleDys < RanDys+Con						
53	Left	87.0% Area 45	−48	24	28	2.42**
		6.6% Area 44				
33	Left	95.5% Area 45	−50	34	12	2.31*
30	Left	87.5% Area 44	−56	6	8	2.29*
RanDys < DoubleDys+Con						
237	Right	56.4% Area 44	52	6	26	3.28***
		33.3% Area 45				

Effects are significant at $P<0.001$***, 0.01**, and 0.05*. Cluster size refers to $P<0.05$, extent $k=30$ voxels

frontal gyrus is discussed to serve as an executive system for access, retrieval, selection and gating of information by the alignment or reactivation of representations (Wagner et al. 1997, Poldrack et al. 1999). Therefore, dyslexic children could be delayed in the retrieval of phonological information for which the inferior frontal gyrus is relevant, and in particular so when this phonological information relates to lexical entries.

The present study contributes to the existing literature on the neurofunctional basis of dyslexia in a very particular way. Based on the papers by Wolf and Bowers (1999), Ramus (2003), Heim and colleagues (2008) and others on cognitively distinct groups of dyslexics, we sought to explain the obvious heterogeneity in neuroimaging data of dyslexia (e.g. Richlan et al. 2011) as a function of distinct cognitive profiles. Indeed, previous work from our group (Heim et al. 2010a,b) had revealed a coupling between reading ability and phonological processing in left area 45, which was opposed to the involvement of right areas 44 and 45 in other types of reading-relevant cognitive tasks such as visual processing, attention, or auditory processing – a pattern that very much resembles the data in the present study. Importantly, in the present study,

Table V

Pearson's correlation coefficient (r) between brain areas with mean peak of activation for the lexicality effect, phonological awareness (BAKO) and reading ability (SLS) ($n=42$)

	Phonological awareness	Reading ability	Correct answers	Word–Word	Output word
Left area 44	n. s.	$r=0.376$; $P=0.014$	n. s.	n. s.	n. s.
Right area 44	n. s.	$r=0.349$; $P=0.024$	$r=0.313$; $P=0.046$	$r=0.309$; $P=0.050$	$r=0.321$; $P=0.041$

again left and right inferior frontal activation patterns were correlated with reading ability scores, demonstrating the yet disregarded importance of Broca's right homologue to reading and dyslexia. Likewise interestingly, the present study revealed a lexicality effect for DoubleDys in Broca's region, which replicates the earlier evidence of the lexicality effect (words vs. pseudowords) coupled to the phonological processing effect in left area 45 in the Heim and coworkers (2010a) study. Given this obvious interaction between lexical and phonological processing, we will now turn to this issue in more detail.

Lexical and phonological processing

The study paradigm allowed testing for independent types of processing, phonological awareness and lexical access. Phonological awareness was explicitly targeted by the phoneme deletion task. Accordingly, overall performance rates correlated well with the individuals' levels of phonological awareness. Lexical access was tested implicitly by contrasting trials containing words only to trials involving at least one pseudoword. A correlation analysis of the behavioral data set conducted inside the scanner revealed, that the performance of the phoneme deletion task was dependent on the individual level of phonological awareness, but not the level of RAN.

Using this paradigm, the present study thus allows a more detailed look into the functional organization of bilateral inferior frontal regions (are 44 and 45) by dividing the dyslexic sample into children with a double deficit or a mere rapid naming deficit. A clear dissociation was found for both subtypes of dyslexia within their activation profile. Double deficit dyslexics showed a significantly reduced lexicality effect in the left inferior frontal gyrus (area 44, 45) whereas the dyslexics with mere rapid naming deficit revealed a reduced lexicality effect in the right inferior frontal gyrus. In previous studies, it was shown that the cytoarchitectonically distinct areas 44 and 45 in left inferior frontal gyrus contributed differentially to lexical access (area 44) and lexical selection (area 45) (Heim et al. 2005, 2009a,b). Within these left inferior frontal gyrus subdivisions dyslexic children (Grande et al. 2011) and adults (Heim et al. 2013) were recently shown to exhibit functional abnormalities. Heim and others (2013) found a strong effect for lexical access in left area 44 for a dyslexic adults sample and in left area 45 for controls. The increased activation cluster for controls seems to extend slightly into area 44. The same pattern of activation was also found by Grande and coauthors (2011) whereas no group differences were observed in area 45. The present study was based on these findings, adding similar activation clusters for dyslexic subgroups in these areas.

The reduced lexicality effect for the DoubleDys group in the left frontal gyrus stands in line with previous findings (Georgiewa et al. 1999, Shaywitz et al. 2002, Bitan et al. 2006, Cao et al. 2006). However, it should be noted that the left-lateralized pattern observed for the DoubleDys group that covered both areas 44 and 45 reflects a contrast between lexical and non-lexical items, not a comparison to baseline. This is important because the inferior frontal gyrus is known to support phonological segmentation, discrimination and monitoring (Zatorre et al. 1992, 1996, Burton et al. 2000). Therefore, one might be tempted to speculate that the effect in area 44 relates to phonological processing. However, in the present study, the effect in area 44 is unlikely to reflect phonological processing difficulties *per se*, because the overall level of activation in this region was only correlated with the reading score, not with any phonological score. Instead, the data might be taken to suggest the interaction of lexicality and phonological awareness (left inferior frontal gyrus) as opposed to rapid access to the phonological word form (right inferior frontal gyrus in the RanDys group). Having to process two lexical items as input and output of a phonological awareness task poses increased demands on the closely linked system of left areas 44 and 45 (Heim et al. 2009b) with their different preference for lexical or non-lexical stimuli (Mechelli et al. 2005). Both these studies used dynamic causal modeling (DCM) as a technique to investigate the dynamic interaction of the two regions. Unfortunately, the scanning parameters of the present study (TR = 5 s) do not permit DCM analyses to further elucidate this matter. Still, the fact that the activation in left area 44, but not left area 45, showed a correlation with reading ability may be taken as evidence for a distinct functional role of these two regions. One might speculate that the role of left area 45 involves linking the lexical entries to their phonological forms, whereas the handling of phonemes in area 44 is the prerequisite for subsequent grapheme-to-phoneme conversion needed for reading (i.e. correlation with reading ability), which, however, was not required in the phonological awareness task itself. Further research on the differential connectivity in subtypes of dyslexia is therefore required in order to understand the mosaic of neurofunctional mechanisms contributing differentially to impaired or successful reading.

Limitation

In the present study, no artifact detection was applied. However, given the small average head motion and the dissociation from BOLD acquisition and speaking, this additional noise is likely to be small and did not prevent the detection of reliable group differences.

As mentioned Table I, the controls showed a significantly higher IQ level than the dyslexics (*P*=0.002), whereas the two dyslexic groups exhibited comparable IQ. The Scheffé test for multiple comparisons indicated that the controls differed significantly from the dyslexics with double deficits (*P*=0.002) but not from the dyslexics with a single rapid naming deficit (*P*=0.086). There was no significant differences in the intelligence level between the two dyslexic groups (*P*=0.204). This is in line with the literature, as the impact of intelligence on phonological processing could not be proved in previous studies (Temple et al. 2001, van Ermingen-Marbach et al. 2013).

CONCLUSIONS

The present neuroimaging study demonstrated the qualitative difference between children with a single vs. a double phonological deficit not only in performance, but also in the neurophysiological data accompanying lexical processing. These findings stress the importance of assessing a dyslexic child's problems individually and with great care, since training success both at the neurofunctional and at the cognitive and performance level may depend upon this.

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