



Developmental dyslexia and widespread activation across the cerebellar hemispheres

Hanne Baillieux^{a,1}, Everhard J.M. Vandervliet^{b,1}, Mario Manto^c, Paul M. Parizel^b, Peter P. De Deyn^d, Peter Mariën^{a,d,*}

^a Department of Linguistics, Vrije Universiteit Brussel, Brussels, Belgium

^b Department of Radiology, University Hospital Antwerp, Antwerp, Belgium

^c Fonds National de la Recherche Scientifique (FNRS) - Hôpital Erasme ULB, Brussels, Belgium

^d Department of Neurology, ZNA A.Z. Middelheim and Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium

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ABSTRACT

Developmental dyslexia is the most common learning disability in school-aged children with an estimated incidence of five to ten percent. The cause and pathophysiological substrate of this developmental disorder is unclear. Recently, a possible involvement of the cerebellum in the pathogenesis of dyslexia has been postulated.

In this study, 15 dyslexic children and 7 age-matched control subjects were investigated by means of functional neuroimaging (fMRI) using a noun-verb association paradigm. Comparison of activation patterns between dyslexic and control subjects revealed distinct and significant differences in cerebral and cerebellar activation. Control subjects showed bilaterally well-defined and focal activation patterns in the frontal and parietal lobes and the posterior regions of the cerebellar hemispheres. The dyslexic children, however, presented widespread and diffuse activations on the cerebral and cerebellar level. Cerebral activations were found in frontal, parietal, temporal and occipital regions. Activations in the cerebellum were found predominantly in the cerebellar cortex, including Crus I, Crus II, hemispheric lobule VI, VII and vermal lobules I, II, III, IV and VII.

This preliminary study is the first to reveal a significant difference in cerebellar functioning between dyslexic children and controls during a semantic association task. As a result, we propose a new hypothesis regarding the pathophysiological mechanisms of developmental dyslexia. Given the sites of activation in the cerebellum in the dyslexic group, a defect of the intra-cerebellar distribution of activity is suspected, suggesting a disorder of the processing or transfer of information within the cerebellar cortex.

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1. Introduction

Developmental dyslexia is traditionally defined as an isolated developmental disorder in children who, despite normal intelligence and conventional classroom experience, fail to sufficiently learn reading skills (American Psychiatric Association, 2000; Beaton, 2004). With an estimated incidence of five to ten percent of school-aged children (Habib, 2000), this condition constitutes the most common learning disorder (Galaburda, LoTurco, & Rosen, 2008). Despite intensive research, the cause of developmental dyslexia remains unknown. Structural neuroimaging studies have

Abbreviations: CF, climbing fiber; PN, Purkinje neurons; CN, cerebellar nuclear neurons; MF, mossy fiber; GC, granule cells; S, stellate cells; G, golgi cells.

* Corresponding author. Address: Department of Neurology, ZNA A.Z. Middelheim Lindendreef 1, B-2020 Antwerp, Belgium. Fax: +32 3 281 37 48.

E-mail address: peter.marien5@telenet.be (P. Mariën).

¹ These authors have equally contributed to the work presented.

focused on several morphological differences in dyslexic versus non-dyslexic children (Galaburda, Sherman, Rosen, Aboitz, & Geschwind, 1985; Galaburda et al., 2008). Structural anomalies of the planum temporale, the inferior frontal gyrus, the corpus callosum, the left temporal lobe and the insula have been proposed as possible explanations for developmental dyslexia (Eckert, 2004; Galaburda et al., 1985; Habib, 2000), but have not been univocally confirmed by studies on larger populations (Beaton, 1997; Robichon, Lévrier, Farnarier, & Habib, 2000; Silani et al., 2005).

Recently, neuroimaging studies with healthy subjects and studies of patients with isolated cerebellar lesions have provided evidence of a cerebellar involvement in reading (for a review see Vlachos, Papathanasiou, & Andreou, 2007). Senaha, Martin, Amaro, Campi, and Caramelli (2005), for instance, investigated the reading process in 13 healthy adults by means of fMRI with two silent reading task conditions (reading of real words and

non-words). Activation in the right cerebellar hemisphere was seen in both the word and nonword reading tasks suggesting cerebellar involvement in reading, phonological assembly and semantic processing. In addition, Moretti, Bava, Torre, Antonello, & Gazzato, 2002 showed that patients with cerebellar lesions made significantly more reading mistakes than a normal control group (Moretti et al., 2002). Based upon this growing body of evidence for a cerebellar involvement in language and cognition (Mariën, Engelborghs, Fabbro, & De Deyn, 2001 for a review; De Smet, Baillieux, Mariën, De Deyn, & Paquier, 2007), clinical and structural neuroimaging studies have underlined a possible involvement of the cerebellum in dyslexia (Eckert et al., 2003; Finch, Nicolson, & Fawcett, 2002; Nicolson, Fawcett, & Dean, 2001; Rae et al., 2002). In this regard, recent MRI studies demonstrated structural cerebellar anomalies in adult dyslexic brains (Brown et al., 2001; Rae et al., 2002). Rae et al. (2002) showed that a group of 11 men with a documented reading disorder did not have the cerebellar asymmetry (right grey matter bigger than left grey matter) that was found in a matched control group. In addition, the degree of cerebellar symmetry correlated with the severity of phonological difficulties in the dyslexic group (Rae et al., 2002). According to Eckert et al. (2003), cerebellar symmetry in dyslexic subjects can be explained by a decreased volume of the right anterior cerebellar lobe. Leonard et al. (2001) reported similar results. In addition, a study of Fawcett and Nicolson (1999) of 59 dyslexic children and 67 matched control subjects showed subtle cerebellar symptoms in the dyslexic group such as difficulties in motor skills, automatization, information processing speed and balance. Based on these findings, Nicolson et al. (1999), Nicolson, Fawcett, and Dean (1995) and Nicolson et al. (2001) introduced the “cerebellar deficit hypothesis”. According to this hypothesis, the automatization of learned skills such as articulation, reading, spelling and phonological abilities is disrupted as a result of a cerebellar dysfunction (Nicolson et al., 1999; Nicolson et al., 1995). A cerebellar deficit in young children might induce a delay in the automatization of articulation, causing deficits in phonological awareness. Therefore, the cerebellar impairment might result in a “phonological core deficit”, which provides an explanatory frame-work for various aspects of developmental dyslexia (Nicolson et al., 1999). Evidence to support this hypothesis was provided by a PET study in six dyslexic adults versus a matched control group of six subjects (Nicolson et al., 1999) who performed either an automatic prelearned sequence or a novel sequence of finger movements. In the group of the dyslexics, significantly lower brain activations were found in the right cerebellar cortex and the left cingulate gyrus when executing the prelearned sequence and in the right cerebellar cortex when learning the new sequence.

The aim of this study is to investigate possible cerebellar involvement in developmental dyslexia by means of a functional neuroimaging study with fMRI using a noun-verb association task. Semantic association tasks are widely used and are known to have a child-friendly character (Gaillard et al., 2000; Holland et al., 2001; Raichle et al., 1994; Seger, Desmond, Glover, & Gabrieli, 2000). In addition, several studies have shown that word generation tasks are especially suitable in arousing cerebellar activations (Frings et al., 2006; Jansen et al., 2005; Petersen, Fox, Posner, Mintun, & Raichle, 1988). By analyzing and comparing cerebellar activation patterns during semantic word generation in dyslexic children and matched controls, the cerebellar-deficit hypothesis will be tested. To the best of our knowledge, this is the first time that the cerebellar involvement in dyslexia is investigated by means of functional neuroimaging in a pediatric population using a language paradigm.

2. Methods

2.1. Participants

Fifteen dyslexic children and seven control subjects of 11 or 12 years participated in this study. Criteria for inclusion were: (1) right-handedness formally assessed by means of the Edinburgh Handedness Inventory (Oldfield, 1971), (2) monolingual native speakers of Dutch, (3) enrollment in normal education, (4) no neurological or psychiatric history, (5) absence of a motor or sensory handicap and (6) no associated learning disabilities or concentration disturbances as evidenced by formal neurocognitive investigations. For the control subjects, an additional inclusion criterion was added that consisted of absence of a familial history of learning disabilities. No psychopharmaceuticals were taken by any of the children. The study was conducted in accordance with the declaration of Helsinki and approved by the local Ethics Committee. Written consent of the parents of the participants was obtained. The dyslexic group consisted of 11 boys and 4 girls (mean age = 11.4 years; SD = 0.7). The control group consisted of 5 boys and 2 girls (mean age = 11.9 years; SD = 0.4). Statistical analysis by means of an independent sample *T*-test showed no significant difference in age between the two groups ($p = .188$).

2.2. Design

The study consisted of two parts. First, the children were investigated by means of a neurocognitive test battery containing measurements of general intelligence (Wechsler Intelligence Scale for Children-III, Wechsler, 2002), visuo-motor concentration (Bourdon-Vos Test, Vos, 1988) and praxis (Rey's figure, Osterrieth, 1944). Reading performance was evaluated by means of three different tests and compared to age-matched norms. All children were asked to read as many words as possible from a list during 1 min (Eén-minuut-test, EMT, Brus & Voeten, 1998), to read for 2 min as many non-words from a list (Van den Bos, Spelberg, Scheepstra, & de Vries, 1998) and to read a short story (Analyse van Individualiseringsvormen, AVI, Visser, van Laarhoven, & ter Beek, 1996). Writing was tested by means of dictation of 30 words and 6 sentences (Leerling-volg-systeem, LVS, Dudal, 1998). Results of the dyslexic group are summarized in Table 1. The same neuropsychological test battery was administered to the control group. Test results are summarized in Table 2.

A diagnosis of developmental dyslexia was based on the following criteria: (1) evidence for normal intelligence, (2) 1 min word-reading characterized by a score below decile 3, (3) general delay of technical reading skills of more than two educational years compared to normative data, (4) writing skills below percentile 25 (Pct. 25), (5) normal visuo-motor concentration and (6) normal praxis.

In the second phase of the study, an fMRI study was conducted using a noun-verb association task. This paradigm was adapted from Petersen et al. (1988), adjusted for fMRI by Benson et al. (1999), Benson et al. (1995) and translated and standardized for native speakers of Dutch (unpublished norms). A series of high frequency nouns were presented via head-phones. The subject was instructed to silently generate a semantically related verb (for example: BOAT-SAILING). The task was practiced with each child 30 min prior to the start of the scanning, using a series of nouns, presented with a 3 s interval, comparable to the actual fMRI paradigm. In order to avoid a learning effect, different nouns were used. During the practice seminar, the participants were first instructed to respond verbally to ten stimuli. After ten correct answers the subjects were instructed to respond silently to the stimuli. After

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