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Implicit learning deficits in dyslexic adults: An fMRI study

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It is assumed that several neuropsychological impairments characterize the cognitive profile of individuals with developmental dyslexia (DD). Phonological and visual processing are often impaired as well as auditory processing, attention, and information processing speed. Although reports in the literature on implicit learning abilities are contradictory, recent neurological and physiological data suggest that these abilities are deficient in individuals with DD.

To evaluate implicit learning we administered a classical version of the serial reaction time task (SRTT) related to sequence learning. Using functional magnetic resonance imaging we investigated brain activation patterns associated with implicit learning deficits in 14 adults with DD matched with 14 normal readers. SRTT results indicated the absence of implicit learning in the DD group and different activations between groups mainly in SMA, inferior parietal areas and cerebellar lobule 6.

These results can be interpreted in the light of the different capacities for the two groups to build an internal model to guide movements. Further, they explain DD individuals' difficulty in domains not directly related to reading ability.

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Introduction

Developmental dyslexia (DD) is defined as a specific reading disability resulting in unexpected, specific, and persistent low reading achievement despite conventional instruction, adequate intelligence and sociocultural opportunity (Shaywitz, 1998). The neuronal correlates of DD were extensively investigated in previous neuroanatomical and neuroimaging studies, and a brain

network critically involved in this developmental disorder was found. Particularly, cortical and subcortical brain regions, including frontal, temporal and parietal cortices, as well as insula and cerebellum seem to be significantly affected in individuals with DD, supporting the phonological processing deficit model of DD (Paulesu et al., 1996; Brunswick et al., 1999; Temple et al., 2001). Although this model describes the major aspects of DD, it cannot be generalized on the basis of deficits exhibited in other domains such as visual processing, rapid processing of sensory stimuli and skill automatization. Regarding visual processing functional neuroimaging studies demonstrate visual motion deficits in DD individuals linked to anomalous activation of the magnocellular pathway using low-luminance and low-contrast stimuli (Eden et al., 1996). These magnocellular dysfunctions may extend to other modalities, such as the auditory or tactile systems. For example, some studies showed that DD individuals fail to perceive short and rapidly varying sounds, thus demonstrating a specific impairment in rapid auditory processing (Tallal, 1980; Tallal et al., 1993; van Ingelghem et al., 2001).

Another domain of DD, which has been studied less than phonological processing and magnocellular pathway models, involves specific deficits related to skill automatization. In particular, some studies demonstrated that children with DD show significant impairments in automatization of gross and fine motor skills. While no deficits were found in single-task conditions, marked deficits became evident in dual-task conditions in which a new task was introduced to test the automaticity of the first one (Nicolson and Fawcett, 1990; Fawcett and Nicolson, 1992). Given these condition-specific features the automatization deficit is probably linked to alterations in cerebellar functions, as also suggested by Nicolson et al. (1999) study. In this study neuronal activity in the cerebellum was reduced in DD individuals both during acquisition of a new sequence and during execution of over-learned tasks.

Evidence from both clinical studies and animal models confirm the role of the cerebellum in acquisition and execution of a sequence. In particular, severe impairments in new sequence

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learning were found in patients with diffuse cortical cerebellar degeneration (Pascual-Leone et al., 1993) and focal cerebellar lesions (Molinari et al., 1997; Gomez-Beldarrain et al., 1998). These results were corroborated in animal studies. Specifically, Nixon and Passingham (2000) reported acquisition deficits in a sequence in monkeys with cerebellar nuclear lesions. Furthermore, it was demonstrated in rats that bilateral extensive lesions of the cerebellar dentate nucleus produce deficiencies in the acquisition of egocentric-based motor sequences (Gaytan-Tocaven and Olvera-Cortes, 2004).

Correct skill automatization may take place under entirely implicit conditions (Seidler et al., 2002) or may result from repetitive trial-and-error training, as also found in normal readers (Jenkins et al., 1994; Jueptner et al., 1997a,b). Both behavioral and neuroimaging methods have been used to study the latter condition resulting from repetitive trial-and-error training (Nicolson and Fawcett, 1990; Fawcett and Nicolson, 1992; Nicolson et al., 1999). Recent studies demonstrated implicit learning deficits in DD using the serial reaction time task (SRTT) initially developed by Nissen and Bullemer (1987). The SRTT results indicate a lack of sequential learning in DD subjects who display similar responses in randomized and sequenced blocks (Vicari et al., 2003, 2005; Howard et al., 2006).

Given this implicit learning impairment in DD subjects, the main objective of the present study was to explore neuronal activations during a classical version of the SRTT learning task in DD adults compared to normal readers.

Materials and methods

Subjects

Fourteen adults with developmental dyslexia (DD, mean age=42.1, range 34–55 years; 10 females and 4 males) and 14 normal readers (C, mean age=37.2, range 28–47 years; 10 females and 4 males) matched for chronological age and sex were selected for the present study. Participants' educational level was also similar in the two groups: 9 dyslexic and 7 controls had a secondary school diploma, and 5 dyslexic and 7 controls an university degree.

A clinical psychologist diagnosed the DD people according to standard exclusionary criteria defined by DSM IV (American Psychiatric Association, 1994). The C group reported no reading difficulties at any age. Reading abilities of the two groups were tested using word and non-word reading from “The Battery for Evaluating Dyslexia and Dysorthography” (Sartori et al., 1995). The DD group obtained significantly lower scores on word (both in terms of accuracy and speed) and non-word (only in terms of speed) reading tasks.

All subjects were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971) and had no history of neurological disorders.

Participants gave their written consent after the procedures had been fully explained. Approval was obtained from local ethics authorities for experiments involving humans.

Serial reaction time task

The task consisted of a reaction-timed keypress response following visual cues. The task started with the participant staring at four horizontally arranged empty boxes (3.3 cm) projected on a

white background. Each box corresponded to one of four keys placed on two separate optical fiber response units, one for each hand; the index and middle fingers of each hand controlled the keys. At fixed inter-trial intervals (ITI) of 1667 ms, one of the boxes turned red and the participants had to press the corresponding key as quickly and accurately as possible. As soon as the subject had pressed a key (regardless of accuracy) the box returned to the baseline color (colorless). Accordingly, the delay between two red colorings varied with the reaction time, and any anticipation of the stimulus onset could be prevented. The trials were presented in seven blocks (R1–R2), each consisting of 54 trials. During the first (R1) and seventh (R2) blocks the trials were presented in a pseudo-random order with the constraint that the same box could not be highlighted in two subsequent trials. In the remaining blocks (S1, S2, S3, S4 and S5) the trials were presented in a nine-element repeated sequence (position: 243413231) that recurred six times for a total of 54 trials. Each block was subdivided into two units (duration 69 s each), consisting of 27 trials (duration 45 s, with a mean trial rate of 0.6 Hz), followed by rest periods during which participants had to stare at the four empty boxes (duration 22 s). Two seconds prior to the onset of each new task unit all boxes turned blue for 1 s to inform the subjects of the start of a new block unit. The total duration of the experiment was 16.5 min.

Participants were not informed of the repetition of the nine-element sequence prior to scanning. After scanning they were asked whether the red box presentation was patterned or not to determine whether they had gained declarative knowledge of the repeated sequence. Next, the degree of declarative knowledge was scored (Rauch et al., 1997): the subjects were informed of the presence of a specific sequence and were invited to reproduce the sequence on the keyboard by making a series of twelve key presses. The final score was based on the longest consecutive string of correct responses, which was then compared with a chance (binomial) distribution. At most, four consecutive elements were correctly assessed; however, an individual score of five or more elements is needed to confirm significant explicit knowledge ($P < 0.05$). The individual scores, hence, confirmed a performance below the average guessing rate, indicating the absence of declarative knowledge of the sequence. At the group level, only few subjects (2 DD and 3 C individuals) made four correct consecutive assessments, which were too few to reach significance ($P = 0.14$). However, the behavioral performances of the subjects in each group who made four correct consecutive assessments completely fitted with the behavior of the entire group. The behavioral data were analyzed with Statistical (StatSoft, Inc., Tulsa, OK, 2001).

Apparatus

A Siemens Vision Magnetom MR system (Siemens Medical Systems, Erlangen, Germany) operating at 1.5 T and equipped with echo-planar imaging was employed to acquire fMRI. A circular polarized volume head coil was used for radio frequency transmission and reception. Positioning was performed so that each participant's head was centered approximately in the scanner bore, and head movement was minimized by mild restraint and cushioning. Visual stimuli were projected onto a screen, positioned on the head coil, using an LCD video projector (Model VPL-351QM, Sony Corp., Tokyo) located inside the MR room and connected to a portable PC (Fujitsu Siemens Computer Mobile,

Genuine Intel) located outside the MR room. Besides stimulus projection the PC controlled recording of keypress responses from the button control units (Fiber Optic Response Pad, Current Designs, Inc., Philadelphia, PA) via an in-house developed control program written in Visual Basic.

MRI acquisition

Each examination started with a localizer MRI, followed by two iterations of automatic 3D-field homogenization ('shimming') and the acquisition of functional and structural magnetic resonance images.

One run of functional data consisted of 289 BOLD sensitive echo-planar-image (EPI) volumes, consisting of 40 contiguous 3.0-mm-thick slices with an inter-slice gap of 0.6 mm. The echo time was 40 ms, repetition time 3.5 s, the matrix size 64 by 64 pixels, and the field-of-view was 192 mm. The first five BOLD images were discarded to remove any T1 saturation effects.

Following fMRI, a high-resolution structural T1-weighted scan was acquired in the sagittal plane using a 3D MPRAGE sequence with the following acquisition parameters: TR: 11.4 ms, inversion time: 300 ms, delay time: 20 ms, flip angle: 15°, FOV: 256 cm, matrix size: 256 × 224 matrix, 160 slices, yielding a 1-mm isotropic voxel size.

fMRI data analysis

SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) was used for fMRI preprocessing and statistical analysis within the generalized linear model (GLM) framework (Worsley et al., 1992; Friston et al., 1995). Each fMRI image was corrected for motion during scanning and coregistered to the first image, while the MPRAGE images were coregistered to the average EPI prior to spatial normalization into standard stereotaxic brain space, using the MNI (Montreal Neurological Institute) template of SPM2. After spatial normalization the fMRI images were spatially smoothed with an isotropic Gaussian kernel of 6.00 mm full-width half-maximum. Temporal filtering was performed by Expectation Maximization, assuming a first-order auto-regressive model plus white noise (Friston et al., 2002a,b). After pre-processing, a 1st-level GLM analysis was performed for each subject, modeling the seven blocks (R1–R2) separately. The contrast images probing brain activation related to each of the seven blocks were included in a second-level mixed effect analysis (ANOVA) across all subjects and blocks, correcting them for within group (DD and C groups) non-sphericity. For this GLM analysis, several contrasts were evaluated. First, the main effect of task versus baseline, collapsed across all seven blocks (R1–R2), was evaluated for each group separately, probing group-specific brain activation patterns related to the mean activity across the entire experiment. A statistical significance at the voxel level of $P \leq 0.0001$ (statistical T -value: 4.73) and at the cluster-level of $P < 0.05$, corrected for multiple comparisons, was used. The interaction effect assessing direct differences between the DD and C groups during the entire experiment ($C > DD$ and $DD > C$) was evaluated within a search volume given by the main effect of task. This included brain regions activated in both groups during the entire experiment (R1–R2) at a statistical threshold of $P < 0.05$, corrected for multiple comparisons by the family-wise error method. This search volume included all brain areas found in the main effect of task versus baseline when analyzing each group separately.

For the interaction effect voxels with a statistical T -value above 3.14 were selected, and areas of statistical significance (voxel level of $P \leq 0.001$, cluster level $P \leq 0.05$, corrected for multiple comparisons) were assessed within the search volume of the main effect of task.

Finally, two contrasts assessing direct differences between the DD and C groups during the first (S1–S2) and last (S4–S5) stages of the sequenced blocks were evaluated within the search volume of the main effect of task. For these contrasts voxels with a statistical T -value above 3.14 were selected, and areas of statistical significance (voxel level of $P \leq 0.001$, cluster-level $P \leq 0.05$, corrected for multiple comparisons) were assessed.

Localization and visualization of brain activations were made using SPM2 and the Montreal Neurological Institute (MNI) stereotaxic space, while the localization of cluster maxima was performed with reference to a standard brain atlas (Duvernoy, 1991) after conversion of the MNI coordinates into Talairach and Tournoux (1998) space.

Results

Behavioral measures

Average values for the median reaction times obtained by the two groups in the 7 blocks of the SRTT are shown in Fig. 1.

The presence of implicit learning was verified by analyzing the performances of both groups throughout the experiment (R1–R2). While the C group performance was modulated throughout blocks (R1–R2) (one-way ANOVA: $F(6,78)=3.1$, $P < 0.01$), the DD subjects' response pattern was not modulated by block presentation order (one-way ANOVA: $F(6,78)=1.1$, $P=0.4$).

A post hoc analysis (Tukey's HSD test) of C subjects' performance revealed a significant increment ($P < 0.05$) in reaction times (from 377.5 ± 72.6 ms to 417.6 ± 62.6 ms) between S5 and R2. This change between the last two blocks is usually considered the most reliable measure of visuo-motor sequence learning and it confirmed the presence of implicit learning presence in the C group. Conversely, in the DD group the

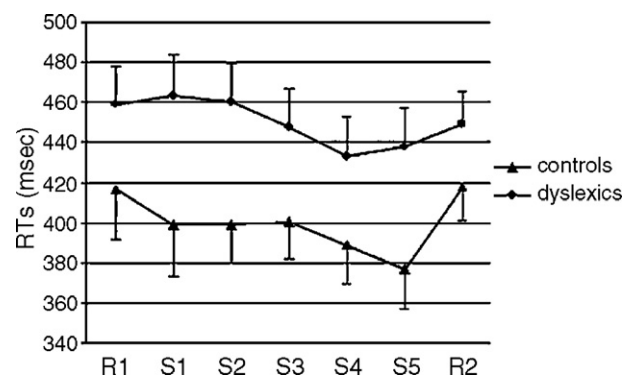


Fig. 1. Median reaction times obtained by fourteen developmental dyslexics and fourteen normal readers. The results reveal an implicit learning effect in the controls but not in the dyslexic group. In particular, in the control group reaction times increase, passing from S5 to R2, $P < 0.01$, while in the dyslexic group reaction times remain practically unvaried. In R1 and R2, when the trials are presented in a pseudorandom order, no significant group differences are found. Vertical bars show standard errors pertaining to each group.

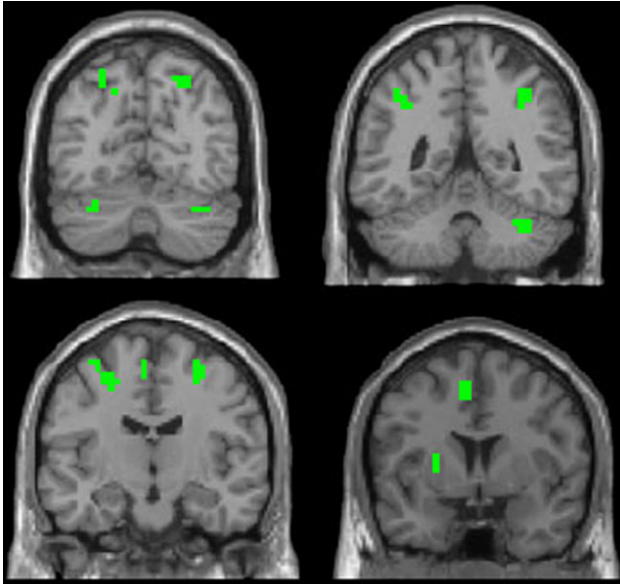


Fig. 2. Brain areas with significant average BOLD activations across the entire experiment (R1–R2) for the control group. In this group significant activations are found in brain areas generally associated with motor sequence learning: the bilateral premotor areas (BA6), the left Supplementary Motor Area (SMA), the bilateral superior (BA7) and inferior parietal lobules (BA40), the cerebellum (bilateral lobule 6), and the left putamen (cluster extent threshold: $P < 0.05$, corrected for multiple comparisons, voxel level: $P < 0.0001$).

reaction times between S5 and R2 remained almost unvaried ($P=1$), passing from 437.7 ± 74.5 ms to 448.6 ± 62.1 ms.

Furthermore, the two groups' performances during the entire experiment were compared by means of a 2×7 ANOVA for repeated measures with group as independent variable and block (R1–R2) as dependent variable. The group effect ($F(1,26)=3.9$, $P=0.05$) and the block effect ($F(6,156)=2.7$, $P=0.01$, $P=0.04$ after Huynh–Feldt correction and $P=0.05$ after Greenhouse–Geisser correction) were significant. The group-by-block interaction ($F(6,156)=0.8$, $P=0.6$) did not reach significance.

The implicit learning effect was also analyzed by comparing the performances of two groups by means of a 2×2 ANOVA for repeated measures, with group as independent variable and block (S5 and R2) as dependent variable. The block effect ($F(1,26)=19.8$, $P < 0.001$) and the group-by-block interaction ($F(1,26)=6.5$, $P < 0.05$) were significant, while the group effect ($F(1,26)=3.3$, $P=0.08$) did not reach significance. The post hoc analysis (Tukey's HSD test) confirmed the learning effect in the C group but not in the DD group. In particular, the reaction times between S5 and R2 increased significantly in the C ($P < 0.001$) but not in the DD group ($P=0.5$).

To determine whether the two groups' reaction times were similar at the beginning of the task a Student's t -test, with group as independent variable and block (R1) as dependent variable, was performed. Because the group specific average reaction times were quite similar (R1: C= 416.2 ± 70.1 , DD= 458.6 ± 91.3) no significant group effect ($t(32)=0.2$, $P=0.4$) was found. This finding allowed excluding motor, cognitive, or motivational differences between groups.

The number of errors and omissions in each group was also analyzed. A 2×7 ANOVA for repeated measures with group as

independent variable and mean of errors in the blocks (R1–R2) as dependent variable showed no effect of the group variable ($F(1,26)=0.6$, $P=0.4$) and no block effect ($F(6,156)=1.2$, $P=0.3$), with a similar number of errors on stimuli in the sequenced and in the random blocks. The group-by-block interaction was not significant either ($F(6,156)=0.8$, $P=0.6$). And, regarding the number of omissions neither the group effect ($F(1,26)=2.6$, $P=0.1$), the block effect ($F(6,156)=0.9$, $P=0.5$) nor the group-by-block interaction ($F(6,156)=1.0$, $P=0.4$) was significant.

fMRI results

The activation patterns in C participants and in DD individuals pertaining to the mean activity across the entire experiment (R1–R2) were analyzed in two separate contrasts, one for each group.

Table 1

Brain areas with significant group-specific activations during the entire experiment (R1–R2) for controls and developmental dyslexic individuals

Brain area	C		DD	
	Coordinates	Statistical values	Coordinates	Statistical values
<i>Cerebellum</i>				
Right	36 -52 -24	$z=6.11$	28 -55 -17	$z=7.29$
	Lobule 6	$p < 0.001$	Lobule 6	$p < 0.001$
			24 -57 -44	$z=5.04$
			Lobule 8	$p < 0.01$
Left	-28 -63 -17	$z=5.34$	-36 -55 -21	$z=5.92$
	Lobule 6	$p < 0.001$	Lobule 6	$p < 0.001$
<i>Basal ganglia</i>				
Left	-24 4 7	$z=4.69$		
	Putamen	$p < 0.05$		
<i>SMA</i>				
Left	-4 -1 52	$z=6.47$		
	BA6	$p < 0.001$		
<i>Premotor area</i>				
Right	28 -9 56	$z=5.18$	40 -20 60	$z=6.02$
	BA6	$p < 0.001$	BA6	$p < 0.001$
Left	-24 -9 48	$z=4.76$	-36 -9 59	$z=4.59$
	BA6	$p < 0.001$	BA6	$p < 0.01$
<i>Superior parietal</i>				
Right	28 -64 47	$z=4.40$		
	BA7	$p < 0.01$		
Left	-16 -68 48	$z=5.22$	-16 -63 58	$z=4.41$
	BA7	$p < 0.001$	BA7	$p < 0.05$
<i>Inferior parietal</i>				
Right	36 -44 43	$z=4.78$	48 -29 42	$z=5.24$
	BA40	$p < 0.001$	BA40	$p < 0.001$
Left	-44 -33 42	$z=5.23$	-44 -40 57	$z=5.73$
	BA40	$p < 0.001$	BA40	$p < 0.001$
	-36 -45 39	$z=4.21$		
	BA40	$p < 0.05$		

In this and the following tables, for each region, the involved anatomical areas are given, as well as the Brodmann areas (Duvernoy, 1991; Tzourio-Mazoyer et al., 2002), the Talairach coordinates (Talairach and Tournoux, 1988) for voxels representing local maxima of activation, as indicated by the maximum z -value and statistical cluster-level significance.

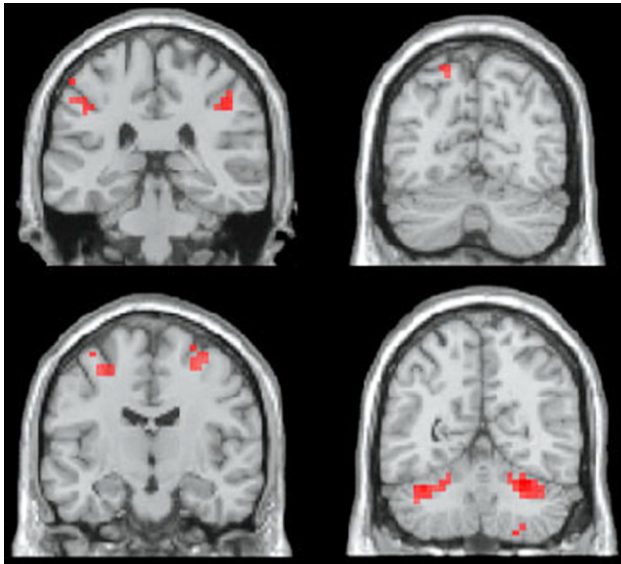


Fig. 3. Brain areas with significant average BOLD activations across the entire experiment (R1–R2) for the developmental dyslexic group. This group activated the bilateral premotor areas (BA6), the cerebellum (bilateral lobule 6 and right lobule 8), the bilateral inferior (BA40) and left superior (BA7) parietal lobules (cluster extent threshold: $P < 0.05$, corrected for multiple comparisons, voxel level: $P < 0.0001$).

In the C group significant activations were found in the bilateral premotor areas (BA6), the left Supplementary Motor Area (SMA), the bilateral superior (BA7) and inferior parietal lobules (BA40), the cerebellum (bilateral lobule 6) and the left putamen (Fig. 2, Table 1). In the DD group significant activations were found in the bilateral premotor areas (BA6), the cerebellum (bilateral lobule 6 and right lobule 8) and the bilateral inferior (BA40) and left superior (BA7) parietal lobules (Fig. 3, Table 1).

As shown in Table 1 most brain areas were activated in both groups, while C only exhibited significant activations located in the left SMA and the left putamen.

A direct comparison between the DD and C groups throughout the entire experiment (R1–R2) was performed within a search

Table 2

Brain areas with significant group differences between controls and developmental dyslexic individuals during the entire experiment (R1–R2)

Brain area	C > DD	DD > C	
		Coordinates	Statistical values
<i>Cerebellum</i>			
Right		32 – 55 – 17	$z = 4.24$
		Lobule 6	$p < 0.05$
<i>Premotor area</i>			
Right		40 – 20 60	$z = 4.12$
		BA6	$p = 0.06$
<i>Inferior parietal</i>			
Right		48 – 29 38	$z = 3.29$
		BA7	$p < 0.05$
Left		– 44 – 36 57	$z = 3.86$
		BA40	$p < 0.05$

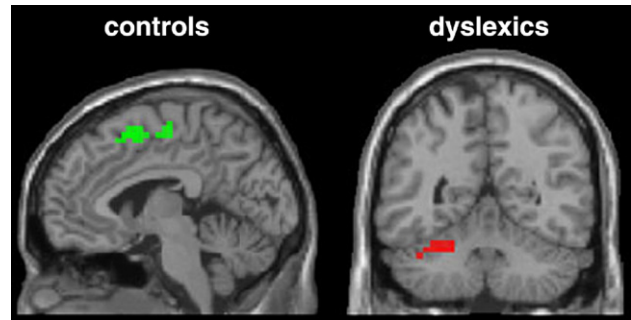


Fig. 4. Brain areas with significant BOLD differences between groups during the first (S1–S2) and the final stages (S4–S5) of the sequenced blocks. During the first stages of the sequenced blocks only the control group (green) evidences higher activations (S1–S2: C > DD) in the left SMA, while during the final stages of the sequenced blocks only developmental dyslexic subjects (red) exhibit significantly higher brain activations (S4–S5: DD > C) in the bilateral cerebellar lobule 6 and in the bilateral inferior parietal lobules (voxel level of $P \leq 0.001$, cluster level $P \leq 0.05$, corrected for multiple comparisons within the search volume of the main effect of task).

volume consisting of brain regions identified by the main effect of task and included all brain areas found in the group-specific analysis. While no significantly higher activations were found in the C subjects (R1–R2: C > DD), DD subjects (R1–R2: DD > C) showed increased BOLD activity in the right cerebellar lobule 6, in the bilateral inferior parietal lobules and a trend towards significant activation ($P = 0.06$) of the right premotor area (Table 2).

Furthermore, the contrast assessing direct differences between the DD and C groups during the first stages of the sequenced blocks (S1–S2) revealed higher activations (S1–S2: C > DD) in the

Table 3

Brain areas with significant group differences between control and developmental dyslexics individuals during the first (S1–S2) and the final stages (S4–S5) of the sequenced blocks

Brain area	S1–S2: C > DD		S4–S5: DD > C	
	Coordinates	Statistical values	Coordinates	Statistical values
<i>Cerebellum</i>				
Right			32 – 55 – 17	$z = 3.32$
			Lobule 6	$p = 0.06$
Left			– 28 – 52 – 21	$z = 3.82$
			Lobule 6	$p < 0.05$
			– 36 – 52 – 21	$z = 3.26$
			Lobule 6	$p < 0.05$
			– 32 – 48 – 25	$z = 3.11$
			Lobule 6	$p < 0.06$
<i>SMA</i>				
Left	– 4 6 48	$z = 3.25$		
	BA6	$p < 0.05$		
	– 4 – 5 52	$z = 3.15$		
	BA6	$p = 0.06$		
<i>Inferior parietal</i>				
Right			48 – 29 42	$z = 3.68$
			BA40	$p = 0.06$
Left			– 44 – 36 57	$z = 3.15$
			BA40	$p = 0.06$

left SMA in C group (Fig. 4, Table 3), while no significantly higher activations were found in DD subjects (S1–S2: DD>C).

The contrast assessing possible direct differences between DD and C groups during the final stages of the sequenced blocks (S4–S5) yielded results similar to the interaction effect across all seven blocks (R1–R2: DD>C) for the DD group. In particular, the DD subjects (S4–S5: DD>C), but not the C subjects (S4–S5: C>DD), exhibited significantly higher brain activations in the bilateral cerebellar lobule 6 and in the bilateral inferior parietal lobules (Fig. 4, Table 3).

Discussion

The present findings document the absence of implicit sequence learning in DD adults, thus confirming previous behavioral findings obtained in children and young people affected by DD (Vicari et al., 2003, 2005; Howard et al., 2006). In particular, the contrast between the last sequenced block (S5) and the last random block (R2) confirmed the impairment of implicit sequence learning in the DD group. While C subjects showed marked implicit learning that modulated their responses in relation to the kind of block (sequenced or random), no effect was evident for DD subjects.

By analyzing the brain activation patterns of normal readers during the entire experiment (R1–R2) significant activations were found in the bilateral premotor regions, Supplementary Motor Area (SMA), bilateral superior and inferior parietal lobules, left putamen and bilateral lobule 6 of the cerebellum (Fig. 2, Table 1).

The activations found in this group fit with those previously described in other studies (for a detailed discussion see Desmond and Fiez, 1998). Namely, activation of the premotor cortex may be related to its involvement in motor execution (Jenkins et al., 1994; Willingham, 1998; Willingham et al., 2002; Gomez-Beldarrain et al., 2002), in the generation of discrete finger movements (Rao et al., 1993; Larsson et al., 1996), in visuo-motor learning (Grafton et al., 1994; Kawashima et al., 1994) and in implicit sequence learning (Jenkins et al., 1994; Grafton et al., 1995). These data confirmed the findings of previous lesion studies in nonhuman primates indicating involvement of the premotor cortex in integration of visual information with motor commands (Halsband and Passingham, 1985).

During implicit sequence learning a progressive transition from externally guided movements, involving premotor areas, to internally generated movements, controlled by SMA, was described (Hazeltine et al., 1997). Therefore, the SMA activation observed in our control group could be related to representation of the sequences at an abstract level and without reference to the environment and, thus, to construction of an internal model of sequences to drive movement (Hazeltine et al., 1997; Grafton et al., 1998).

Since the SRTT is a motor task that requires learning a sequence of spatial response locations rather than a mere sequence of movements (Willingham et al., 2000), the activations of posterior parietal areas can be interpreted in terms of spatial attention, as documented by lesion, electrophysiological, and functional neuroimaging studies (Robinson et al., 1978; Corbetta et al., 1993; Corbetta, 1998). Along the same lines, Hazeltine and Ivry (2002) more recently advanced that this kind of sequential learning involves the formation of associations among series of

spatial locations, each presented and responded to as a chain of discrete events.

Just the presence of chains of sequential events in the SRTT calls into action the basal ganglia, which are intimately connected to the cortical areas involved in the performance of sequential motor behavior (Takada et al., 1998). Stimulus properties and attentional constraints were reported to influence activation of the basal ganglia during SRTT (Hazeltine et al., 1997). Experimental, clinical and neuroimaging studies evidenced their role in learning and executing sequential movements, suggesting active involvement of the putamen during pre-learned sequence performance (Berridge and Whishaw, 1992; Cromwell and Berridge, 1996; Miyachi et al., 1997; Jueptner and Weiller, 1998; Matsumoto et al., 1999; Tanji, 2001). Therefore, the activation of the putamen, observed in the present control group, is not surprising.

The cerebellum also has a well-known function in implicit learning (Rauch et al., 1995; Molinari et al., 1997; Jueptner et al., 1997b; Gomez-Beldarrain et al., 1998; Exner et al., 2002; Torriero et al., 2004). It is believed that the cerebellar contribution to the SRTT is linked to its ability to establish associations between a series of spatial locations and the corresponding motor responses (Exner et al., 2002). Note that during SRTT, as in other progressively learned motor responses, cerebellar activity gradually declines as the difference between expected and actual responses decreases (Hazeltine et al., 1997). Lesion studies in primates (Nixon and Passingham, 2001) also showed that following bilateral cerebellar lesions monkeys failed to show reaction-time gains in response to predictable visual stimuli, thus supporting the hypothesis that the cerebellar function in motor learning is to prepare responses to predictable sensory events. However, it is important to underline that in cats the inferior olive neurons fire in response to unexpected unpredictable stimuli, thus supporting a cerebellar function of “new event detector” (Oscarsson, 1980; Simpson et al., 1996). Interestingly, the cerebellar activations were specifically concentrated in lobule 6, a neo-cerebellar region with a documented role in implicit learning. For instance, in a meta-analysis Desmond and Fiez (1998) summarized several neuroimaging studies that confirmed the role of lobule 6 for sequence learning, probed by SRTT. Likewise, circumscribed lesions of lobule 6 and cerebellar nuclei confirmed its crucial role in motor learning of conditioned responses (Yeo and Hardiman, 1992).

By analyzing the brain activation patterns of DD subjects during the entire experiment (R1–R2) significant activations were found in the bilateral premotor regions, the bilateral inferior and left superior parietal lobules, bilateral lobule 6 and right lobule 8 of the cerebellum (Fig. 3, Table 1). Note that no activation was found in the SMA and putamen, at odds with the results obtained in the C group.

A direct comparison between groups revealed no significantly higher activations in C subjects (R1–R2: C>DD) in the entire experiment (Table 2). However, during the initial stages of the sequenced blocks (S1–S2) significantly higher activation in the left SMA was found in the C group (Fig. 4, Table 3).

The direct comparison between groups revealed significantly higher brain activations in the DD subjects (R1–R2: DD>C) in the right cerebellar lobule 6, the bilateral inferior parietal lobules and a trend toward significance in the right premotor area throughout the entire experiment (Table 2). Note that a similar activation pattern was maintained even in the final stages of the sequenced blocks (S4–S5: DD>C) (Fig. 4, Table 3).

Taken together these findings demonstrate different activations and with different times between groups mainly in the SMA, inferior parietal areas and cerebellar lobule 6, and can be interpreted in light of the different capacities of the two groups to build an internal model to guide movements. In particular, the early higher activation in the SMA of the normal readers' group could be associated with the construction of an internal model of the repeated sequence (Grafton et al., 1998). Accordingly, a number of PET studies reported early increased activation in the SMA during the initial acquisition of implicit motor skills (Grafton et al., 1992, 1994, 1995; Hazeltine et al., 1997). Interestingly, during the entire experiment, and especially in the final stages of the sequenced blocks when the response becomes automatized and there is less need for external visual cues to drive movements (Jenkins et al., 1994; Hazeltine et al., 1997; Grafton et al., 1998), the parietal cortices are less activated in the C group. Conversely, in the DD group the lack of activation in the SMA associated with higher parietal activations could be related to their difficulty in building the internal model and to the long-lasting need to anchor execution of the motor sequence to external visuo-spatial stimuli.

The DD subjects' difficulty in learning the task implicitly was also evidenced by their high, sustained cerebellar activation, especially during the final stages of the sequenced blocks.

As reported above, in controls functional neuroimaging studies showed activations during earlier phases of sequential learning and progressive reductions during later phases in several foci of the cerebellar cortex (Jenkins et al., 1994; Hazeltine et al., 1997; Jueptner et al., 1997a,b). Namely, as learning proceeds and error signal arising from the comparison between expected and actual movements decreases, the cerebellar engagement progressively diminishes. Animal models confirmed cerebellar involvement in the acquisition of a new procedure, mainly during the first stages. When a task was learned before the cerebellar lesion the animals maintained the pre-lesion acquired procedures, thus demonstrating the central role of the cerebellum in acquiring, but not in preserving, the learned procedural competencies (Dahhaoui et al., 1992; Leggio et al., 1999). The opposite pattern of cerebellar activation in the DD group seems to indicate their difficulty in building an internal model to guide sequential movements (Seitz et al., 1994; Imamizu et al., 2000; Tracy et al., 2001). Recently, it was proposed that both the cerebellum and the parietal cortex play a role in sensori-motor prediction (Blakemore and Sirigu, 2003). In particular, these structures seem involved in the detection of and adaptation to mismatches between expected and actual movements, particularly when visual feedback is relevant (Sirigu et al., 1999). The parietal cortex receives input from the cerebellum via the thalamus, and there are opposite connections via the pons. The two regions likely work in parallel to predict the sensory consequences of movement and to monitor and correct it, thus allowing learning to occur.

The involvement of the cerebellar structures in DD was described in some recent studies. Namely, Rae et al. (1998, 2002) documented reduced volume of right cerebellar gray matter in DD adults. Other authors have also found reduced cerebellar regions in both adults and children with DD, namely, in the right anterior lobe (Leonard et al., 2002; Eckert et al., 2003) and bilaterally in the posterior lobes (Brown et al., 2001; Eckert et al., 2003). In a pioneering neuroimaging study Nicolson et al. (1999) reported higher cerebellar activation in normal readers compared to DD subjects who behaviorally displayed a lack of “automatization” when they tried

to learn a sequence by trial and error. At first glance our results showing a higher cerebellar activation in DD subjects do not seem to fit with their neuroimaging data. However, it has to be taken into account that in Nicolson's study only the performances recorded in the last phases of an over-learned sequence may be considered “implicit” and are comparable to our frankly implicit task. In any case, note also that in Nicolson's study the cerebellar activity of DD subjects did not significantly decrease when the cerebellar activations recorded in the early task stages were compared to those of the late stages. This finding, although overlooked by the authors, is consistent with the present results indicating higher cerebellar activation during the entire implicit task.

In normal readers once the sequence is acquired the cerebellar mechanisms become less active and other subcortical structures are recruited, as if two distinct cerebral systems were involved in implicit learning (Doyon et al., 2002, 2003). These systems include a cerebello-cortical network mainly involved in the early phases of sequence learning and a striato-cortical network recruited in later stages and essential for long-term skill retention. The role of the basal ganglia in the later stages of learning is evidenced by several clinical and experimental studies. While the putamen is activated in over-learned sequences, the caudate nucleus seems to be involved in the initial phases of the learning process (Jueptner et al., 1997a, b; Miyachi et al., 2002). Consistently, the putamen activation found in our normal readers may have been the neural correlate of sequence consolidation since it is active once the learned sequence has been stored. However, further observations are needed to support this interpretation since putamen activation was not confirmed by the direct comparison of the two groups.

In conclusion, the present fMRI findings show a neural correlate for the absence of implicit learning in the DD group mainly characterized by higher activation of the cerebellum and parietal cortex areas, especially in the final stages of the experiment. The implicit learning deficit associated with this altered activation pattern in DD subjects may have a role in determining some of the symptoms of developmental dyslexia. In particular, the atypical cerebellar activation pattern could explain the difficulties encountered by this population in other domains, even those not directly linked to phonological processing, such as visual and rapid stimuli processing.

Reading is a complex cognitive activity that involves functions arising from different networks of brain structures. To achieve reading fluency, the skill must be automatized. The cerebellum appears to have all the potentialities to facilitate the numerous and coordinated operations involved in proficient reading.

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