Structural correlates of implicit memory learning deficits in developmental dyslexia

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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 a conventional instruction, adequate intelligence and socio-cultural opportunity (1). From an epidemiological point of view, there are reported both sporadic and familial cases of DD (2), with an increasing evidence that such a disorder might be regarded as a genetic syndrome (3). Voxel-based morphometry (VBM) is a spatially-specific and unbiased method of analysis of MR images reflecting the regional grey (GM) and white matter (WM) volume at a voxel scale (4). Such a technique uses an operator independent approach and provides quantitative information reflecting regional brain abnormalities. Previous VBM studies have already successfully applied VBM to subjects with DD, to selectively test the *a priori* hypothesis that regards DD as an isolated phonological deficit (5, 6, 7). However, there is an increasing evidence that DD is not only associated to an isolated phonological deficit but presents with additional abnormalities, thus resulting in a multi-domain impairment. To our knowledge, no previous VBM studies have directly investigated cortical and sub-cortical structures underlying more general cognitive functions, i.e. implicit memory learning. A specific support to the hypothesis that DD may be regarded as a deficit of implicit memory learning comes from a recent fMRI study (8). Subjects with DD compared to normal readers (NR) have shown an abnormal pattern of activation in areas related to implicit learning memory, when performing a task related to sequence learning. Aim of the present study was to investigate whether any structural abnormality in regions involved in implicit memory learning might be responsible for the deficits occurring to subjects with DD.

METHODS Ten individuals with DD and 10 NR, all right handed, were recruited for the present study (see TABLE 1). Brain MRI scans were performed at 1.5T (Siemens, Magnetom Vision, Erlangen, Germany). In a single session, a 3D T1-weighted turbo-flash magnetization-prepared rapid-acquisition gradient echo (MPRAGE) (TR/TE=11.4/4.4 ms, TI=20ms, flip angle=15°) sequence was obtained from all subjects. The MPRAGE sequence was acquired in a single slab, with a sagittal orientation, a 256×224 matrix size over a 256x256 mm^2 field of view, with an effective slice thickness of 1 mm. The MPRAGE images were then processed using SPM 2 (Wellcome Dept. Cogn. Neurol., London; http://www.fil.ion.ucl.ac.uk/spm). To optimize brain extraction and tissue segmentation, these images underwent an iterative procedure, according to the optimized VBM approach (4). The signal intensity in every voxel of GM, WM and cerebro-spinal fluid (CSF) maps represents the probability of belonging to a given class of tissue and reflects the regional density of such a tissue. Statistical analysis of the regional GM and WM density was performed after smoothing the normalised images with a 12 mm^3 FWHM Gaussian kernel. We addressed the analysis, using SVC, to those specific brain regions involved in implicit learning memory (8): supplementary and premotor cortices, parietal lobes, basal ganglia, cerebellum and its deep nuclei. An ANCOVA model (GM or WM volumes were entered as nuisance covariate) for GM and WM respectively, was used to compare regional differences in GM and WM density between subjects with DD and NR (with a critical threshold of $p \leq 0.005$ at the voxel level and $p \leq 0.05$ at the cluster level, corrected for multiple comparisons).

RESULTS NR compared to subjects with DD, showed an increase of GM density in the right posterior-superior parietal lobule, precuneus and supplementary motor area (SMA), and in the right dentate and interposed cerebellar nuclei (see FIGURE 1). The opposite contrast did not reveal any significant difference.

DISCUSSION. The regional GM abnormalities that we observed in subjects with DD fit well with those generally described in previous implicit sequence learning studies (10). These abnormalities might affect the reading processes and, at least partially, explain some of the reading deficits observed in subjects with DD. Moreover, a dysfunction of the neural network that sub-serves the implicit memory learning seems to be a putative candidate to account for multiple deficits that have been described in the DD syndrome. Our results highlight the importance to consider DD as a heterogeneous condition and an expression of multiple causes.

Sex (F/M)	9/1	9/1
Mean age (SD) [range] years	40.7 (6.7) [34-51]	40.8 (7.0) [32-53]
Median education level (range) years	17 (13-17)	17 (13-17)

TABLE 1. Demographic data for subjects with dyslexia and normal readers

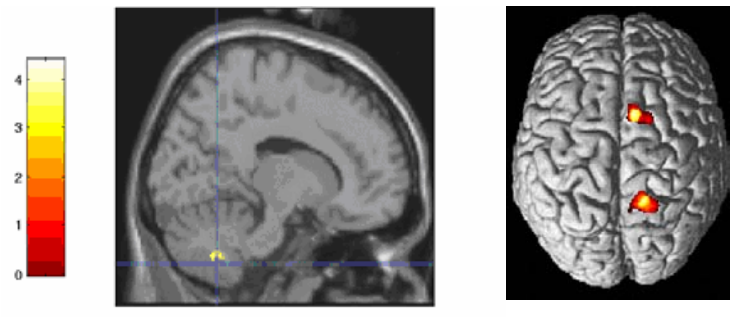

FIGURE 1. Brain areas with significant reductions of GM density in subjects with developmental dyslexia compared to normal readers: right posterior-superior parietal lobule, precuneus and supplementary motor area (SMA), and right dentate and interposed cerebellar nuclei.

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