

# Altered structural architecture of the striatum is associated with impaired motor learning in Multiple Sclerosis

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**Introduction.** The behavioural evidence for altered motor skill learning in Multiple Sclerosis (MS)<sup>1</sup> suggests that MS pathology may impair mechanisms of adaptive plasticity required for learning and recovery. The striatum is a deep grey matter structure known to be functionally relevant for both higher motor control and learning<sup>2</sup>. The evidence for localized MS-related pathology within the striatum<sup>3</sup> along with disease-related disruption of its connections with the neocortex suggests a role of the striatum in impairing motor learning in MS. Here we tested the hypothesis that impaired learning performance in MS was associated with localized changes in the striatal structural architecture, either explained by localized grey matter pathology or damage to surrounding white matter. We also assessed the functional consequences of these behaviourally relevant structural changes.

**Methods.** 23 MS patients and 12 controls learned a repeating sequence of right hand movements during 15 days of practice of a visuomotor tracking task. In each subject, learning was quantified by the mean tracking error across days of practice, which represented individual learning performance and was used for testing imaging correlations. Learning data were tested for outlier detection and no outlier was found. Shape analysis on T1 weighted images using FIRST vertex analysis from FSL assessed localized between-group differences in the structural architecture of the striatum as well as brain-behaviour correlations, corrected for multiple comparisons and controlling for differences in brain volume. Vertex analysis output displayed 3D structures with surface vectors indicating the direction of change. Subjects underwent a baseline fMRI scan during the first exposure to the learning task and a second fMRI scan at the end of the training period. Group level fMRI analysis identified between-session task-related BOLD-signal changes associated with individual measures of learning performance ( $z > 2.3$ ,  $p < 0.05$  corrected for multiple comparisons).

**Results.** In patients, variations in mean learning performance significantly correlated with variations in the structural architecture of the right caudate and bilateral putamen (blue areas in **Fig.1**). The direction of this change indicates a thinning of the medial surface of the caudate, while the lateral surface shows an enlargement of grey matter tissue. In the putamen, the vectors pointed inwards, reflecting thinning of the structure in association with worse learning performance (blue arrows in **Fig.1**). In controls, similar brain-behaviour correlations were found in analogous regions of the right putamen only (blue areas in **Fig.2**). Functional results showed a significant between-group difference in the association between learning performance and signal change in dorsal parietal regions. Specifically, while in controls better learning performance was associated with higher signal changes in parietal regions (**Fig.3**), patients showed no significant relationship, resulting in a significant difference between the groups.

Figure 1

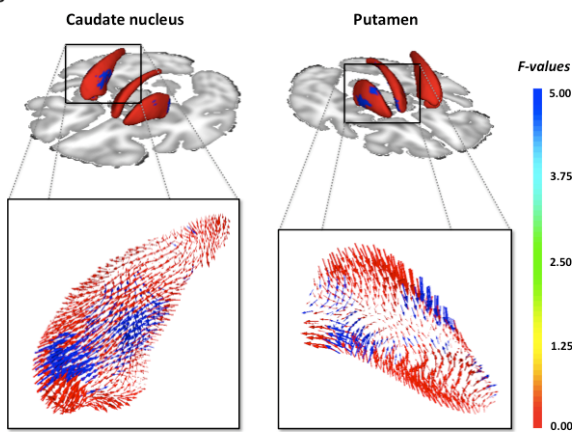
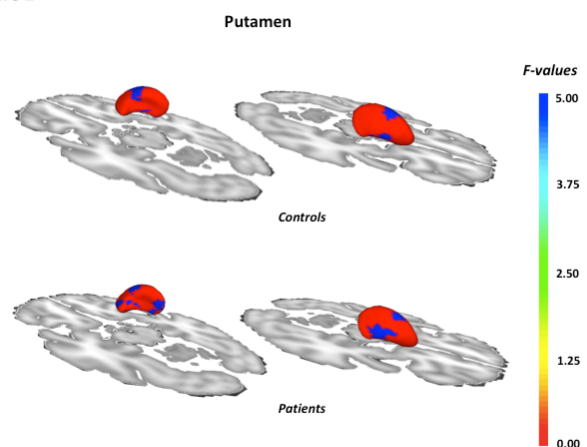
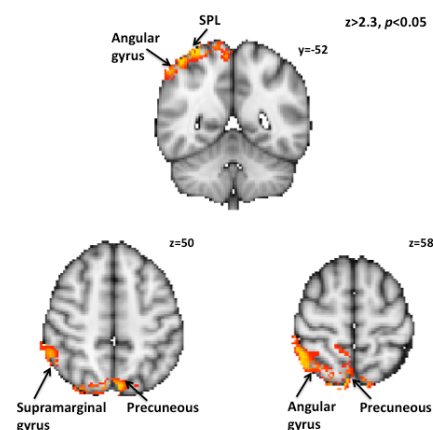


Figure 2



**Discussion.** Individual learning performance co-varied with localized bilateral changes in striatal structural architecture over and above the global effect of brain atrophy in patients. Similar, less marked co-variation also was found in controls. This correlation suggests the importance of the structural integrity of this region for learning performance in patients. Results from vertex analysis also suggest that both localized deep grey and white matter changes may contribute to these correlations. Further investigations are required to clarify the contribution of white vs. grey matter damage to localized changes in striatal shape, as well as the effect of MS pathology on these changes. Functional results showed that better learners had higher activation of dorsal parietal regions implicated in retrieval of learned visuomotor representations<sup>4</sup>. These regions, anatomically connected with dorsal striatal areas in primates<sup>5</sup>, are relevant for normal motor learning<sup>6</sup>. Functional differences in learning performance between patients and controls in parietal regions suggest that local structural damage may propagate functionally throughout the striatal-cortical network. In conclusion, these results highlight the importance of the striatum for normal motor learning and provide novel evidence for specific behavioral consequences of subcortical dysfunction in MS.

Figure 3



**References.** 1 Tomassini V et al., ECTRIMS 2009; 2 Lehericy S et al., PNAS 2005; 3 Henry RG et al., JNNP 2008; 4 Sakai K et al., J Neurosci 1998; 5 Yeterian EH et al., J Comp Neurol 1993; 6 Yin HH et al., Nat Neurosci 2009