Impact of cerebellar atrophy on cortical grey matter and cerebellar peduncles as assessed by voxel based morphometry and diffusion imaging

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Introduction

The cerebellum is involved in a number of low level and high level functions mediated through the cerebellar peduncles white matter (WM). Both the medial (MCP) and the superior cerebellar peduncle (SCP) have connexions with the cerebral cortex, the former mostly including afferent fibers to the cerebellar cortex, and the latter projecting efferent fibers to both the thalamus and the red nucleus [1]. Atrophy of the cerebellar cortex is known to produce a range of different symptoms, especially motor deficits, although no macroscopic WM changes are usually detected by conventional MRI modalities. The aim of this study was to evaluate the impact of cerebellar atrophy on both cerebral GM atrophy and WM microstructure of the MCP and SCP fiber bundles, by using conventional T1 contrast MRI and diffusion MRI (dMRI) respectively. dMRI was also used to investigate the relationship between WM integrity and motor functions as evaluated by clinical scores.

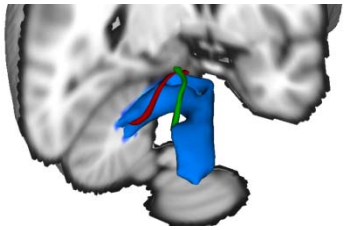

Figure 1: Average tracts of the MCP (blue), left SCP (green) and right SCP (red) with voxels belonging to at least 50% of the subjects. Note th decussation of the SCP bundles which could be reconstructed with the tractography method used.

Methods

Subjects: 30 normal controls (NC) [F/M=23/7; mean age ±SD =54.4±5.5 y] and 7 cerebellar atrophy patients (ATR) [2 with spinocerebellar ataxia type 2, 1 with Friedreich's ataxia and 4 with undetermined etiology, F/M=4/3; mean age ±SD =49.8±7.9 y]
DTI data acquisition: dMRI data were obtained along 61 non-collinear directions, with b values of 0 and 1000 s.mm^{-2} on a 3 T Siemens Allegra scanner resulting in 45 contiguous slices volumes with a 2.3 mm isotropic reconstructed voxel size.
DTI processing: fractional anisotropy (FA) and radial diffusivity (RD) were computed from the diffusion tensor (DT) fitted with weighted linear least-square (with Camino [2]) after preprocessing steps correcting for head movements and eddy currents based on non-linear registration to a T2 weighted volume with FSL [3].
Tractography: The MCP and SCP were reconstructed with multi-fiber probabilistic tractography carried out using 10000 iterations of the PICo algorithm [4] applied to fiber orientation distribution functions estimated with QBall and PAS (used for MCP and SCP respectively). The tracts were transformed to MNI space and only voxels belonging to at least 50% of subjects were kept for further analysis (Fig. 1).
GM analysis: voxel based morphometry (VBM) was applied to segmented GM maps warped to MNI space (with SPM 8) for NC and ATR patients entered as two independent groups. Age and gender were set as nuisance variables and T-contrasts evaluated with family-wise error (FWE) corrections with significance level chosen for $p < 0.05$.
WM analysis: The same analysis as above was applied to dMRI RD maps restricted to the voxels of the MCP and SCP belonging to the template shown in Fig 1.
GM and WM relationship: voxelwise post-hoc correlation was performed between the mean cerebellum GM density and the RD values of each voxel in the MCP and SCP.
WM and clinical scores: Total ataxia scores and each subtest score (posture, coordination, speech, oculomotor) were evaluated for correlation with the mean FA of the MCP and SCP, using a one-tailed Pearson product-moment correlation test.

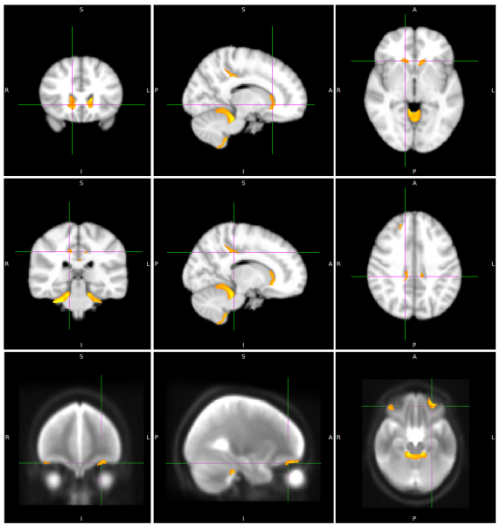

Figure 2: significant differences in GM density between ATR and NC subjects was found in the caudate nucleus (top), cingulate gyrus (middle) and orbito-frontal cortex (bottom) (FWE $p < 0.05$)

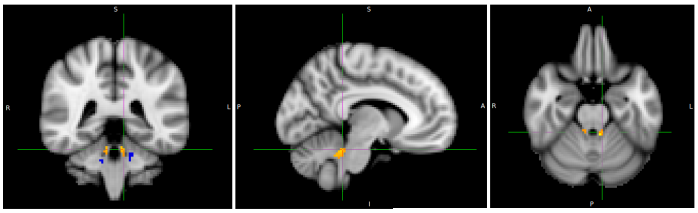

Figure 3: voxels with significant differences in RD between NC and ATR subjects in MCP (blue) and SCP (orange). Significant correlation between RD and cerebellum mean GM density were found in most of these voxels.

Results

GM analysis: In addition of the cerebellum, significant atrophy, in ATR patients compared to NC, was found in three main bilateral areas: in the head of the caudate nucleus, in the cingulate gyrus and in the orbitofrontal cortex (Fig 2)
WM analysis: A significant [ATR > NC] contrast was found for RD in both bilateral clusters in the MCP (Fig 3, blue) and larger ones in the SCP (Fig 3, orange).
GM and WM relationship: the voxelwise correlation analysis between voxels of the MCP and SCP and the GM mean density of the cerebellum showed a significant correlation for most of the voxels found from the RD contrast.
WM and clinical scores: mean FA of MCP was found to be significantly correlated to patients' total ataxia score [R=-0.7, p=0.03] (Fig 4), and when examining subtest scores, to coordination [R=-0.74 , p=0.03] and oculomotor [R=-0.70, p=0.04] scores. In contrast, speech [R=-0.60, p=0.08] and posture [R=-0.54 , p=0.10] scores correlation did not reach significance level. No significant correlation was found between ataxia and mean FA of the SCP.

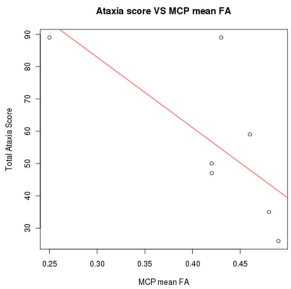

Figure 4: linear regression of total ataxia score to mean FA measured in the MCP

Discussion and conclusion

This study demonstrates that GM cerebellar atrophy is associated to a significant reduction of local GM volumes in several brain structures including the caudate nucleus, known to be implicated with the cerebellum in initiation of voluntary movements, the cingulate gyrus, known to have connexions with the pontine nuclei and to support initiation and goal-directed behaviour, and the orbitofrontal cortex, thought to have connexions with the cerebellum vermis. The MCP and SCP RD significant difference between NC and ATR patients, and correlation with mean cerebellar GM, suggests that WM damage in cerebellar peduncles caused by cerebellar atrophy can be directly assessed in-vivo. Furthermore the significant correlation between the MCP mean FA and the total ataxia score, and some of its subscores, supports the potential use of diffusion imaging and tractography in clinical settings as a useful marker of WM damage in patients with cerebellar atrophy.

References

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