The contribution of cerebellar white matter damage to cortical grey matter: evidence from voxel based morphometry and diffusion imaging

Giusy Olivito[1,2], Michael Dayan[3], Marco Molinari[1], Maria Leggio[1,2], and Marco Bozzali[3]

[1]Ataxia Laboratory, Santa Lucia Foundation, Rome, Lazio, Italy, [2]Department of Psychology, "Sapienza" University, Rome, Italy, [3]Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Lazio, Italy

Introduction

Over the last few decades, the role of the cerebellum in the modulation of higher level functions has been extensivily investigated (1;2;3). From an anatomical point of view, the afferent system arises from a wide area of the cerebral cortex and travels into the cerebellum through the middle cerebellar peduncle (MCP). Conversely, fibers from the cerebellum projects to the cerebral cortex through the superior cerebellar peduncle (SCP) with strictly contralateral interconnections (4;5). However, the interaction mechanisms between cerebellum and cerebral cortex in subserving higher level functions still remain unclear. Based on recent evidence, a cerebellar focal lesion can result in cerebral functional alteration due to specific structural modifications of the contralateral cerebral cortex (6). The aim of the current study was not only to evaluate the impact of focal cerebellar lesions on cerebral grey matter (GM) with conventional MRI, for a better understanding of cerebro-cerebellar pathways, but also to assess with diffusion MRI (dMRI) the contribution of cerebellar peduncles white matter (WM) damage to cortical GM modifications. Finally, this work investigated the usefulness of this analysis for single case evaluation of cerebellar lesions.

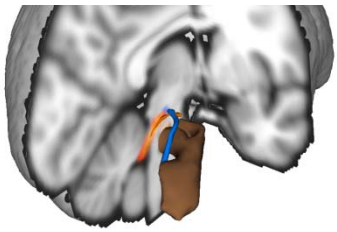

Figure 1: Average tracts of the MCP (brown), left SCP (orange) and right SCP (blue) with voxels belonging to at least 50% of the subjects. Note the decussation of the SCP bundles which could be successfully reconstructed.

Methods

Subjects: 30 normal controls (NC) [F/M=23/7; mean age ± SD = 54.4 ± 5.5 years] and 8 patients with unilateral cerebellar lesion, 4 in the left (LES-L) [F/M=2/2; mean age ± SD = 50.2 ± 8.5 years] and 4 in the right hemisphere (LES-R) [F/M=1/3; mean age ± SD = 45.2 ± 11.9 years]

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: radial diffusivity (RD) was computed from the diffusion tensor (DT) fitted with weighted linear least-square with Camino after preprocessing steps correcting for head movements and eddy currents based on non-linear registration to a T2 weighted volume with FSL.

Tractography: The MCP and SCP were reconstructed with multi-fiber probabilistic tractography carried out using 10000 iterations of the PICo algorithm (7) 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) based on a pooled two-sample T-test was applied to cortical GM maps warped to MNI space (with SPM 8) for NC and LES-R patients entered as two independent groups. The same analysis was carried out for NC and LES-L patients. Age and gender were set as nuisance variables and T-contrasts evaluated with voxel significance set at $p < 0.0001$, and corrected for family-wise error (FWE) at cluster level with significance level chosen for $p < 0.05$.

Single-case study: the same GM analysis was used for single case patient. A similar WM analysis was also carried out, based on VBM of RD maps restricted to voxels of the MCP and SCP belonging to the template shown in Fig 1

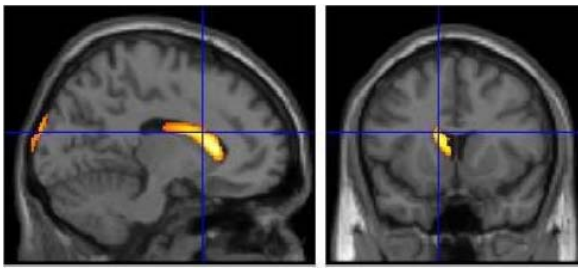

Figure 2: LES-L Vs NC between-group voxel-based comparison o cerebral GM density (left of patient on the right). Decrease in local GM volume was found in both the contralateral caudate and in the occipital lobe of both hemisphere.

Results

GM analysis: a widespread pattern of cerebral GM atrophy contralateral to the cerebellar lesion side was found in both LES-R and LES-L patient groups with respect to NC. When comparing these two groups to NC, the most significant changes were found in the contralateral caudate nucleus and occipital lobe (Fig 2). Interestingly, the same significant areas were found ipsilaterally: the right occipital lobe for LES-R patients (Fig 2) and the left occipital lobe and left caudate for LES-L patients.

Single-case study: the GM analysis showed significant reduction in local GM volume in the contralateral caudate of half of the patients (4/8) while no significant reduction was found in the ipsilateral cortex. The WM analysis in SCP lesioned patients showed an increase of RD in both the lesioned SCP and the ipsilateral MCP (2/2 patients). For MCP lesioned patients, in addition of the lesion site, a significant increase of RD was found in the ispilateral SCP, for half of the patients (3/6). Remarkably, half of patients with SCP lesions and half of those with MCP lesions showed RD decrease in the contralateral tract.

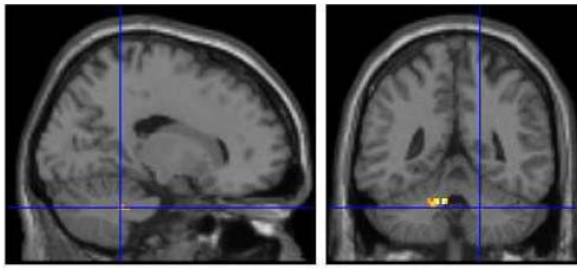

Figure 3: Single case analysis of patient with lesion in the right hemisphere (left of patient on the right). In addition of an importan decrease of RD in the lesion side, significant RD decrease was also found in the contralateral WM. This pattern was seen in half of the patients.

Discussion and conclusion

The present study confirms previous VBM findings (6) demonstrating that focal cerebellar damage can result in cerebral GM atrophy. Our group analysis demonstrated that another region of the brain could be prone to significant GM volume reduction: the caudate nucleus, known to be implicated with the cerebellum in initiation of voluntary movements. We also demonstrated GM cortex atrophy ispilaterally to the lesion, corroborated by the RD decrease observed in tracts contralateral to the lesion. The fact we could find the decrease of caudate GM volume in half of the patients with a single case analysis demonstrates the potential diagnostic usefulness of such an approach. It allowed finding a decrease in RD not only at the lesion site but also in ipsilateral and contralateral tracts. In light of these results and the very conservative statistical approach used, based on a Crawford's modified T-test, it is thought that single case analysis can prove useful for the prognostic assessment of patients presenting with cerebellar lesions.

References

1.Schamahmann and Pandya (1997), International Review of Neurobiology , 41:31-60; **2**. Riva and Giorgi (2000), Brain, 123: 1051-1061; **3**. Molinari et al. (2002), Neuroscience, 111: 863-870; **4.** Middleton and Strick (1994), Science, 266: 458-461; **5.** Ramnani (2006), Nature Reviews Neuroscience, 7: 511-514; **6.** Clausi et al. (2009), Neuroscience, 162: 827-835: **7.** Parker et al. (2003), J. Magn. Reson. Imaging, 18, 242-254.