Functional connectivity in patients with Progressive Supranuclear Palsy is modulated by cerebellar intermittent theta burst stimulation

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TARGET AUDIENCE Clinical and basic scientists with an itnerest in teh combination of MRI and TMS, and/or PSP.

Pourpouse Progressive Supranuclear Palsy (PSP) is an atypical degenerative parkinsonism clinically characterized by postural instability, sopranuclear gaze palsy and frontal behavioral dysfunctions (1). Non-invasive brain stimulation methods, such as repetitive Transcranial Magnetic Stimulation (rTMS), are currently used to modulate the excitability of the cerebral cortex, providing important insights into mechanisms of cortical plasticity (2). rTMS has been intensively investigated as a therapeutic tool in the specialist area of movement disorders showing some promising results (3). Intermittent Theta-Burst Stimulation (iTBS) is a rTMS protocol that induces focal long-lasting changes in cortical excitability (4). A recent study conducted in a group of PSP patients demonstrated that this approach can induce cortical plasticity in M1 that persists almost unchanged after 1-year follow-up (5). Functional and structural changes along the Dentatorubrothalamic tract have been associated with PSP pathology (6). The aim of the present study is to investigate the impact of cerebellar iTBS on Functional Connectivity (FC) in a group of PSP patients using Resting State fMRI.

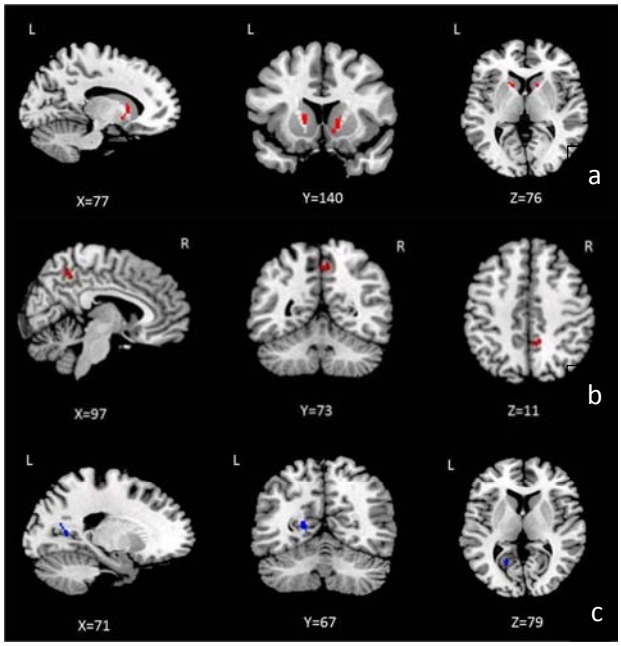

Fig.1 In post iTBS session were observed significant changes (p< 0.005 unc) in functional connectivity: DMN: a) increasing of right and left caudatum activation. SMN : b) decreasing of right precuneus and c) increasing of left precuneus/suporacalcarine cortex activation.

MATERIALS AND METHODS We recruited 8 PSP patients [M/F= 4/4; mean (SD) age= 70.12 (7.6)]. All patients were evaluated by administering the *clinical rating scale* (7, 8). TMS Two iTBS trains, one in each cerebellar hemisphere, were applied daily from Monday to Friday, for 2 weeks. iTBS protocol consisted in bursts of 3 pulses at high frequency, 50 Hz, repeated at intervals of 200 ms, in short trains, for a total number of 600 pulse. MRI MRI scans were acquired before and after the two week iTBS treatment. All imaging was obtained using head only 3.0 T MR scanner. The MRI acquisition protocol included: Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms, Matrix = 256x 24, n. slices=176, thick. 1 mm) acquired as anatomical reference; 2) T2-weighted EPI sensitized to BOLD contrast (TR=2080 ms, TE=30 ms, 32 axial slices parallel to AC-PC line, matrix=64x64, pixel size =3x3 mm 2, slice thickness=2.5 mm, flip angle=70°) for resting state (7-min and 20-sec period for 220 volumes). During this acquisition, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. fMRI data were processed using MATLAB R200 7B (Math-Work, Natick, MA) and SPM8, including correction for motion and slice-timing, and normalisation. In-house software was used to remove the global temporal drift using a 3rd order polynomial fit, the realignment parameters, and the signal averaged over whole brain voxels. Data were band-pass filtered to remove high frequency variations. A model-free analysis was employed by using independent component analysis (ICA) implemented in the GIFT package, in order to allow a simultaneous separation into individual components. ICA spatial maps were converted to Z-scores and reviewed to confirm the identification of the functional networks consistently described in previous works (9). A second level of analysis was performed on resulting images using a paired T-test model in SPM8 to compare the images acquire before and at the end of iTBS session.

RESULTS Two out of 8 patients were excluded for the poor quality of their MR images due to motion artefacts. Resting-state fMRI revealed an increase of functional connectivity within the default-mode network (DMN) bilaterally in the caudate nucleus after iTBS session (respectively p-unc = 0.004 and p-unc = 0.001, at cluster level) (Fig. 1a). When analyzing the sensory motor network (SMN), in post iTBS session images we observed a reduction of FC in the right precuneus (p. corr = 0.011) (Figure 1 b), and an increased of FC (p. unc = 0.001) in the left parietal lobe (Figure 1c). No significant changes were observed in any of the other considered networks.

CONCLUSION Our analysis provides new evidence that iTBS is able to induce modifications of functional connectivity in PSP patients. Several imaging studies demonstrated the presence of PSP pathology specific alterations of caudate nucleues, such as atrophy (6), increased total iron level (10), increased apparent diffusion coefficient (11) and magnetization transfer ratio reduction (12). Moreover, Caudate Nucleus was shown to be connected to mediodorsal thalamic nucleus in humans, suggesting an integrative role of these two regions (13). Here we hypothesize that the bilateral increasing of the caudate nucleus activation could be an indirect effect of the Thalamus stimulation through cerebellar iTBS, supporting the hypothesis of integration mechanisms between them. Furthermore, the alterations observed in the SMN suggest the presence of an asymmetric network that could be modified through cerebellar stimulation. Although the present study provide new evidence of the role of iTBS as tool modulate cortical connectivity, further studies are necessary to increase the sample size and to confirm our preliminary findings.

REFERENCES 1) William and Lee (2009) Lancet Neurol 8: 270-279 ; 2) Koch (2010) Func Neurol 25: 159-163: 3) Ridding and Rothwell (2007) Nat Rev Neurosci 8: 559-567 4) Huang et al. (2005) Neuron 45:201-206 5) Conte et al. (2012) Cerebral Cortex 22: 693-700 6) Withwell et al. (2011) Parkinsonism and related Disorders 17: 599-605; 7) Golbe and Ohman-Strickland (2007) Brain 130: 1552-1565 8) Litvan et al. (1996) Neurology 47: 1-9; 9) Rosazza et al. (2011) Neurol Sci 32: 773-785; 10) Boelmans et al. (2012) Mov Disorders 27: 421-427 11) Seppi et al. (2003) Neurology 60:922–927; 12) Eckert et al. (2004) Neuroimage 21:229–235 13) Eckert et al. (2012) Human Brain Mapping 33: 2627-2637.