

Effect of rTMS on cerebello-thalamo-cortical connectivity in Essential Tremor

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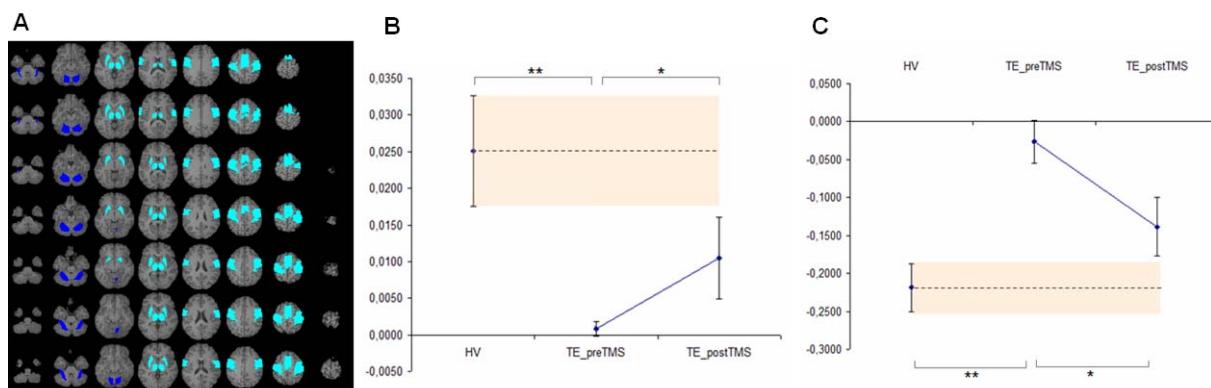
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Introduction: Essential tremor (ET) is a movement disorder that involves cerebellar impairments. The therapeutic strategies using medication remain often unsatisfactory. Recently, repetitive magnetic transcranial stimulation (rTMS) has shown a therapeutic benefit in ET patients. A single session of rTMS applied over the cerebellum of ET patients showed short lasting reduction in the amplitude of tremor (Giromeli et al. 2002). Here, we investigated the mechanisms of rTMS applied over the cerebellum by studying its effects on the cerebello-cortical functional connectivity within the sensorimotor network.

Methods: 11 patients diagnosed with ET (mean age = 53.0 ± 14.6 years) and 11 matching healthy volunteers (HV) (mean age = 53.2 ± 16.5 years) participated in the study. Patients received 5 daily sessions of rTMS (900 impulses at 1 Hz on each hemisphere, intensity=0.9 x adjusted resting motor threshold) on the VIIA cerebellar lobule localized with a neuronavigation system. At day 1 before the rTMS and at day 5 after the rTMS, clinical assessment and tremor quantification were performed before the acquisition of resting state BOLD echo planar fMRI (3T TRIO 24-channel TIM Siemens scanner). fMRI parameters were: 46 oblique axial slices, TR = 3.3s, TE = 30ms, $\alpha = 90^\circ$, FOV 128 x 128, voxel size 1.5 x 1.5 x 2.5, 200 volumes acquired. Functional connectivity was measured using Bayesian statistics taking into account the total correlation and the integration (Marrelec et al. 2008) to compute 2-group and paired-wise comparisons (HV versus TE at day 1; TE at day 1 versus TE at day 5). The evidence values ($|e|$ in dB) indicated the probability of a true difference at a threshold superior to 0.909 (Coynel et al. 2010). Two networks were analyzed: the sensorimotor network (SMN) including the motor territories of the cerebellum (Figure 1); the default brain network (DBN) including the cerebellar vermis. The integration and correlation values were calculated between the cerebellum and the brain regions in each network.

Results: The total Fahn-Tolosa-Marin score was significantly improved and the amplitude of tremor was significantly reduced at day 5 compared to day 1. At day 1, HV had higher integration levels than the patients in both the SMN and the DBN. At day 5, patients showed higher levels of integration than at day 1 in the SMN, but not in the DBN ($|e|=0.511$). At day 5, signal time course in lobules VI/VIII of the cerebellum was more anti-correlated with the rest of the SMN than at day 1, which was not the case for the DBN ($|e|=0.449$).

Discussion: At baseline, patients showed reduced functional connectivity in both the SMN and the DBN. 5 days of cerebellar rTMS in TE patients partially restored the cerebello-thalamo-cortical connectivity in the SMN towards the level of the control group, the time series being more anti-correlated. This effect was specific to the SMN as it was not observed in the DBN. Cerebellar outputs via the ventromedial thalamus have an inhibitory influence over the motor cortex (Popa et al. 2010) and ET is associated with reduced GABAergic function (Boecker et al. 2010). Therefore, cerebellar rTMS may re-establish the inhibitory influence of the cerebellum over the motor circuit. The replication of this rTMS protocol with MRS or flumazenil-PET could help deepening these findings.



sensorimotor functional connectivity network obtained using Bayesian statistics including the cerebellum (VI and VIII), the thalamus, the putamen, the precentral gyrus, the postcentral gyrus, the supplementary motor area was defined using an MNI based anatomical parcelisation (A); Mean value \pm standard deviation of integrations (B) and correlations (C) for HV and TE patients (pre_TMS = day 1, post_TMS = day 5). $** |e| > 0.995$, $* 0.909 < |e| < 0.995$.

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