Brain functional MRI changes in multiple sclerosis patients treated with Thetrahydrocannabinol: Cannabidiol (THC:CBD) oromucosal spray for spasticity

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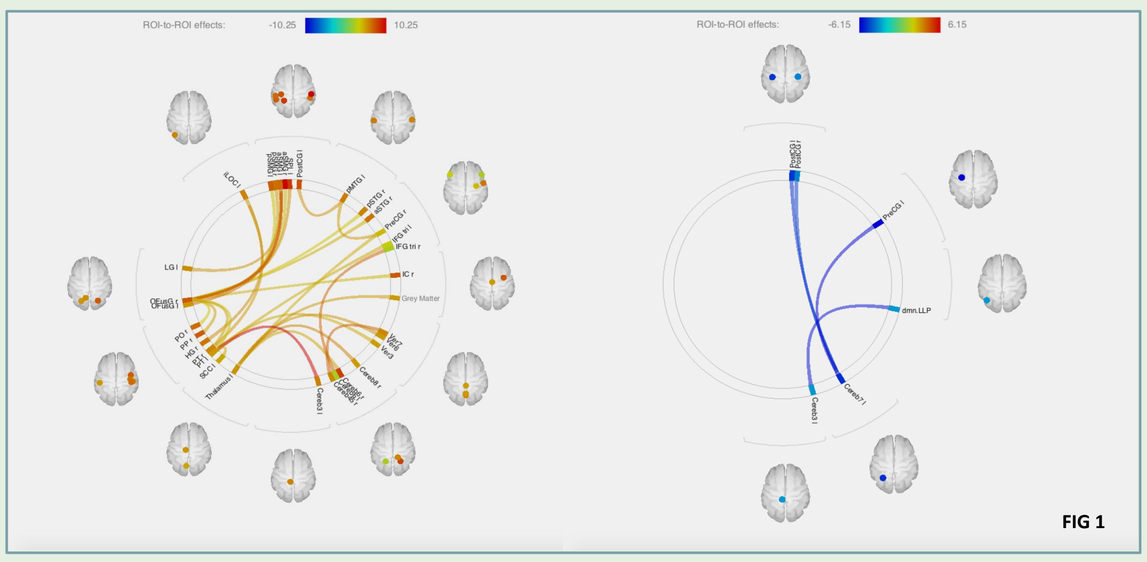
INTRODUCTION: THC:CBD is a second-line agent for the treatment of spasticity in MS with efficacy in about 40% of patients, according to clinical trials. Although THC:CBD mechanism of action is not completely understood, it acts through interaction with CB1 and CB2 receptors and modulates synaptic transmission in excitatory and inhibitory connections. Therapeutic effects on spasticity likely involve modulation of nociceptive and corticospinal pathways. Aim of this study is to investigate brain networks changes on resting state functional MRI (RS-fMRI) of MS patients treated with THC:CBD and to detect the effect of THC:CBD on the connectivity of specific brain areas in responders and non-responders, before and after treatment, comparing RS-fMRI changes.

METHODS: In this pilot study, we planned to include 12 MS patients eligible for treatment with THC:CBD oromucosal spray and followed at Verona University Hospital MS Center. Inclusion criteria were: 1) moderate to severe spasticity defined by a score of 4 or greater on the Numerical Rating Scale for Spasticity (NRS), 2) ineffectiveness of the treatment with current antispastic drugs. Patients were evaluated at baseline before treatment start (T0) and after 4 weeks of THC:CBD treatment at a stable dose following the titration phase (T1). Clinical variables included: 1) EDSS score, 2) NRS, 3) ambulation index, 4) 25-foot walking test, if applicable. Response to treatment was defined as a ≥20% reduction on the NRS score at T1 compared to T0. Brain MRI was performed at T0 and T1 on a 1,5 T scanner, acquiring RS-fMRI with T2-weighted EPI sequence (TR=3000 ms, TE=50 ms, slice thickness=4 mm, ETL= 57, 30 slice, 80 dynamics, time= 240 s). Connectivity changes were compared before and after treatment in the whole group and according to response status, using functional connectivity toolbox (CONN, version 15.h). Each exam was first preprocessed using default CONN pipeline, then a second level group analysis step was applied. ROI (region of interest)-to-ROI and seed-to-voxel connectivity were evaluated, using false discovery rate (FDR)-corrected statistical significance thresholds of $p<0.05$ and $p<0.01$, respectively.

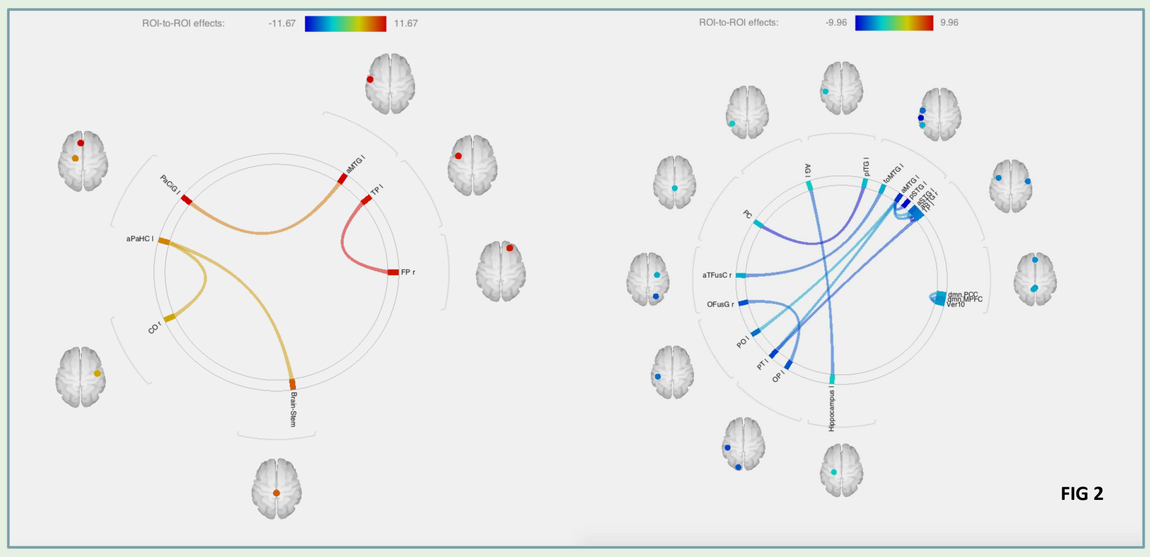
RESULTS: between January and September 2014, 15 consecutive patients were enrolled in the study. Of these, 12 (7 males, 5 females) completed all the assessments and entered data analysis. Median age was 51 years (36 - 73), disease duration 21.5 years (10-37), EDSS score 6.0 (4.5-8.0), and baseline NRS score 8 (5-9). The clinical course was relapsing-remitting in 2 and secondary progressive in 10 patients. Seven patients (58,3%) resulted THC:CBD responders at T1.

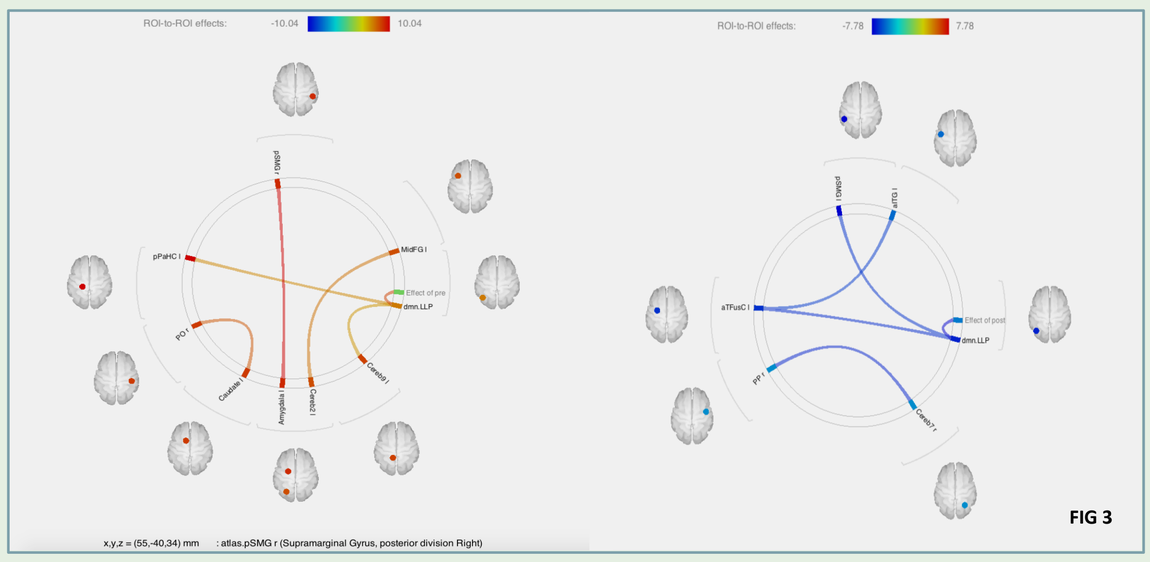
On RS-fMRI ROI-to-ROI analysis we observed a significant association between TCH:CBD therapy and global brain connectivity increase, decreased connectivity of motor areas, and bidirectional connectivity modulation of the left cerebellum with a number of cortical areas, particularly the left pre-central and post-central gyrus bilaterally (figure 1).

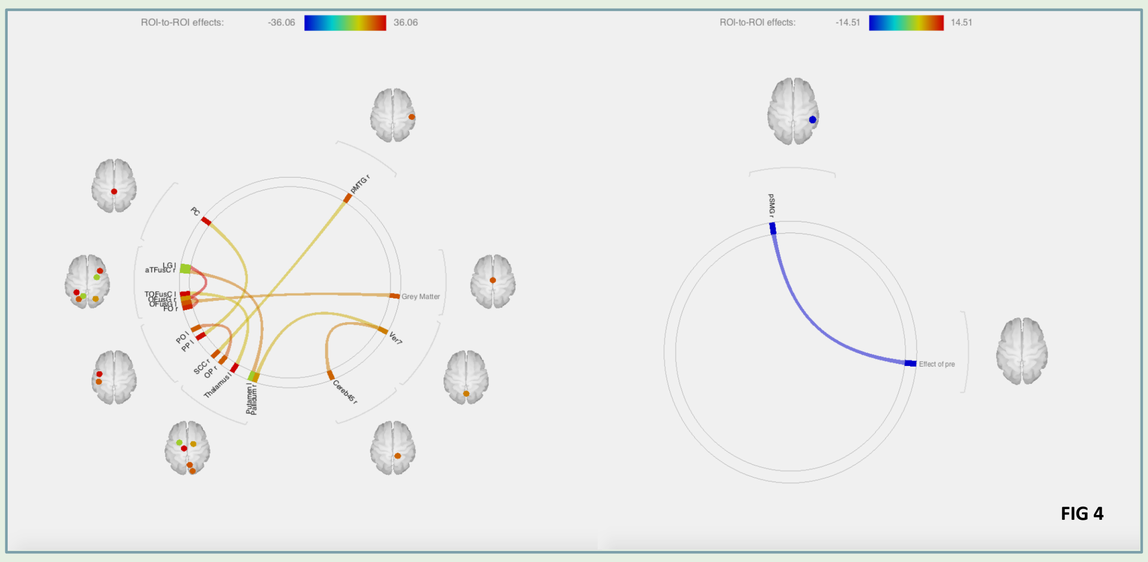
The global brain connectivity at T0 was lower in non-responders compared to responders (figure 2). This difference was still present, although attenuated, during THC:CBD treatment (figure 3). The global growth of connection was more evident in responders (figure 4), while motor areas connectivity reduction was more pronounced in non-responders (figure 5). Seed–to–voxel analysis on the whole study group at T1 compared to T0 showed a significant connectivity increase of left pre-central and post-central gyri with several ipsilateral and contralateral cortical areas of the brain (figure 6).

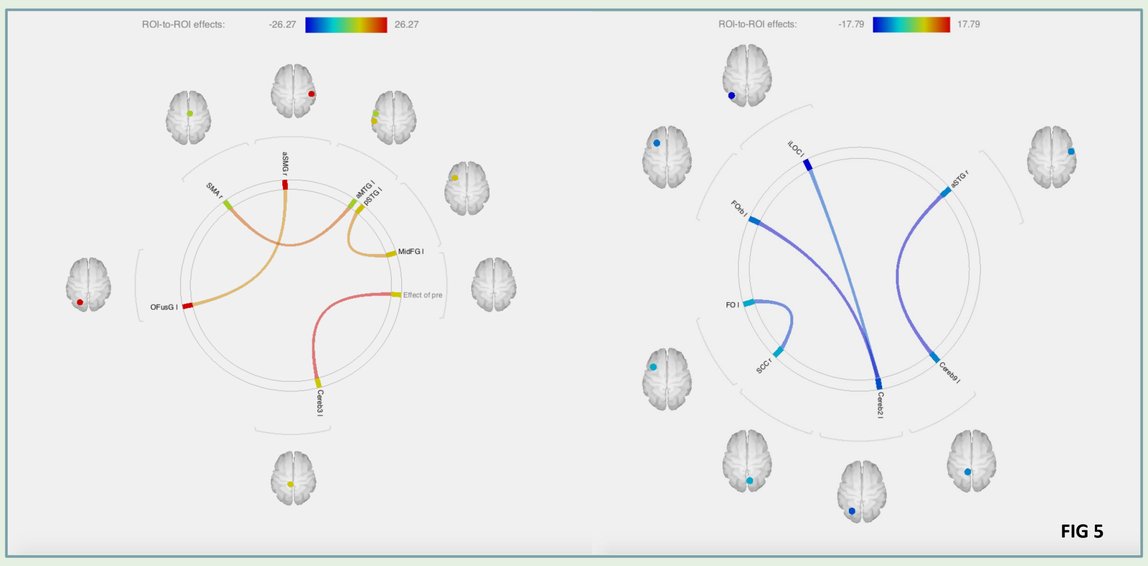


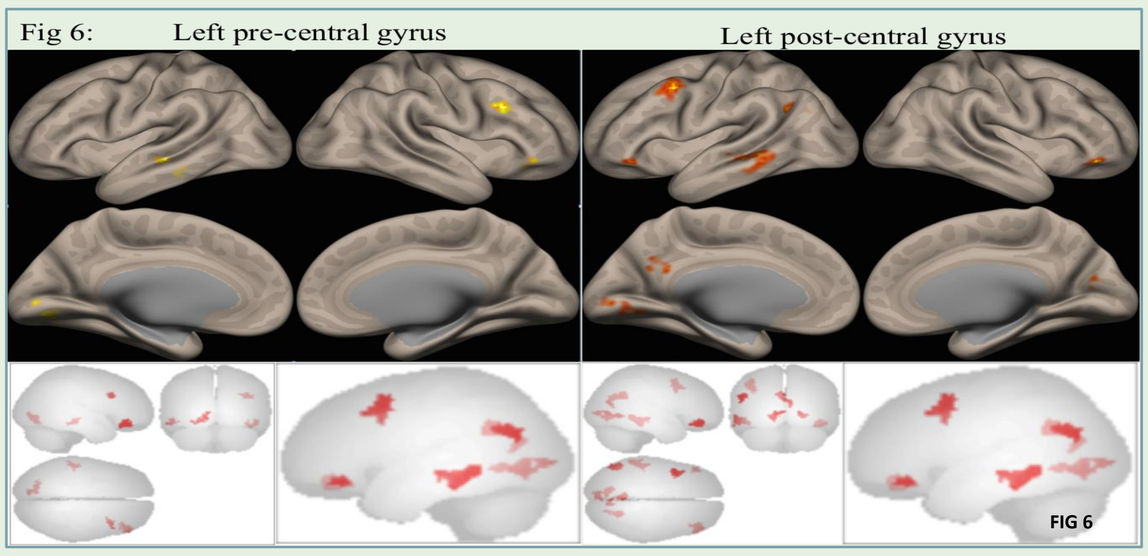
LEGEND: Figure 1: fMRI ROI-to-ROI analysis comparing all study subjects before and after THC:CBD initiation. A global brain connectivity increase (yellow and red lines) and cerebellum-cortical areas connectivity decrease (blue lines) were shown. **Figure 2**: ROI-to-ROI analysis comparing non-responders to responders at T0. A reduced global brain connectivity was observed in non-responders. **Figure 3**: ROI-to-ROI analysis comparing non-responders to responders at T1. After THC:CBD initiation, there was a tendency toward increased connectivity**. Figure 4**: ROI-to-ROI analysis comparing responders before and after THC:CBD. **Figure 5**: ROI-to-ROI analysis comparing non-responders before and after THC:CBD.











CONCLUSIONS: THC:CBD administration appears to increase overall brain connectivity of MS patients with spasticity, particularly in treatment responders. Modulation of motor areas and cerebellum connectivity seems to play a role in THC:CBD effect. Low pre-treatment global brain connectivity is associated with lack of response to THC:CBD.