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Effect of total sleep deprivation and light therapy on cortico-limbic connectivity in bipolar depression: a Dynamic Causal Modeling study

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BACKGROUND:

The identification of predictors of antidepressant response in bipolar depression may provide new potential enhancements in treatment selection. With this aim several authors focused their attention on cortico-limbic circuitry [1,2]. The chronotherapeutic combination of repeated total sleep deprivation and light therapy (TSD+LT) can acutely reverse depressive symptoms and has been proposed as a model of antidepressant treatment. We investigated the effect of TSD+LT on effective connectivity and neural responses to negative facial expressions in bipolar derpression.

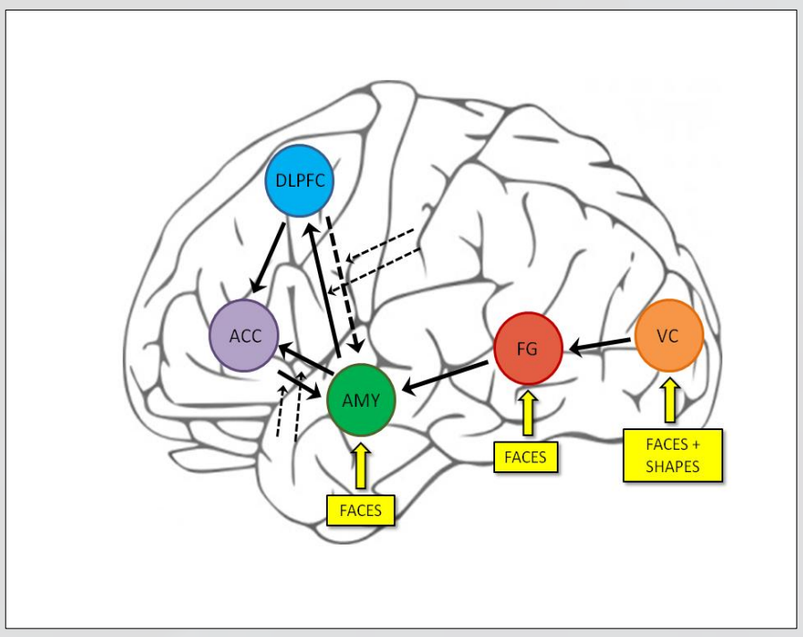

Fig.2 DCM model space

METHOD:

We used fMRI with Dynamic Causal Modeling (DCM) of relationships between regional activations, to study the effect of chronotherapeutics on neural responses to emotional faces in healthy controls (HC, n=35) and bipolar depressed patients either responder (RBD, n=26), or non responder (nRBD, n=11) to 3 consecutive TSD+LT. The activation paradigm was the emotional faces task developed by Hariri et al [3]. Twenty-four DCM models, exploring model space between anterior cingulate cortex (ACC), dorsolatelar prefrontal cortex (DLPFC), Amygdala, fusiform gyrus, and visual cortex were constructed (Fig.2). Bayesian Model Averaging provided DCM parameters, subsequently entered into statistical analyses.

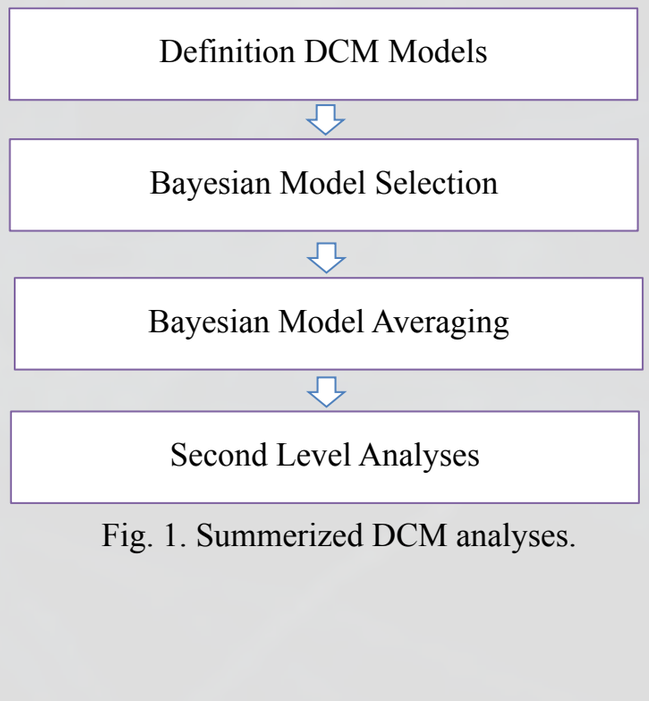

Fig. 1. Summerized DCM analyses.

RESULTS :

After treatment, patients significantly increased their neural responses in DLPFC, ACC and insula to emotional stimuli, but nRBD had lower baseline and endpoint neural responses than RBD (p_{FWE}<0.05; Fig. 3). DCM showed that only RBD patients had a significant increased intrinsic connectivity from DLPFC to ACC (t=2.74; p=0.011), and reduced the modulatory effect of the task on the connection Amy-DLPFC (t=2.2; p=0.037), Fig. 4.

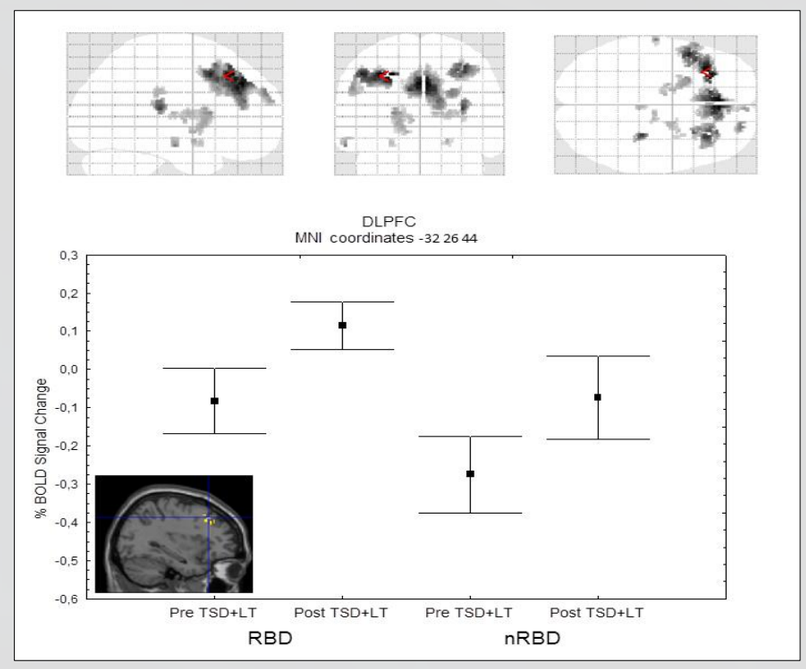

Fig. 3 fMRI Results

CONCLUSIONS:

A successful antidepressant treatment was associated to an increased functional activity and connectivity within cortico-limbic network. This pattern of change may result from a normalization of serotonergic and dopaminergic activity in ACC associated with a TSD [4]. Subtyping depressed patients with fMRI is just beginning, but future research may help to provide a new potential enhancement in appropriate treatment .

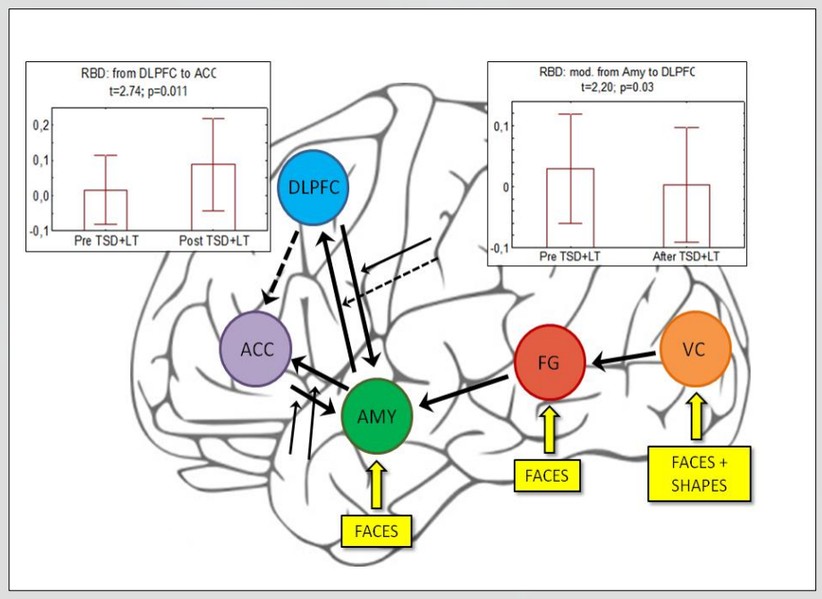

Fig. 4. DCM results

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Introduction: The combination of chronotherapeutic antidepressant techniques such as repeated total sleep deprivation (TSD) and light therapy (LT) has been shown to cause rapid and sustained antidepressant effects in bipolar depression that occur in a matter of hours/days. Disturbances in emotions and affective processing are core features of the disorder, with affective instability being paralleled by mood-congruent biases processing in information processing which influence evaluative processes, social judgment, decision-making, attention, and memory. Regulatory interactions of frontal and prefrontal structure with the amygdala (Amy) are critical for emotional processing. Furthermore, consistent finding highlighted that an elevated metabolism in anterior cingulate cortex (ACC), an area involved in affective/cognitive control of autonomic responses to stressful or emotional events, was a predictor of antidepressant response to sleep deprivation. Moreover, clinical improvement was associated with a decreased metabolic activity in ACC [1]. The aim of the present study was to investigate the effective connectivity between Amy and ACC in responders (RBD) or not responders (nRBD) bipolar depressed patients to TSD and LT and in healthy control (HC). Dynamic Causal Modeling (DCM) was performed to assess effective connectivity, this technique, differently from others such as Psycho-Physiologigal Interaction, allow to model causal relationships and directionality in connectivity among selected brain regions.

Methods: Thirty-four depressed patients having a diagnosis of bipolar disorder were recruited. All patients were administered 3 consecutive TSD cycles and LT in the morning. RBD (26), nRBD (11) and HC (35) images were entered in a fMRI and DCM analysis. The activation paradigm was an emotional implicit task with faces which express anger or fear [2]. The seed regions were data driven and identified from fMRI analysis. Five DCM models which explored all the possible input targets and connections (bidirectional and unidirectional) between ACC and Amy were constructed. Bayesian model Averaging was used to obtain DCM parameters, these parameter were then entered in a non parametric statistic (Kruskal–Wallis test) to analyze differences between groups.

Results: Non parametric test found significant differences in ACC to Amy connection ($H=18.53$; $df=2$; $N=72$; $p=0.001$). Non-parametric multiple comparison evidenced that RBD had a reduced ACC-Amy connectivity compared other groups ($p<0.001$). Other comparisons were not significant.

Conclusion: Responders to TSD and LT showed a reduced top-down ACC-Amy connectivity compared to HC and not responders. This data is line with previous findings which highlighted that RBD was characterized by a hyper activity in ACC before TSD and its reduction was associated to an amelioration of symptomatology in this group [1]. This pattern of change may result from a normalization of serotonergic and dopaminergic activity in ACC associated with a TSD [1]. Subtyping depressed patients with fMRI is just beginning, but future research may help to provide a new potential enhancement in appropriate treatment selection.

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Keywords

Bipolar disorders

Antidepressants: clinical

Neuroimaging: functional