FRONTO-LIMBIC DISCONNECTION IN BIPOLAR DISORDER

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BACKGROUND

Bipolar disorder (BD) is a severe, disabling and life-threatening illness. Disturbances in emotion and affective processing are core features of the disorder, with affective instability being paralleled by mood-congruent biases in information processing which influence evaluative processes, social judgment, decision-making, attention, and memory. Several lines of evidence, coming both from neuropsychological studies and functional and structural brain imaging reports, suggest that disruptions in neural connectivity could play a key role in the mechanistic explanation of these cognitive and emotional symptoms. Dynamic causal modeling (DCM) can be used to analyze the Blood oxygen level dependent (BOLD) responses in order to measure effective connectivity by describing how the present state of one neuronal population causes dynamics (i.e., rate of change) in another, and how these interactions change under the influence of external perturbations (i.e., experimental manipulations). In literature only few studies evaluated effective connectivity (EC) with DCM in bipolar patients. In the present study we performed DCM of functional neuroimaging data to investigate the effective connectivity in a specific cortico-limbic network including prefrontal areas, cingulate cortex and amygdala in a sample of bipolar depressed patients.

MATERIALS AND METHODS

We evaluated a total of 52 consecutive patients affected by bipolar disorder during a major depressive episode, without psychotic features, and 40 healthy subjects. DCM was performed on fMRI activation to a face-matching paradigm task. Effective connectivity was estimated with DCM in a trinodal neural model including anatomically defined regions of dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) and the amygdala (AMY). Six alternative models with different endogenous connections and task inputs were constructed for each subject. All models were defined as bilinear and stochastic. In the first three models (A, B, C) driving inputs entered via the amygdala, while in the last three (D, E, F) via both amygala and DLPFC. For all the proposed models we fixed a forward and backward connection between ACC and AMY, and a unidirectional connection from DLPFC to AMY.
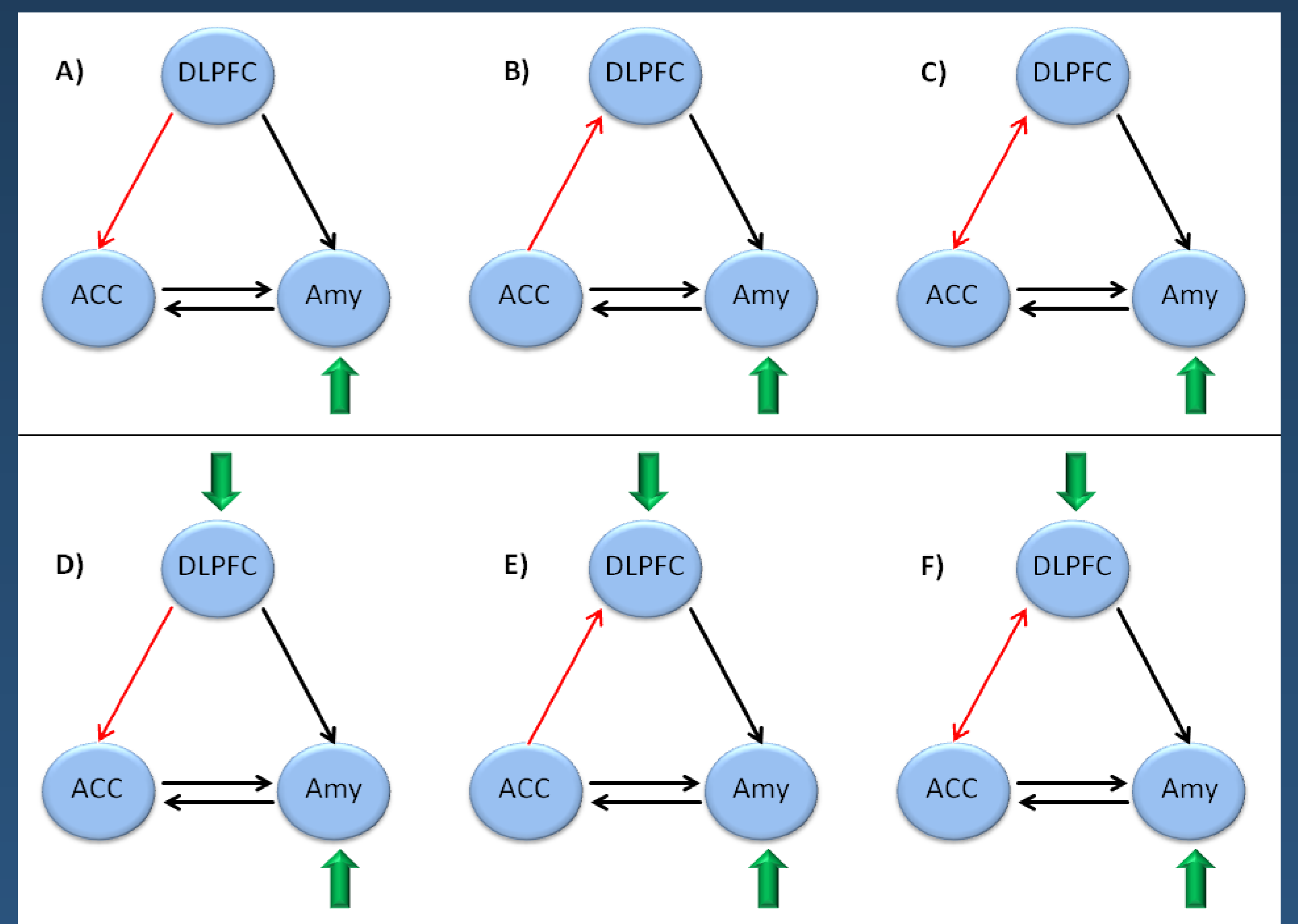

Figure 1. The six trinodal competitive models for DCM. Green arrows represent facial stimuli inputs. In the first family of models (A, B, C) the input enters the network from Amygdala (Amy), whereas in the second family of models (D, E, F), the inputs enter both from Amy and Dorsolateral prefrontal cortex (DLPFC).

RESULTS

The best model was the same across all subjects, and consists in a forward connection from DLPFC to AMY and from DLPFC to ACC and with a bidirectional connection between ACC and AMY. However patients with bipolar disorder showed a significantly reduced endogenous connectivity in the DLPFC to Amy connection during the emotional processing task. There was no significant group effect upon the endogenous connection from Amy to ACC, from ACC to Amy and from DLPFC to ACC.

CONCLUSIONS:

Both DLPFC and ACC are part of a network involved in emotion regulation and share strong reciprocal connections with the amygdalae. These regions are fundamental in voluntary emotion regulation strategies, including reappraisal and redirection, and previous findings based on a variety of functional neuroimaging techniques showed that an irregular functioning of these brain structures might be involved in the cognitive and emotional deficits characteristic of bipolar disorder. Thus, our finding of a reduced connectivity between DLPFC and amygdala may reflect abnormal modulation of mood and emotion typical of bipolar patients.

HC = 0.047 ± 0.067
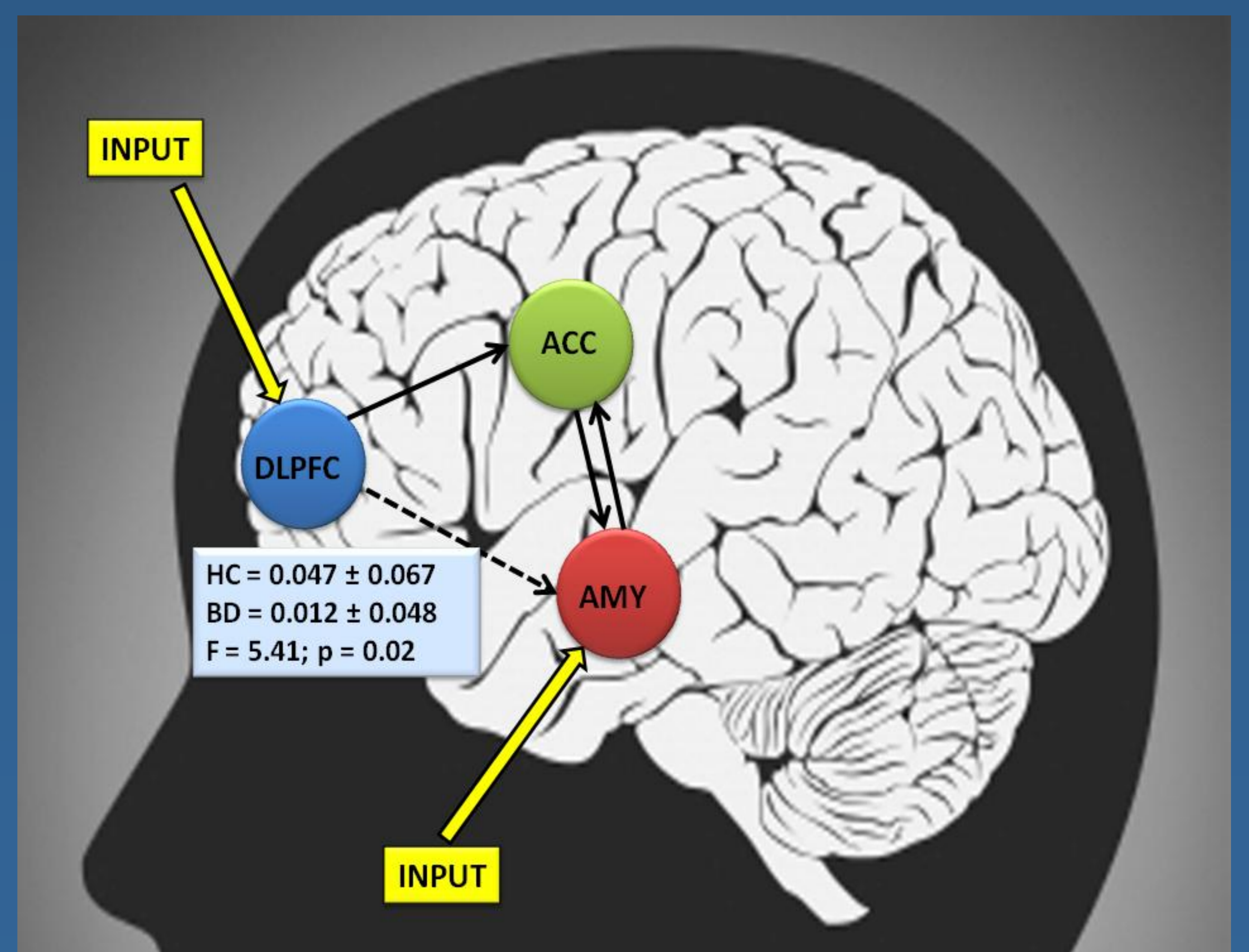BD = 0.012 ± 0.048
F = 5.41; p = 0.02

Figure 2. DCMs results: decreased effective connectivity (EC) between dorsolateral prefrontal cortex and amygdala during emotion labeling in bipolar disorder. Black arrows: no significant EC differences between BD and HC. Dotted arrow: significant lower EC in BD patients versus HC between DLPFC and Amy. Yellow arrows: driving inputs.