Dorsal raphe nucleus functional connectivity in depression and relationship to antidepressant treatment response.

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**Background**: Brainstem raphe nuclei contain serotonergic (5-HT) neurons that project o cortical and subcortical mood regulating areas such as the medial prefrontal cortex (mPFC) and amygdala. The Dorsal raphe nucleus (DRN) is the largest group of 5-HT neurons. As most commonly used antidepressants increase 5-HT neurotransmission, we hypothesized that DRN connectivity with regions of the mood regulating circuit will be related to antidepressant response. In this study, we investigated DRN resting state connectivity differences between depressed and healthy subjects and correlated baseline abnormalities to response to a 3-month clinical trial of antidepressant treatment.

**Methods**: 12 medication free depressed subjects (Age: 26±4; 9F, Baseline HAM-D depression score: 19±4.; Post-treatment HAM-D score: 11±8) and 15 closely matched healthy subjects (Age: 25±3 yr., 6F) were included in the study and went through 3T fMRI scanning. Resting state data was collected while subjects had eyes open and looked at a fixation cross. Bilateral DRN region of interest template was drawn individually on the structural images of 12 healthy subjects in conjunction with an experienced neuroradiologist using operationalized criteria based on standard brainstem anatomy atlases1,2. A common DRN ROI template was constructed in the MNI space using the data from the 12 healthy subjects. This ROI was used to extract resting state time series from all subjects and whole brain voxel-wise correlation maps were generated. Finally, correlation between percentage decrease in depression scores after 12 weeks of treatment and baseline DRN connectivity was calculated for the depressed subjects.

**Results**: At baseline, healthy subjects had greater DRN-mPFC connectivity compared to depressed subjects (p = 0.01, cluster-wise corrected). A negative correlation was seen between DRN-mPFC connectivity and percentage decrease in HAM-D scores after 12 weeks of antidepressant treatment i.e. the lower the DRN-mPFC connectivity at baseline the greater the antidepressant treatment response.

**Conclusions**: Decreased DRN-mPFC connectivity may serve as a biomarker of antidepressant treatment response.