Organization for Human Brain Mapping 2013 Abstract

Title: Ventral tegmental area functional connectivity predicts antipsychotic drug response in schizophrenia

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Category: Disorders of the Nervous System: Schizophrenia and Psychotic Disorders

Abstract (3829/4000 characters):

Introduction:
Antipsychotic drugs (APDs) alleviate some of the symptoms of schizophrenia, but up to 30% of patients do not respond to these drugs (Harrow, 1997). Currently, treatment responders and non-responders can only be identified after lengthy medication trials. Imaging research in schizophrenia has revealed altered functional connectivity (FC) between brain regions, thought to reflect changes to the underlying neural circuitry associated with the disease. We sought to identify pre-treatment differences in FC that were predictive of eventual response to APDs, which could serve as biomarkers of treatment response. Importantly, in unmedicated patients with schizophrenia, elevated dopamine turnover and release have been documented and found to be predictive of good treatment response to APDs (Abi-Dargham, 2000, 2009; Laruelle, 1996). Based on this information, we hypothesized that the strength of FC between the ventral tegmental area (VTA, the source of the mesocorticolimbic dopaminergic projections thought to be critical for APD action) and one or more brain regions before treatment would be predictive of response to APDs.

Methods:
23 unmedicated patients with schizophrenia were scanned using resting-state fMRI (RSfMRI) in a longitudinal study of APD response. Patients were scanned upon enrollment, and, following this initial scan, began treatment with the APD risperidone on a flexible dosing regimen. After 6 days of treatment, patients returned for a second scan and symptom ratings. Patients returned weekly for the next 5 weeks for symptom ratings and medication adjustments. Symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS). Treatment response was defined as the residual after the week 6 BPRS score was corrected for the baseline BPRS score.

RSfMRI scans were acquired on a Siemens 3T Allegra MRI scanner during a 5-min gradient recalled EPI sequence (TR/TE = 2100/30 msec, 26 axial slices, 225 acquisitions). High-resolution structural scans were acquired using the 3D T1-weighted MPRAGE sequence (TR/TE/TI = 2300/3.93/1100 msec).

A 3-mm spherical region in the VTA (MNI: 0, -16, -7) and a 3-mm control region in the left occipital cortex (MNI: -25, -98, -12) were identified for FC analysis. Following standard data preprocessing and motion scrubbing (Power, 2012; Carp, 2012), the first eigenvariate of the BOLD time series from each region was extracted for all participants. Each region’s BOLD time series was correlated to that of all other voxels in the brain to produce a FC map from each region for each participant, which were converted to normally distributed values using Fisher’s r-to-Z transform prior to analysis.

Results:
Treatment response was correlated with the pre-treatment FC strength between VTA to ventromedial prefrontal cortex, posterior cingulate cortex, precuneus, and lateral parietal cortex, which are all regions of the default mode network (DMN, p < 0.05, FDR-corrected; Fig. 1). Fig. 2 describes the variance of this relationship. There was no relationship between pre-treatment FC from an occipital control seed region and treatment response (p < 0.05, FDR-corrected).
Conclusions:

Our data suggest that a high degree of functional separation between the VTA and the DMN may be a useful pretreatment biomarker of APD response. DMN activity has been reported as abnormal in schizophrenia (Whitfield-Gabrieli, 2012). This abnormal activity is thought to alter the brain’s ability to switch between its default mode and its active processing mode (whose salience network includes the VTA). In healthy individuals, greater correlation between these modes occurs during attention lapses (Weissman, 2006). In schizophrenia, impaired switching between modes is hypothesized to be a mechanism of hallucinations and delusions (Whitfield-Gabrieli, 2012). We propose that impaired switching between these two modes of brain activity may also be a biomarker of poor response to APDs, independent of symptom severity.

Figures:

**Figure 1.** Regions where pre-treatment functional connectivity from the VTA is positively correlated with treatment response ($p < 0.05$, FDR-corrected). Results are overlaid on a single-subject T1 image of an extracted brain displayed in neurologic convention (left on left).

**Figure 2.** Relationship between the pre-treatment VTA to precuneus functional connectivity strength and treatment response ($n = 18$).
References:


