SCHIZOPHRENIA is a severe, lifelong mental illness that often leads to profound disability. Physicians treat schizophrenia using antipsychotic drugs (APDs), which generally act as antagonists on the dopaminergic D_2 receptors. Patient responses to these drugs are variable and currently unpredictable, presenting a significant challenge to physicians.

Widespread evidence supports the role of dopamine in patient response to APDs. Notably, dopaminergic neurons originating in the ventral tegmental area (VTA) project to many regions that show changes in blood flow after APD treatment.

BASED ON THIS INFORMATION, WE HYPOTHESIZED THAT:

- THERE ARE SPECIFIC DEFICITS IN FC IN UNMEDIATED SCHIZOPHRENIA
- THESE DEFICITS ARE AFFECTED BY APD TREATMENT
- VTA FC TO ONE OR MORE REGIONS OF THE BRAIN CAN PREDICT PATIENT RESPONSE TO APDS.

1. There is a significant decrease in VTA FC in unmedicated schizophrenia compared to matched healthy controls. While this is the first study to look at VTA FC, previous studies have reported decreased FC to these regions in schizophrenia. Other studies report reduced thalamic metabolism and decreased dopaminergic projections to the thalamus in schizophrenia, as well as abnormalities in the intracellular integration of dopamine with other neurotransmitter systems.

2. APD treatment reverses some, but not all, VTA FC deficits. VTA to thalamus FC was restored following one week of APD treatment; other regions showed no change in VTA FC. APDs act on the dopaminergic D_2 receptor, which is thought to inhibit activity of the indirect pathway of the basal ganglia. This would lead to decreased inhibition of the thalamus by the VTA in unmedicated schizophrenia, which would be corrected with APDs. Thalamic FC to the regions with remaining VTA FC deficits was restored with treatment.

3. VTA FC to the dACC is positively correlated with treatment response; VTA FC to the DMN is negatively correlated with treatment response. Previous studies have predicted APD response before initiating treatment, and found it to depend on dopamine release. It was also reported that FC of the DMN increased with an acute dose of L-dopa and decreased with an acute dose of haloperidol (both change dopamine levels).

FUNCTIONAL CONNECTIVITY AS A BIOMARKER FOR TREATMENT RESPONSE IN SCHIZOPHRENIA

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