Functional and Micro-Architectural Characterization of the Ventral Tegmental Area in Parkinson's Disease with Depressive Symptoms

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Background: Clinically significant depressive disturbances occur in 40-50% of patients with Parkinson's Disease (PD) and often precede the onset of any measurable motor symptoms. Cross-sectional studies indicate a majority of those affected experience "non-major" forms of depression, often underdiagnosed by traditional diagnostic tools for major depressive disorder, leading to significant untreated morbidity in this patient group. A PD-specific pathogenesis is thought to occur through both deficiencies in the mesocortical noradrenergic and serotonergic projections and mesocorticolimbic dopaminergic projections. Given between 40 to 77% of dopaminergic neurons in the ventral tegmental area (VTA) are lost in the progression of PD, impaired dopaminergic stimulation from the VTA may contribute to the development of depressive symptoms in patients with PD.

Methods: 53 patients with PD were recruited for the study. Whole brain correlational tractography analysis was completed with the left and right VTA marked as seeds for the identification of projections that significantly correlated with Hospital Anxiety and Depression Scale depression (HADS-d) scores with a FDR $p<0.05$. Restricted diffusion imaging (RDI) metrics were reconstructed using Q-space-diffeomorphic-reconstruction methodology, providing "beyond-DTI" microscale information. rs-fMRI seed-to-whole brain analysis was performed for bilateral VTA-atlased regions for estimation of VTA functional connectivity (FC) maps significantly correlated with HADS-d scores with a non-parametric threshold-free cluster enhancement protocol.

Results: Whole-brain correlational tractography results summarized in fig. 1. Seed-to-whole brain rs-fMRI analyses show significant positive correlation between depression scores and FC values of the left VTA and right occipital pole. Significant negative correlation is seen between depression scores and FC values of the left VTA and bilateral supramarginal gyri and precuneus cortex. No significant rs-fMRI results were seen for the right VTA.

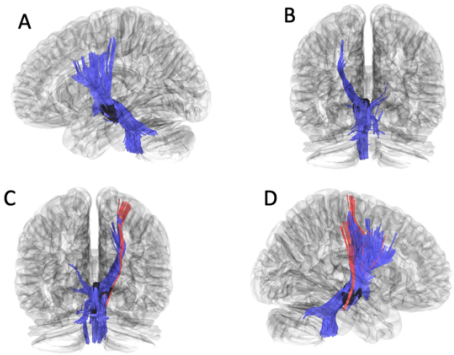

Fig. 1: Sagittal (A) and posterior-anterior (B) visualizations of L VTA RDI tracts significantly correlated with depression scores. Red indicates positive correlation; blue indicates negative correlation
Posterior-anterior (C) and sagittal (D) visualizations of R VTA RDI tracts significantly correlated with depression scores. Red indicates positive correlation; blue indicates negative correlation

Conclusions: Correlational tractography results show axonal loss within the VTA is associated with depressive symptom severity and the presence of a right-lateralized compensatory mechanism within the region. Results also indicate the benefit of RDI and other "beyond-DTI" diffusion metrics in the study of non-motor symptoms of PD. Left-lateralization of functional connectivity changes also supports the presence of right-VTA compensatory mechanisms in the development of depressive symptoms. Overall, the findings support the theory of dysfunctional mesocorticolimbic dopaminergic projections uniquely contributing to the development of depressive symptoms in PD, supporting the need for therapeutics targeted to this pathway.