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

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Objectives

We aim to describe the magnitude and direction of functional connectivity and diffusion spectrum imaging changes in the VTA as related to increasing severity of depressive symptoms within a cohort of patients with early-to-intermediate stage PD

Introduction

Depressive symptoms in PD:

- Clinically significant depressive disturbances occur in 40-50% of patients with PD[1]
- Cross-sectional studies indicate slightly less than half of those with depressive symptoms experience major depression, with most experiencing "non-major" forms of depression[2]
- Depression leads to significant morbidity in this patient group

Pathophysiology of depressive symptoms in PD:

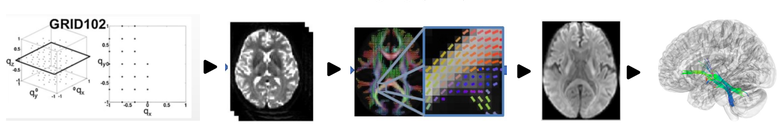
- PD-specific pathogenesis is thought to occur through both deficiencies in mesocortical noradrenergic and serotonergic projections and mesocorticolimbic dopamine projections[3]

Involvement of the Ventral Tegmental Area:

- The VTA and its projections within the salience network have traditionally been associated with reward processing and dysfunctions are seen in many neuropsychiatric illnesses[4]
- Between 40 to 77% of dopaminergic neurons in the VTA are lost in the development of severe PD[5]
- PET studies have elucidated orbitofrontal hypometabolism unique to depression in PD which may reflect impaired dopaminergic stimulation from the VTA[6]

Methods

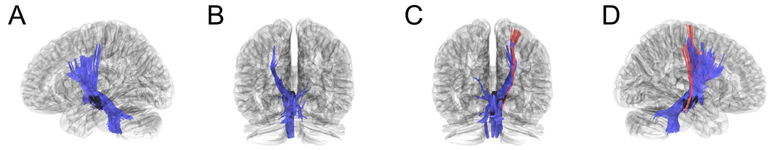
DSI data processed and analyzed for correlational tractography using DSI studio Q-space-diffeomorphic-reconstruction (QSDR) methodology used to reconstruct restricted diffusion imaging (RDI) [7]



rs-fMRI analyses performed using CONN toolbox with standard preprocessing and denoising protocols

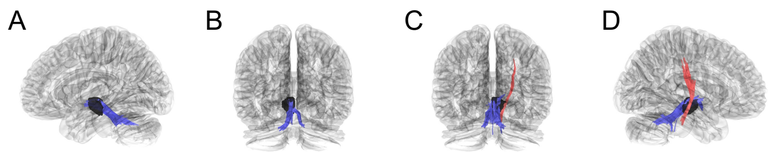
Results

RDI: significant decreases in RDI metric correlated with increasing depression scores for bilateral VTA; separate tracts with significant increases in RDI metric correlated with increasing depression score in R VTA



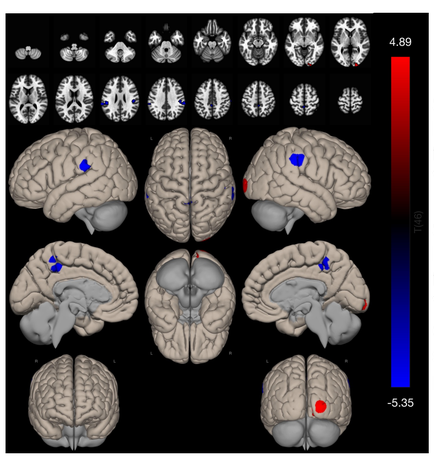
Sagittal and posterior-anterior visualizations of Left (A, B) and Right (C, D) VTA RDI tracts significantly correlated with depression scores. Red indicates positive correlation; blue indicates negative correlation

QA: significant decreases in RDI metric correlated with increasing depression scores for bilateral VTA; separate tracts with significant increases in RDI metric correlated with increasing depression score in R VTA



Sagittal and posterior-anterior visualizations of Left (A, B) and Right (C, D) VTA RDI tracts significantly correlated with depression scores. Red indicates positive correlation; blue indicates negative correlation

Seed-to-whole brain resting-state functional connectivity analysis with the L VTA as the ROI



Significant positive correlation between depression scores and functional connectivity values of L VTA and (1) right occipital pole

Significant negative correlation between depression scores and functional connectivity values of L VTA and
(2) right supramarginal, (3) left supramarginal gyrus, and (4) precuneus cortex

Discussion

- RDI decreases are associated with demyelination while increases are associated with cell infiltrations;[8] QA decreases are associated with axonal loss[9]
- Correlational tractography results could indicate axonal loss within the VTA being associated with depressive symptoms with a lateralized compensatory mechanism unique to the right side VTA
- Results also show more sensitive diffusion metrics may be required to study the non-motor symptoms associated with Parkinson's disease
- Left sided functional connectivity changes with no significant results on the right side supports right-sided VTA compensation in the development of depressive symptoms
- Abnormal activations of the lateral occipital regions, salience networks containing the supramarginal gyri, and precuneus have been associated with the development of major depressive disorder in health cohorts [10]

Conclusion and Future Directions

- Sensitive diffusion metrics including restricted diffusion imaging (RDI) and quantitative anisotropy may be required to study the tract changes associated with non-motor symptoms in Parkinson's disease
- Functional connectivity mapping of the ventral tegmental area in Parkinson's shows the region may contribute to a unique pathogenesis of depressive symptoms as compared with healthy cohorts
- Both DSI and rs-fMRI show a potential right-sided compensatory mechanism that will require further longitudinal study

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