CSF alpha synuclein levels modulate BOLD connectivity of executive control network regions in Parkinson's disease

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TARGET AUDIENCE: Researchers interested in applications of fMRI to investigate mechanisms of neurodegenerative disease.

INTRODUCTION: Parkinson's disease (PD) is a progressive movement disorder pathologically characterized by alpha-synuclein (α-syn) deposition along with alterations to neurotransmitter function, especially dopamine and acetylcholine. Clinically, many patients suffer from non-motor symptoms such as executive predominant cognitive impairment. These are linked to structural changes to the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate (ACC)[1]. Indeed, early localization of Lewy Bodies (alpha synuclein deposits) is evident in the brain stem and frontal cortex, and later present in higher order sensory association areas[2]. One promising biomarker of PD includes CSF α-syn levels, but its specific role for understanding PD pathogenesis and progression is unknown. *The purpose of this work was to assess the relation of α-syn levels with functional connectivity of the frontal regions involved in executive function to other brain regions involved in cognitive control using BOLD fMRI.*

METHODS: Thirty-six adults (age = 59.8±10.1 years, 22M/12F) were selected from the Parkinson's Progression Markers Initiative public database that were scanned using identical imaging parameters. Only those subjects were chosen for whom the α-syn levels were measured in a CSF sample within three months of imaging. CSF levels of α-syn serve as excellent surrogates for brain levels of α-syn. ***Data:*** T1-weighted MPRAGE GRAPPA. Sagittal images were acquired on 3T (Siemens) with TR/TE = 2300/2.98 ms, TI = 900 ms, resolution=1mm^3 isotropic. Resting state BOLD fMRI. Echo-planar imaging parameters were TR/TE = 2400/25 ms, resolution = 3.29 mm^3 isotropic, 210 dynamics. CSF-α-syn values (pg/ml) were noted from the database. ***Analysis:*** All T1-weighted (T1w) data were registered to a standard 2 mm MNI template using FSL-FLIRT[3]. The anatomical images were segmented into gray matter, white matter, and CSF using FSL-FAST[4]. Total gray matter volume was calculated in FSL. BOLD data was first registered to the T1w images and then to the 2 mm MNI atlas. Motion correction of BOLD data was performed using MCFLIRT. Resting state connectivity was evaluated using seed-to-voxel analysis in the Conn (14.n) toolbox[5]. fMRI data was smoothed using a 7 mm kernel and corrected for baseline drift. Physiological noise was corrected using the CompCor[6] algorithm with three principal components from white matter and CSF each. The data was filtered using 0.008-0.09 Hz passband. Age and CSF measures were centered and scaled using a generalized linear model (GLM) analysis. To account for cortical atrophy, total gray matter volume was also included as a regressor in the GLM model. The left and right OFC, DLPFC, and ACC were chosen as ROIs from the WFU Pickatlas for connectivity analysis. Relation between CSF-α-syn on functional connectivity strength was evaluated while correcting for age and gray matter differences. A voxel wise threshold of 0.05 was applied followed by a FDR correction with a cluster level threshold of p=0.05. Two sided tests for positive and negative effects were performed and Spearman's correlations (ρ) were calculated.

RESULTS: The mean CSF-α-syn levels in the 36 subjects was 1698±790 pg/ml. Mean gray matter volume was 142236±6193 mm^3 and showed a trend for inverse correlation with CSF-α-syn levels (ρ = -0.32, p = 0.06). No significant correlation was detected between age and CSF-α-syn. ***OFC:*** High CSF-α-syn was associated with low connectivity in the bilateral motor regions and the inferior occipital cortex (**Figures 1a and 1b**). ***DLPFC*** *(images not shown):* High CSF-α-syn was associated with high connectivity with bilateral posterior cingulate (ρ = 0.39, p <0.05), occipital (ρ = 0.39, p <0.05) and perirhinal cortex (ρ = 0.48, p <0.005) and with low connectivity with the ACC (ρ = -0.44, p <0.01). ***ACC*** *(images not shown):* High CSF-α-syn was associated with high connectivity of ACC with the left temporal cortex (ρ = 0.52, p <0.005).

DISCUSSION: High CSF-α-syn is associated with decreased connectivity in the executive control network and sensory cortex likely due to the preferential degeneration of projection neurons and coincident Lewy Bodies in these regions. Loss of cholinergic neurons may result in a cholinergic imbalance in the posterior regions and alter connectivity of the DLPFC and ACC with the posterior regions to initiate compensatory mechanisms. Whether the connectivity was significantly different from controls or if similar trends would be observed in controls has not been ascertained yet and will be assessed in the future. Lateralized hemispheric difference will also be evaluated by considering the left and right side ROIs separately.

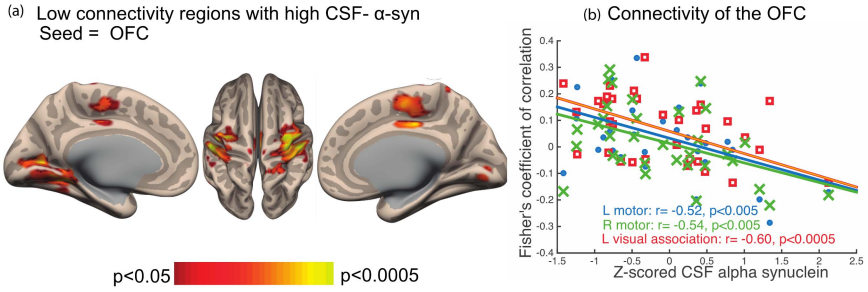

Figure 1(a)*: Cluster wise thresholded map of three clusters showing low connectivity to the OFC with high CSF-α-syn levels; L Motor, R Motor, and the bilateral visual cortex. Negative correlations for these regions are depicted in blue circles, red squares, and green crosses respectively in* ***(b)****.*

CONCLUSION: This study identified neural networks that are likely to be associated with pathologic progression of Parkinson's disease, and illustrates alterations of functional connectivity in the presence of varying CSF α-syn.

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