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Brain Metabolic Changes Underlying Symptoms in Primary Progressive Aphasia

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Background: Primary progressive aphasia (PPA) is a syndrome of progressive language impairment caused by neurodegenerative disease (Mesulam, 1982). Using resting state functional magnetic resonance imaging, we have shown that connectivity between three language network regions (inferior frontal gyrus, middle temporal gyrus, and anterior temporal lobe) is decreased in PPA. Furthermore, we demonstrated selective connectivity disruptions corresponding to grammar, repetition, naming, and word comprehension deficits (Bonakdarpour et al., 2017 & 2019). While we established the relationship between cortical thinning and resting connectivity changes, the contribution of brain metabolic changes to PPA symptoms remained to be investigated. Using Fluorodeoxy-glucose positron emission tomography (FDG-PET), other groups have previously shown that these same regions also exhibit hypometabolism (Rabinovici et al., 2014). However, the relationship between hypometabolism and PPA symptoms has not been well determined. The current investigation sought to determine changes in brain metabolism and their correlations with aphasic symptoms in PPA.

Methodology: Twenty-seven PPA right-handed individuals (14 female, average age 67), and 11 demographically matched healthy controls participated in this study. Diagnosis of PPA subtype was made by clinical consensus using established criteria (Mesulam et al, 2009). FDG-PET scans were performed for each participant, where fluorescently dyed glucose uptake was detected using PET via a Siemens Biograph TruePointTreV PET-CT system. Participants additionally underwent a battery of language assessment behavioral testing, including Northwestern Anagram Test for grammar, Peabody Picture Verbal Test for word comprehension, Boston Naming Test for picture naming, and Western Aphasia Test repetition subtest for repetition. Scan images were preprocessed using Statistical Parametric Mapping 12 (SPM12) software. Metabolic differences between control and PPA participants were compared via t-test. SPM12 was also used to perform a regressionanalysis on PPA participant metabolism data using behavioral scores as regressors to determine regional hypometabolism correlation to behavior.

Results: Visualization of t-test results ($p<0.001$, uncorrected) showed patterns of hypometabolism unique to each PPA subtype: these included hypometabolism in the left inferior frontal gyrus (IFG) and premotor regions for agrammatic PPA, left temporoparietal junction for logopenic PPA, and left anterior temporal lobe (ATL) for semantic PPA. Post hoc regression analysis found areas of regional hypometabolism correlated with decreased behavioral scores ($p<0.001$). Deficits in naming and word comprehension were found to correlate with decreased metabolism in the ATL.

Decreased grammar scores correlated with decreased metabolism in IFG. We did not find a significant relationship between repetition and hypometabolism.

Conclusion: Hypometabolism by PPA subtype aligns with previously observed decreases in functional connectivity. Hypometabolic correlations with behavioral scores are found in anatomic regions with known corresponding behavioral function, with symptoms of agrammatism linked to left frontal regions involved in language production and naming and word comprehension linked to the temporal tip. These results also suggest that decreased connectivity between language regions could partly be due to decreased brain activity in those areas. Our future investigation will focus on determining how much factors such as atrophy (cortical thinning), brain metabolism, and decrease brain connectivity, contribute to patients' symptoms. Findings will help us better understand the underlying causes of symptoms in PPA.

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