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Psychosis in Neurodegenerative Disease: Associations with Structural Brain Networks and Neuropathology

Understanding the biological foundations for psychosis has the potential to make treatments more precise, individualized, and effective. Psychosis occurs in a subset of patients with every major neurodegenerative disease (NDG). We compared prevalence rates of psychotic symptoms in a large autopsy-based cohort to systematically identify differences in nature or content of psychosis. We then analyzed how specific psychotic symptoms correspond to focal changes in structural gray matter morphology. We studied 372 patients with autopsy-confirmed NDG, characterizing the specific psychosis content subtype and frequency via retrospective chart review. Patients included 111 with Alzheimer's disease (AD), 59 with LBD and concomitant AD (LBD/AD), 133 with frontotemporal lobar degeneration (FTLD) with tau inclusions (including progressive supranuclear palsy, corticobasal degeneration, or Pick's neuropathology), and 69 with FTLD-TDP, including Types A-C. Patients underwent T1 MP-RAGE structural magnetic resonance imaging scanning, and voxel-based morphometric (VBM) analysis (SPM12 with VBM12 toolbox default parameters) to examine brain-behavior correlations of psychotic features. Of 372 patients, 111 had psychosis during their disease. Hallucinations were significantly more common in patients with LBD/AD pathology (Braak Parkinson stage 5-6 LBD), including misperception, peripheral hallucinations, hallucinations that moved, hallucinations of people/animals/objects, delusions regarding a place or misidentification, and the feeling of a presence. Patients with FTLD-TDP were significantly more likely to experience delusions, including paranoia, delusions of misidentification, and self-elevating delusions such as grandiosity and erotomania, compared to patients with AD and FTLD-tau. T-values for structural VBM ranged from 3.5 – 5.6, corrected for family-wise error at $p<0.05$, determined via permutation. Patients with paranoid delusions were more likely to have atrophy in reward circuits, including the nucleus accumbens, rostral caudate, and subgenual cingulate compared to patients with the same pathologies without delusions. Patients with delusions of misidentification were significantly more likely to have structural damage to the fusiform gyrus. The nature and content of psychosis meaningfully assist prediction of underlying NDG pathology. Also, in the context of NDG, damage to brain structures involved in reward processing (nucleus accumbens) and resolving ambiguity during decision making (basal ganglia) predicts psychotic symptoms. This study emphasizes the diagnostic importance of carefully characterizing patients' psychoses during a dementia workup to predict underlying neuropathology. It also raises the question of the degree to which psychosis arises through combined neurochemical and neural network mechanisms.