Neuroanatomical signature of medical conditions and medication use identifies prodromal risk factors of Alzheimer's and Parkinson's disease.

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Objectives. We sought to leverage brain MRI to **identify novel prodromal risk factors** of Alzheimer's and Parkinson's disease. We tested whether the **neuroanatomical signatures of medical conditions/medications** were associated with early disease stages of Alzheimer's and Parkinson's disease.

Methods. We leveraged MRI data from 36,000 adults in the UK Biobank, together with detailed disease codes (lifetime ICD-10 [International Classification of Diseases – 10th edition]) from hospital and primary care records, as well as self-reported regular medications (ATC [Anatomical Therapeutic Chemical] codes). We utilised Best Linear Unbiased Predictors to identify the neuroanatomical signature associated with each ICD-10 or ATC code, which we applied to Alzheimer's and Parkinson's databases that included individuals in early disease stages (prior to diagnosis of Alzheimer's dementia or Parkinson's disease). We tested whether each neuroanatomical signature was associated with disease risk and followed up on significant associations using Mendelian Randomisation to generate causal hypotheses about the disease aetiology.

Results. We found 93 associations with Alzheimer's disease, and 20 with Parkinson's disease (after Bonferroni multiple testing correction). Our results implicated known risk factors for AD (e.g., lipid-modifying agent, mood disorders, injuries to the head or diabetes) and PD (e.g., injuries to the neck, influenza, and pneumonia) via brain regions previously implicated in the disease progression (e.g., hippocampus, amygdala, entorhinal gyrus for AD, thalamus and superior temporal gyrus for PD). We identified several novel potential risk factors related to inflammation and corticosteroids, renal failure, or conditions affecting women's health (Alzheimer's); digestive and epilepsy (Parkinson's). Mendelian randomisation further identified two possible causal pathways to Alzheimer's disease, including one linking the STX6 gene to dermatological drug use (D11) and the neuroanatomical signature of the entorhinal gyrus.

Conclusions. This study **breaks new ground** in understanding the link between health events and neurodegenerative risk by leveraging brain MRI from 36,000 UK Biobank participants. Beyond confirming established factors like head injuries and diabetes, we uncovered **novel, potentially modifiable risk pathways**, such as the role of dermatological drugs/conditions and the STX6 gene in Alzheimer's pathology. By integrating neuroimaging with genetic and pharmacological data, we **clarify how health events shape may brain vulnerability**, offering actionable insights for risk reduction. This work **highlights** the **power of brain MRI to reveal hidden connections between health, medication, and long-term disease risk**.