Rare neurodegenerative disorders PSP and CBD reveal differential regional neuroinflammatory signatures in the human post-mortem brain.

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INTRODUCTION

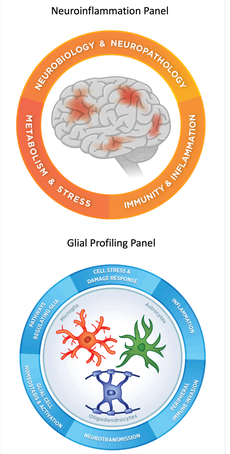
The concept that neuroinflammation plays an important role in the pathogenesis of neurodegenerative conditions such as Alzheimer's and Parkinson's disease has gained traction in recent years, culminating in trials of immunotherapies in these conditions.

Far less is known about the role of inflammation in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), two rare "Parkinson-Plus" neurodegenerative tauopathies that currently have no effective treatments.

METHODS

Here we sought to determine if neuroinflammation plays a role in pathogenesis of both PSP and CBD relative to age-matched controls in the prefrontal cortex (PFC) and putamen (PUT) in post-mortem brain tissue.

We report on gene expression differences from 10 PSP, 10 CBD, and 10 age- and sex-matched controls using the nCounter® Neuroinflammation and Glial panels (~1,500 genes).



CONCLUSION & NEXT STEPS

Together these data show that neuroinflammation plays a role in the pathogenesis of both PSP and CBD, but that inflammation is more localised to the PFC of the CBD cohort and more widespread in PSP. Validation using GeoMx® Digital Spatial Profiling with the whole transcriptome atlas is underway. This will enable us to better understand differences in disease-specific regional signatures, including covariates such as tau localisation.

RESULTS

Differential gene expression analysis revealed regional differences between disease tissue and controls and within the disease cohorts (PSP vs. CBD). Compared to controls, inflammatory genes were upregulated in both the **putamen and PFC in the PSP cohort,** while the inflammatory signature was **only found in the PFC of the CBD brains** (Figures 1,4).

In both brain regions, cell type profiling revealed increased microglia, infiltrating macrophages and neutrophils in both CBD and PSP compared to controls. Oligodendrocyte scores were higher in the PSP PFC samples specifically. (Figure 2).

Focusing only on the most affected region in each disease, pathway analysis of the PFC revealed increased expression of immune and inflammatory pathways in the CBD cohort compared to controls. In the putamen, immune pathways were enriched in PSP vs controls, with IFN signalling and response pathways being most enriched. In both regions, the control samples were enriched for neuronal signalling pathways (Figure 3).

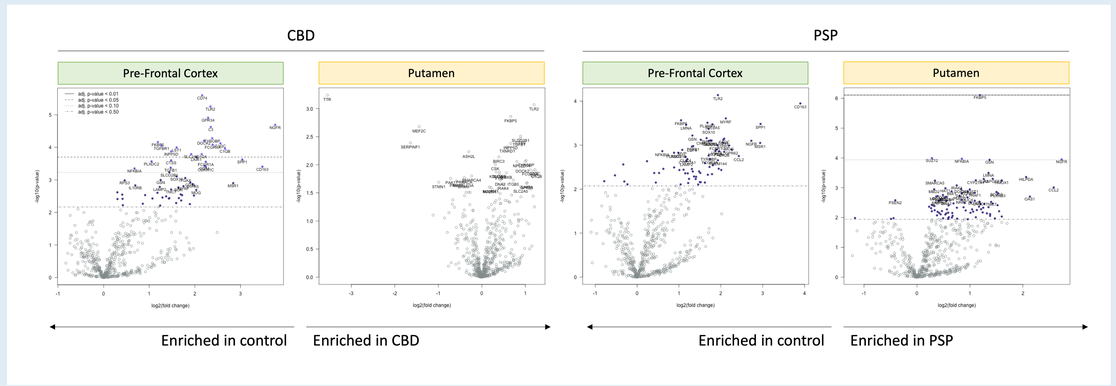


Figure 1. Volcano plots comparing differential expression in brains from CBD (left) and PSP (right) pre-frontal cortex and putamen with controls.

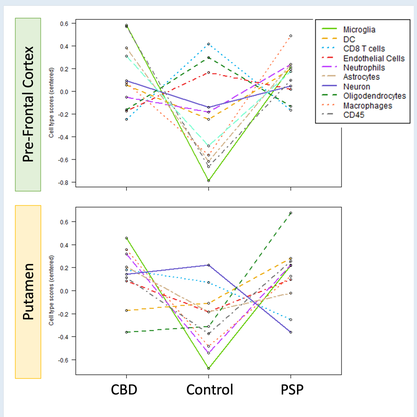


Figure 2. Cell type signature scoring in pre-frontal cortex (top) and putamen (bottom).

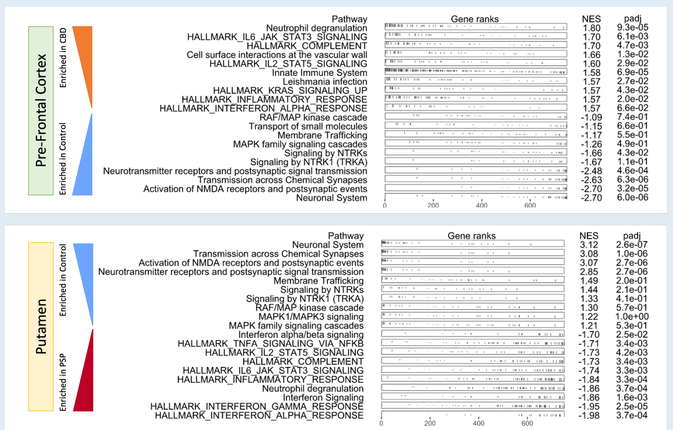
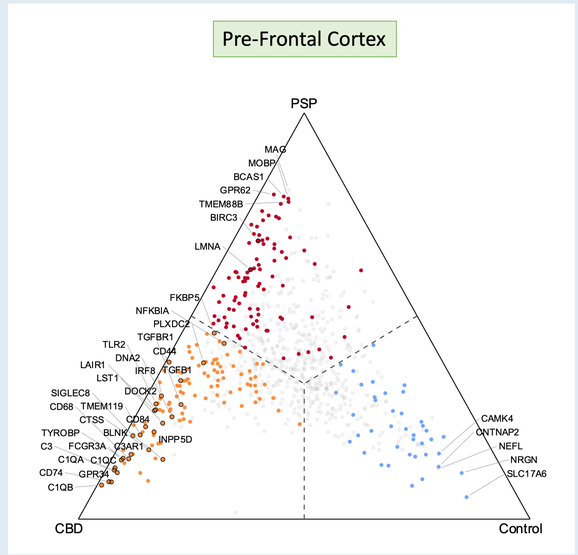


Figure 3. Gene set enrichment analysis of the most-affected region for each disease compared to controls. NES = normalised enrichment score.



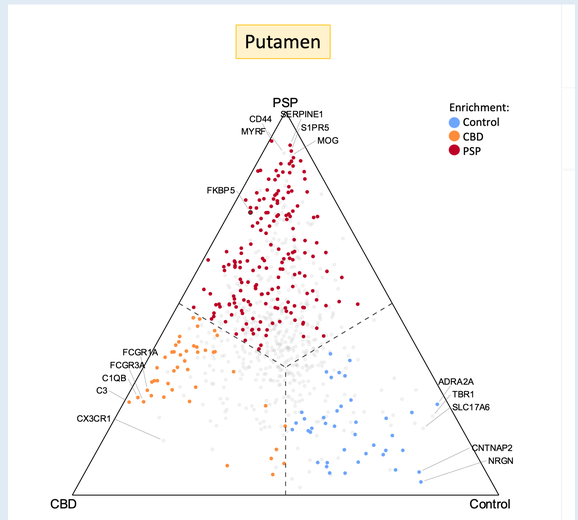


Figure 4. Three way differential expression plots for pre-frontal cortex (top) and putamen (bottom) regions displaying genes differentially expressed between control (blue), CBD (orange) and PSP (red) cohorts. Genes shown in colour are enriched by at least 50% with p-value<0.05.

Thank you to Nanostring Technologies for generously supporting this project

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