IN BRIEF

COVID-19

COVID-19 database launched in the USA

The US National Institutes of Health has created the COVID-19 Neuro Databank/Biobank (NeuroCOVID), a database to enable recording and tracking of neurological involvement in COVID-19. Health-care providers in the USA can submit anonymized information online about neurological symptoms, comorbidities, disease course, complications, sequelae and outcomes of patients with COVID-19. Biospecimens collected for research or clinical management can also be provided to the biobank.

ORIGINAL ARTICLE National Institutes of Health. NIH launches database to track neurological symptoms associated with COVID-19. *NIH* https://www.nih.gov/news-events/news-releases/nih-launches-database-track-neurological-symptoms-associated-covid-19 (2021)

ALZHEIMER DISEASE

Tau inclusion turnover could be a target

Tau inclusions are dynamic structures that turnover every few weeks, according to new research. Croft et al. used long-term optical pulse labelling to study the formation of tau inclusions in organotypic brain slice culture models. Tau inclusions initially formed within hours to a few days but were then renewed regularly with an initial half-life of ~1 week, which lengthened to ~3 weeks over time. The finding raises the possibility of therapeutic strategies that involve interruption of the renewal process to prevent further formation of tau inclusions.

ORIGINAL ARTICLE Croft, C. L. et al. Photodynamic studies reveal rapid formation and appreciable turnover of tau inclusions. *Acta Neuropath.* https://doi.org/10.1007/s00401-021-02264-9 (2021)

PARKINSON DISEASE

RNA biomarkers of Parkinson disease

Regulatory circular RNAs (circRNAs) could be diagnostic biomarkers of Parkinson disease (PD), a new study has shown. Expression of 87 circRNAs in blood mononuclear cells from 60 patients with idiopathic PD was analysed, and 6 were found to be downregulated in patients with PD compared with healthy controls. Several of the proteins that these circRNAs bind to, and therefore regulate, are associated with neurodegeneration, including fused in sarcoma (FUS) and TAR DNA-binding protein 43 (TDP43), so their dysregulation could also offer insight into the molecular pathways affected in PD.

ORIGINAL ARTICLE Ravanidis, S. et al. Differentially expressed circular RNAs in peripheral blood mononuclear cells of patients with Parkinson's disease. *Mov. Disord.* https://doi.org/10.1002/mds.28467 (2021)

HUNTINGTON DISEASE

Neurodevelopment affected by HD mutation

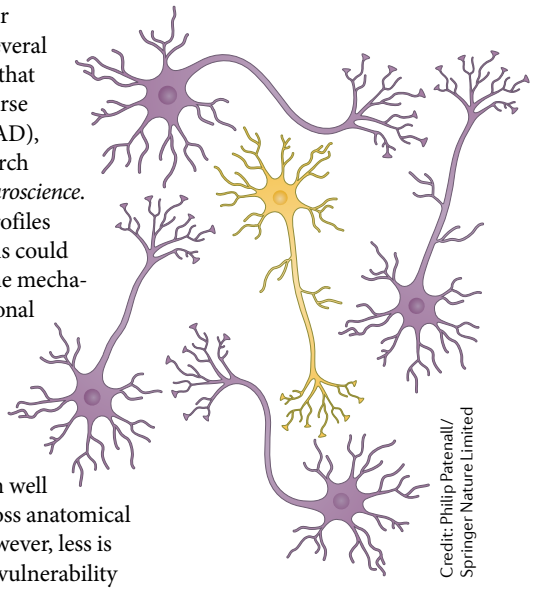
Retrospective analysis of brains from people with Huntington disease (HD) has shown that developmental malformations are more common among people with HD than among controls without HD. People with HD were 6.4–8.2-fold more likely to have malformations than controls; the most common malformations were periventricular nodular heterotopias. Malformations were associated with heterozygous CAG expansions of 40–52 repeats in the *HTT* gene and were more common among women. The findings provide evidence that the repeat expansion in *HTT* that causes HD also affects neurodevelopment.

ORIGINAL ARTICLE Hickman, R. A. et al. Developmental malformations in Huntington disease: neuropathologic evidence of focal neuronal migration defects in a subset of adult brains. *Acta Neuropath.* https://doi.org/10.1007/s00401-021-02269-4 (2021)

ALZHEIMER DISEASE

Markers of vulnerable neurons identified in Alzheimer disease

The transcription factor RORB is a marker of several populations of neuron that are lost early in the course of Alzheimer disease (AD), according to new research published in *Nature Neuroscience*. The gene expression profiles of these cell populations could provide insights into the mechanisms of selective neuronal vulnerability in AD.



Credit: Philip Patenall/ Springer Nature Limited

The tendency for some neurons to die early in the course of AD and for others to survive longer has been well characterized at the gross anatomical and network levels; however, less is known about selective vulnerability at the level of individual cells. The new study was led by Lea Grinberg and Martin Kampmann, who aimed to identify molecular signatures of vulnerable cell populations in AD.

The researchers analysed post-mortem samples of the entorhinal cortex (EC) and superior frontal gyrus (SFG) from ten male individuals with varying degrees of tau pathology, as determined by Braak staging. They performed single-nucleus RNA sequencing (snRNAseq) on each sample and used clustering analysis to identify cell-type populations.

"Using a single-cell approach was essential, because we were looking for the 'needle in the haystack' — the specific neuronal subpopulations that are most vulnerable to disease," explains Kampmann.

Compared with Braak stage 0, the relative abundance of excitatory neurons was reduced at Braak stages 2 and 6 in the EC, and at Braak stage 6 in the SFG. Although these changes were not statistically significant, they were consistent with previous data.

"For many decades, we have known that excitatory neurons located in layer II of the entorhinal cortex are the first cortical neurons to accumulate tau pathology," explains Grinberg. "However, even neurons within layer II show different levels of vulnerability."

The researchers performed subclustering of the excitatory neuron population and identified 9 subpopulations in the EC and 11 in the SFG. Three EC subpopulations showed a statistically significant ~50–60% reduction in relative abundance at Braak stage 2 compared with Braak stage 0, indicating depletion early in the disease course. Compared with the other clusters, these vulnerable subpopulations specifically expressed *RORB*.

The researchers performed immunofluorescence for RORB and phosphorylated tau (p-tau) on EC samples from a new cohort of 26 individuals with AD. p-Tau was detected more often in RORB-positive neurons than in RORB-negative neurons, suggesting that depletion of RORB-positive neurons is caused by tau pathology.

"We identified specific neuronal subtypes in the human EC that are lost early in AD," says Kampmann. "The differentially expressed genes in these neurons now provide us with mechanistic hypotheses for the causes of their vulnerability."

Sarah Lemprière

ORIGINAL ARTICLE Leng, K. et al. Molecular characterization of selectively vulnerable neurons in Alzheimer's disease. *Nat. Neurosci.* https://doi.org/10.1038/s41593-020-00764-7 (2021)