IN BRIEF

ALZHEIMER DISEASE

Tau seeding starts early in the entorhinal cortex

In Alzheimer disease (AD), tau pathology has a characteristic pattern of progression that corresponds to different disease stages and reflects neurodegenerative damage, but the region in which tau pathology first takes root has been unclear. Immunostaining of brain tissue from patients with AD first detects neurofibrillary tangles of phosphorylated tau in the locus coeruleus, but evidence suggests that this pathology is preceded by tau aggregation in the transentorhinal and entorhinal cortices (TRE–EC). A new study used a sensitive cellular biosensor assay to detect submicroscopic aggregates of tau, representing tau seeding activity, in post-mortem brain tissue from individuals with AD. The team found that tau seeding activity was evident earlier in the TRE–EC than in the locus coeruleus, suggesting that the TRE–EC and not the locus coeruleus represents the source of pathological tau seeding in AD.

ORIGINAL ARTICLE Kaufman, S. K. et al. Tau seeding activity begins in the transentorhinal/entorhinal regions and anticipates phospho-tau pathology in Alzheimer's disease and PART. *Acta Neuropathol.* https://doi.org/10.1007/s00401-018-1855-6 (2018)

MULTIPLE SCLEROSIS

New biomarker predicts disability in MS

The heterogeneity of multiple sclerosis (MS) makes prognosis and prediction of progression to disability problematic. However, research has now found that the ratio of different classes of immunoglobulin light chain in the cerebrospinal fluid (CSF) predicts progression to disability in patients with MS. The researchers detected an increased ratio of immunoglobulin κ:λ free light chains in the CSF of patients with MS compared with controls, and a high ratio was associated with a low Expanded Disability Status Scale score at follow-up 5 years after the diagnostic lumbar puncture. The change in immunoglobulin ratio resulted from the selective expansion of CSF plasmablasts expressing the κ class of immunoglobulin light chain. The κ:λ free light chain ratio could represent a useful early predictor of disability and facilitate the stratification of patients with MS in clinical trials.

ORIGINAL ARTICLE Rathbone, E. et al. Cerebrospinal fluid immunoglobulin light chain ratios predict disease progression in multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* https://doi.org/10.1136/jnnp-2018-317947 (2018)

PARKINSON DISEASE

Deep brain stimulation boosts motor connectivity

Levodopa and deep brain stimulation (DBS) therapies have similar clinical benefits in patients with Parkinson disease (PD), but new research suggests that they exert very different effects on the functional architecture of the brain. In the new study, investigators carried out functional MRI in 13 patients with PD who had severe motor symptoms and dyskinesia. The individuals were imaged in the presence or absence of levodopa treatment and before and after the implantation of DBS electrodes into the subthalamic nucleus. Levodopa and DBS elicited a similar alleviation of symptoms, but DBS alone resulted in a substantial increase in connectivity within the left and right motor cortices and between the motor cortices and the cerebellum and thalamus. Further study of these changes in connectivity might reveal the exact mechanism by which DBS exerts its therapeutic effect in PD, which could enable the refinement and improvement of this procedure.

ORIGINAL ARTICLE Mueller, K. et al. Brain connectivity changes when comparing effects of subthalamic deep brain stimulation with levodopa treatment in Parkinson's disease. *Neuroimage Clin.* https://doi.org/10.1016/j.nicl.2018.05.006 (2018)

STROKE

Selective neuronal loss could limit penumbral rescue after stroke

Reperfusion therapies have transformed the therapeutic landscape for acute ischaemic stroke, but functional outcomes are still suboptimal in many patients. To address this issue, investigators have turned their attention to the penumbra — that is, the potentially salvageable brain tissue surrounding the ischaemic core. In a new study, Jean-Claude Baron and colleagues have shown that penumbral tissue rescued from impending infarction by reperfusion therapies is not intact and exhibits selective neuronal loss (SNL) that might be targeted therapeutically to enhance functional recovery.

The new study, reported in *Brain*, was prompted by previous research in rat models of stroke, which found SNL in association with microglial activation in salvaged penumbral tissue. "The idea was to see whether we could also demonstrate SNL and microglial activation in the rescued penumbra in humans and, if so, whether they were closely associated, as in rats," explains Baron.

The study included 16 patients with acute middle cerebral artery stroke, all of whom had evidence of salvaged penumbral tissue on the basis of CT perfusion data, neurological improvement in the first 24 h after the stroke event and normal follow-up MRI. The patients underwent PET with the tracers ^{11}C-flumazenil and ^{11}C-PK11195, which detect neuronal loss and microglial activation, respectively.

The researchers were able to confirm the existence of SNL in the salvaged penumbra. Surprisingly, however, microglial activation was found to be minimal or non-existent in this tissue.

The close association between microglial activation and SNL in the rat penumbra has led to suggestions

EPILEPSY

Drop seizures cut by cannabidiol

Cannabidiol treatment reduces seizure frequency in patients with Lennox–Gastaut syndrome, a new phase III, double-blind placebo-controlled trial has confirmed. Investigators found that a low dose of cannabidiol cut seizure frequency by more than a third.

The Lennox–Gastaut syndrome is a severe type of childhood epilepsy characterized by abnormal EEG signs, cognitive impairment and disabling drop seizures that can result in serious injury. Although several treatments have been approved for the Lennox–Gastaut syndrome, currently available agents fail to halt seizures in most patients.

"There has been interest in cannabis-based therapies for epilepsy dating back more than a millennium," explains Orrin Devinsky, lead author of the new trial. "More recently, cannabidiol was shown to be effective in a number of animal models of epilepsy. Based on these observations, I reached out to GW Pharmaceuticals to explore open-label and then randomized trials of cannabidiol for epilepsy."

The team recruited 225 individuals with the Lennox–Gastaut syndrome from 30 centres around the globe. After a 28-day baseline period, participants were randomly assigned to receive 10 mg or 20 mg per kg of body weight of oral cannabidiol solution daily or a matching placebo for 14 weeks. Therapy was given in addition to each patient's pre-existing antiepileptic medication routine.

The median reduction in drop seizure frequency from baseline was significantly greater in the groups who received cannabidiol (41.9% for the 20 mg group and 37.2% for the 10 mg group) than in the placebo group (17.2%). Importantly, adverse effects were reported in 94% of patients who received the high 20 mg dose of cannabidiol, but were reported in 84% of patients who received the low 10 mg dose, compared with 72% of those who received placebo.