IN BRIEF

MOTOR NEURON DISEASE

Ultrasound success removes barriers to targeted drug delivery in amyotrophic lateral sclerosis

Magnetic resonance-guided focused ultrasound (MRgFUS) can be used to transiently and focally permeabilize the blood–brain barrier (BBB), thereby enabling targeted delivery of therapeutic agents into specific brain regions. In a new study, researchers demonstrated that MRgFUS safely and reversibly permeabilized the BBB in eloquent primary motor cortex in four patients with amyotrophic lateral sclerosis (ALS). Opening of the BBB was confirmed by MRI detection of gadolinium leakage into the parenchyma at the target site. Previous studies have shown that MRgFUS can be used in humans to safely open the BBB in non-eloquent areas of cortex, but the new study indicates that the approach could be extended to eloquent cortex. In ALS, therapeutics would ideally be targeted specifically to the motor cortex, so this work provides the foundation for combining MRgFUS with therapeutic agents for targeted drug delivery in the condition.

ORIGINAL ARTICLE Abrahao, A. et al. First-in-human trial of blood–brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound. *Nat. Commun.* **10**, 4373 (2019)

DEMENTIA

Prodromal frontotemporal dementia associated with changes in ventricular volume

Abnormal increases in ventricular volumes occur in the prodromal phase of genetic frontotemporal dementia (FTD), a recent study has indicated. The study included individuals from families with genetic FTD who were enrolled in the Genetic Frontotemporal Dementia Initiative. The participants included 46 presymptomatic people with mutations in *MAPT*, *PGRN* or *C9orf72*, and 56 people from the same families who carried no FTD-associated mutations. Analysis of MRI data obtained at baseline and 1 year later showed that total ventricular volumes were larger in mutation carriers than in non-carriers up to 4 years before estimated symptom onset. The investigators say that their findings support the use of ventricular volume as an index of symptom onset in people with FTD-associated mutations, but long-term follow-up is needed to confirm this conclusion.

ORIGINAL ARTICLE Tavares, T. et al. Ventricular volume expansion in presymptomatic genetic frontotemporal dementia. *Neurology* https://doi.org/10.1212/WNL.0000000000008386 (2019)

NEUROPSYCHIATRIC DISORDERS

Protein processing dysfunction in schizophrenia

Expression of proteins involved in the unfolded protein response (UPR) is altered in schizophrenia, according to new research. On the basis that protein processing and subcellular targeting are abnormal in schizophrenia, Pitna Kim and colleagues looked for dysregulation of the UPR, which normally maintains cellular homeostasis by preventing a build-up of unfolded or incorrectly folded proteins. The investigators measured levels of the initial stress sensors in the UPR and their downstream targets in the brains of people with schizophrenia and in controls. Levels of some initial sensors were altered, as were levels of some downstream targets. The findings indicate that dysregulation of the UPR and consequent alterations in protein processing contribute to the pathogenesis of schizophrenia.

ORIGINAL ARTICLE Kim, P. et al. Dysregulation of the unfolded protein response (UPR) in the dorsolateral prefrontal cortex in elderly patients with schizophrenia. *Mol. Psychiatry* https://doi.org/10.1038/s41380-019-0537-7 (2019)

MULTIPLE SCLEROSIS

Putting multiple sclerosis on the genomic map

A new study from the International Multiple Sclerosis Genetics Consortium (IMSGC) has used a large set of genetic and genomic data to construct a 'genomic map' of susceptibility to multiple sclerosis (MS). The research team reported novel susceptibility variants for MS and highlighted the potential contributions of various immune cell populations to MS susceptibility.

"We go beyond a simple genetic map that identifies the single nucleotide polymorphisms (SNPs) associated with MS," explains corresponding author Philip De Jager, who is based at Columbia University, New York, USA. "We used a host of data to prioritize the gene(s) affected by each variant, to identify which cell types express an excess of susceptibility genes, and to assemble the variants into groups that may work together to disrupt immune pathways in a way that contributes to MS onset."

The IMSGC analysed genetic and genomic data from 47,429 individuals with MS and 68,374 unaffected controls. The analysis uncovered 233 genetic variants that were associated with increased susceptibility to MS. Of these variants, 32 resided within the MHC — a chromosomal region that has already been strongly implicated in MS — and one was located on the X chromosome. As the authors point out, the X-linked variant is intriguing because MS disproportionately affects women.

Many of the non-MHC autosomal variants were located in non-coding regions of the genome, and the researchers identified 551 genes that were likely to be influenced by these variants. The affected genes could be

ALZHEIMER DISEASE

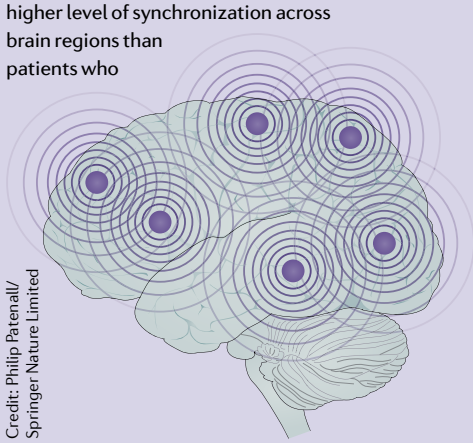
Changes in network synchronization herald Alzheimer Disease

Changes in synchronization of activity across brain regions accompany conversion from mild cognitive impairment (MCI) to Alzheimer disease (AD), according to a new study published in *Brain*. The findings could lead to better prediction of outcome for patients with MCI.

Magnetoencephalography (MEG) studies have previously identified hypersynchronization of activity across networks of brain regions in patients with MCI who go on to develop AD. This altered synchronization is thought to reflect synaptic dysfunction. The new study, led by Sandra Pusil, built on previous findings by performing repeat MEG recordings in the same patients to investigate the network changes associated with conversion to AD.

Pusil and colleagues performed a baseline MEG recording followed by 3 years of cognitive and clinical assessments in 145 patients with MCI. Twenty-seven patients progressed to a diagnosis of probable AD during the 3 years and underwent a second MEG recording. Patients who did not progress to AD underwent repeat MEG at the end of the study.

In the baseline MEG recordings, the patients who later developed AD had a higher level of synchronization across brain regions than patients who



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