and placebo analgesia. Placebo analgesia can affect almost all placebo-controlled clinical trials and the effect might sometimes exceed that of potent painkillers, including opioids. Vachon-Pressau and colleagues[8] reported the first large-scale brain imaging study using a double-blind design aiming to investigate the brain areas involved in placebo analgesia in 63 patients with chronic low back pain. Patients were randomly assigned into three groups to receive placebo, no treatment, or active analgesics. Patients receiving placebo had higher self-reported pain relief than those with no treatment and this was predicted by several psychological traits measured at baseline, such as increased emotional awareness. Authors further found that the response to placebo was predicted by modifications of the structure or function of key brain areas in pain modulation, encompassing the anterior cingulate cortex, sensorimotor cortex, prefrontal cortex, and periaqueductal grey—which play a role in the response to active analgesics—but also by brain characteristics not previously associated with analgesia, such as subcortical volume asymmetry. Thus, placebo responses in patients with low back pain were partially predictable by combining psychological and brain imaging models. Whether these models will be able to predict placebo responders in future clinical trials remains to be established.

Overall, these translational pain studies in 2018 have contributed to our understanding of pain and analgesia. We hope that they will also advance the therapeutic management of chronic pain, which is still a crucial unmet medical need.

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Neurology met sleep medicine in 2018

In 2018, several mechanistic and interventional studies have illuminated our knowledge at the intersection between clinical neurology and sleep medicine. Narcolepsy due to hypocretin deficiency is a primary sleep disorder that can lead to excessive daytime sleepiness, and in which humoral immunological responses against hypocretin neurons are suspected. A study reported the detection of cytotoxic CD8+ T cells specific for hypocretin neurons in both peripheral blood and CSF in some patients with narcolepsy.[1] This finding reinforced the hypothesis of an autoimmune pathology in narcolepsy and identified these T cells as a potential diagnostic or prognostic biomarker. Regarding plasticity of hypocretin neurons, opioid effects were reported in both humans and mice. Hypocretin neurons were protected from neuronal death by long-term morphine administration in wild-type mice,[2] and neurogenesis was not the mechanism of hypocretin neuron protection. Additionally, morphine administration reduced cataplexy attacks in narcoleptic mouse models. Of relevance, about 54% more hypocretin neurons were found in five people with heroin addiction post-mortem than in control brains.[2] This translational finding indicates pathways to protect or even restore hypocretin function.

Two clinical randomised trials[3,4] tested the safety and efficacy of sodium oxybate for hypersomnolence and both trials reported positive results. In a randomised trial of 12 patients with Parkinson's disease who had excessive daytime sleepiness, sodium oxybate significantly reduced sleepiness compared with placebo, with a moderate


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effect on mean sleep latency in the objective multiple sleep latency test (increase of 2·9 min [95% CI 2·1 to 3·8]; p=0·002) and the subjective Epworth Sleepiness Scale score (–4·2 points [95% CI –5·3 to –3·0]; p=0·001).[3] Moreover, sodium oxybate enhanced sleep itself as measured by increased slow-wave sleep duration (increase of 72·7 min [95% CI 55·7 to 89·7]; p<0·001). In a second multicentre, open-label trial of 63 paediatric patients with narcolepsy who were taking sodium oxybate and then either transferred to placebo or continued on the drug for 2 weeks, patients continuing taking sodium oxybate exhibited significant improvements in both sleepiness and cataplexy compared with patients who were given placebo.[4] Additionally, patients who were withdrawn from sodium oxybate had a greater increase in the frequency of cataplexy attacks (median increase of 12·7 attacks per week) compared with patients continuing sodium oxybate (median increase of 0·3 attacks per week).[4] The safety of sodium oxybate in paediatric narcolepsy was consistent with that observed in adult patients. Notably, both studies confirmed that newly diagnosed obstructive or central sleep apnoea can occur in some patients after sodium oxybate treatment.[3,4]

Subjective daytime sleepiness and sleep-wake regulation might be features of dementia development. In elderly people without dementia, baseline excessive daytime sleepiness was significantly associated with increased amyloid β accumulation in the cingulate cortex and the parietal-precuneus lobe.[5] These findings are important because elderly patients with excessive daytime sleepiness might be more vulnerable to amyloid β-associated neurodegeneration, and early identification and treatment of the sleep abnormality might slow down the accumulation of amyloid β in the brain.[5]

Disrupted nocturnal sleep or sleep deprivation can lead to increased amyloid β concentrations in CSF and deposition in the brain,[6] but does not seem to be associated with genetic risk (APOE genotype) for Alzheimer's disease.[7] These findings on the adverse consequences of disrupted nocturnal sleep and sleep deprivation on amyloid β accumulation in the brain point towards disrupted sleep as an independent risk factor in Alzheimer's disease pathogenesis.[6,7]

Abnormal movements during REM sleep are part of the symptomatology of REM behavioural sleep disorder and can be a prodromal symptom in α-synuclein neurodegenerative diseases. A prospective case-control study compared patients with idiopathic REM behavioural sleep disorder with healthy controls and patients with Parkinson's disease using PET and SPECT to assess autonomic and dopaminergic function.[8] Patients with idiopathic REM behavioural sleep disorder had impaired enteric parasympathetic and cardiac sympathetic function compared with healthy controls. Significantly greater damage in the locus coeruleus and the putamen were also detected in patients with REM behavioural sleep disorder compared with healthy controls, although 15 (71%) of 21 patients with this sleep disorder had dihydroxyphenylalanine (DOPA) uptake within normal ranges.[8] No significant differences in the autonomic nervous system or neuromelanin signalling in the locus coeruleus were detected between patients with Parkinson's disease and those with REM behavioural sleep disorder, although patients with Parkinson's disease had significantly decreased DOPA uptake in the putamen than those with this sleep disorder (p<0·0001).[8] Although the pathology of REM behavioural sleep disorder might begin in peripheral autonomic nerves and then spread to the locus coeruleus, most patients maintain normal DOPA uptake in the putamen. REM behavioural sleep disorder can be also a prodromal symptom of dementia with Lewy bodies. Follow-up of patients with this sleep disorder showed gradual cognitive impairment (word learning and memory deficiencies) associated with later development of dementia with Lewy bodies.[9]

Restless legs syndrome is a common wake-sleep disorder resulting in impaired quality of life. Subthalamic nucleus deep-brain stimulation has been proved effective in patients with Parkinson's disease and moderate or severe restless legs syndrome.[10] 11 (50%) of 22 patients reported about a 50% improvement in restless legs syndrome and six (27%) had complete disappearance of symptoms, with efficacy sustained over 2 years.[10] This study provides clinical evidence for the efficacy of subthalamic nucleus deep-brain stimulation in patients with Parkinson's disease who have restless legs syndrome. Whether this intervention might be used in those with restless legs syndrome only is both an ethical as well as a clinical dilemma.

In an elegant physiological study in mice, glutamatergic neurons in the paraventricular thalamus were shown to have an important role in the regulation of the transition from sleep to wakefulness.[11] Neuronal projections from the nucleus accumbens and hypocretin neurons to the

paraventricular thalamus were important to maintain wakefulness, and this nucleus is now identified as a crucial brain structure in sleep-wake regulation.[11]

In summary, these 2018 studies have greatly progressed our knowledge on excessive sleepiness, cognitive health, biomarkers, and brain nuclei relevant to both sleep and wakefulness.

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Advances on neurological infections in 2018

In neurological research, the realm of infections has grown to include potential infectious causes of nervous system disorders of unknown aetiology, not only the pathogenesis of neurological infections and improvements in antimicrobial therapy, but also the use of infectious agents as vectors for gene therapy. In our view, the most important developments in this field in 2018 were related to pathogenesis and treatment.

Microbes and viruses might contribute to the onset and progression of Alzheimer's disease. A study[1] reports the construction of an integrated network of genomic, transcriptomic, proteomic, and histopathological data from three independent cohorts of patients with Alzheimer's disease via next generation sequencing of post-mortem brain tissue.[1] These data showed increased nucleic acids and proteins from human herpesvirus 6A and 7 in four brain regions of patients with Alzheimer's disease compared with healthy controls. The study showed that viral copy number was associated with modulators of the metabolism of amyloid precursor protein. The findings suggest that viral proteins might be working as transcription factors modulating genes in this disorder. However, the causative role of these viruses in the aetiology and pathogenesis of Alzheimer's disease is still highly speculative. The replication of these findings and establishment of animal models of chronic CNS dysfunction caused by herpes virus infections is now warranted.

Treatment is another important aspect of neurological infections and includes the development of a wide range of antibiotics penetrating easily into the meningeal and CNS compartments. However, acute bacterial meningitis still carries a high mortality and long-term morbidity due to delayed presentation, delayed treatment initiation, and a small number of diagnostic facilities. Thus, to improve the course of acute bacterial meningitis, early adjunctive therapeutic strategies, such as neurocritical care and treatment of brain oedema with intravenous dexamethasone, were implemented. A prospective study of 90 patients admitted to a hospital in Ethiopia with diagnosis of acute bacterial meningitis investigated short-term outcomes.[2] Causative bacteria, mainly *Streptococcus pneumoniae* or *Neisseria meningitidis*, were isolated in only 26 (29%) patients, and more than half of the 90 patients had either unfavourable outcomes (33 [37%] patients) or died (20 [22%] patients). Risk factors for increased morbidity and mortality were impaired level of consciousness, dexamethasone therapy, and fever persisting for