

SYNAPTIC PLASTICITY

Sleep calms firing rates

Experience-dependent changes in the strength of individual synapses form the basis of learning and information storage in the brain. It has been hypothesized that these changes must be offset by mechanisms that return the activity of a network to a 'set point' to prevent its destabilization. Torrado Pacheco et al. now demonstrate bidirectional homeostatic plasticity in the rat cortex and show that downward firing rate homeostasis (FRH) takes place exclusively during sleep.

Previous studies have shown that sensory deprivation, such as that resulting from surgical eye closure (monocular deprivation (MD)) causes a rapid decrease in the firing rates of cortical neurons in the contralateral hemisphere, followed by a gradual restoration of firing to baseline levels. However, evidence that such homeostatic mechanisms can work in the opposite direction to counteract potentiated neural

activity (that is, downward FRH) has been elusive.

Here, Torrado Pacheco et al. recorded from individual pyramidal neurons in rat visual cortex (V1) for 11 consecutive days. During this period, the animals underwent MD, followed by eye reopening (ER) on day 5 of MD (after firing rates had returned to baseline). The authors found that ER caused firing rates in the contralateral V1 to double within 24 hours, followed by a gradual decline to baseline levels over the next 2 days, indicating that bidirectional regulation of firing rates towards a set point takes place in V1 after experimental manipulation of sensory input.

The downward FRH that occurred after ER was unaffected when the animals were treated with an NMDA receptor antagonist, suggesting that homeostatic, rather than Hebbian, plasticity mechanisms underlie the return of baseline

firing rates. Indeed, the authors found evidence for the involvement of synaptic scaling, a well-known form of homeostatic plasticity in which synaptic strengths are adjusted in a uniform manner to stabilize network activity. An examination of miniature excitatory postsynaptic currents (mEPSCs; an indicator of synaptic strength) in acute slices of V1 collected in the days after ER revealed a decrease in mEPSC amplitudes that coincided with the period of downward FRH and demonstrated properties consistent with synaptic scaling.

One much-discussed theory, the 'synaptic homeostasis hypothesis', suggests that a key function of sleep is to enable the homeostatic downregulation of synaptic strength and neural activity, in order to counteract a net potentiation of these properties during periods of wakefulness. The authors were here able to combine their chronic electrophysiological recordings with measurements of arousal to investigate whether downward FRH is gated by an animal's sleep-wake state. They discovered that downward

“upward and downward homeostatic mechanisms occur within different parts of the sleep-wake cycle”

INFECTIOUS DISEASES

A CNS gateway for SARS-CoV-2

Many individuals with COVID-19 exhibit neurological symptoms, suggesting that severe acute respiratory syndrome coronavirus (SARS-CoV-2), the virus responsible for the disease, is able to enter the CNS. In support of this possibility, a new study documents the presence of SARS-CoV-2 RNA and protein in various areas of the nasopharynx and the brain in humans, suggesting that the virus can enter the CNS via the neural-mucosal interface in the olfactory mucosa in the nose.

This study was conducted on autopsy material from 33 individuals diagnosed with COVID-19. In 31 of these people, SARS-CoV-2 RNA was detected by quantitative PCR with reverse transcription (RT-qPCR) before death. The other two individuals exhibited clinical symptoms highly suggestive of COVID-19 but did not have their infections confirmed by such testing. Approximately one-third

“the olfactory mucosa exhibited the highest levels of viral RNA load in approximately two-thirds of the samples”

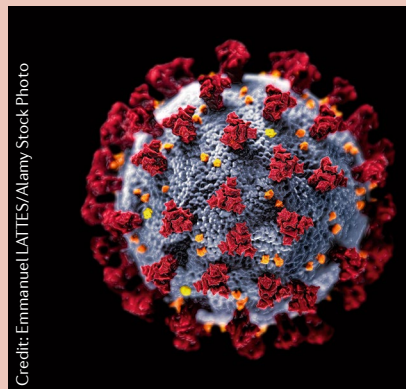
of the 33 people had documented COVID-19-associated neurological symptoms, including impaired consciousness, behavioural changes, intraventricular haemorrhage, acute cerebral ischaemia and headache.

The authors assessed SARS-CoV-2 RNA load by RT-qPCR in various oropharyngeal and nasopharyngeal regions and areas of the CNS (olfactory bulb, medulla and cerebellum) in the patient tissue samples. They detected viral RNA in the CNS (mostly in the olfactory bulb and/or medulla) in about one-third of patient samples. Of note, the level of SARS-CoV-2 RNA in the CNS inversely correlated with the disease duration experienced by the individuals; that is, short disease duration was associated with high CNS viral RNA loads, whereas long disease duration was associated with low CNS viral RNA loads.

Many individuals with COVID-19 exhibit alterations in smell and taste. Interestingly, the olfactory mucosa

exhibited the highest levels of viral RNA load in approximately two-thirds of the samples. The olfactory mucosa is a region in the nasal cavity in which olfactory neurons and nerve fibres are in close proximity to the external environment, suggesting it may be an entry point for SARS-CoV-2 into the human brain. Viral RNA was also detected in eye tissues and the oral mucosa, albeit at lower levels, indicating they may also be routes of entry for the virus into the CNS.

Next, the authors assessed the local distribution of SARS-CoV-2 in



Credit: Emmanuel LATTES/Alamy Stock Photo

IN BRIEF

NEURAL CIRCUITS

Higher-order learning

Higher-order auditory thalamus (higher-order medial geniculate, HO-MG), with its projections to layer 1 (L1) auditory cortex, is a possible node of integration of memory-related top-down signals with externally generated sensory input. Calcium signals recorded in HO-MG terminals while mice performed an associative memory task showed complex learning-related plastic changes that were regulated by local presynaptic inhibition and correlated with behavioural responses. This indicates that HO-MG terminals are a highly plastic conduit for memory-related information transmission in associative learning.

ORIGINAL ARTICLE Pardi, M. B. et al. A thalamocortical top-down circuit for associative memory. *Science* **370**, 844–848 (2020)

SPATIAL NAVIGATION

Mapping environmental richness

Spatial navigation is aided by cognitive map of the environment encoded by specialized cells (such as place cells) in the hippocampus. Spatial coding characteristics of hippocampal place cells were monitored while rats navigated either a cue-rich environment or an environment with few features (cue poor). Place cells in the superficial sublayer of the hippocampus showed increased activity in cue-poor environments and used a rate code that was driven mostly by intra-hippocampal inputs. By contrast, cells in deeper layers were more active in cue-rich environments and used phase codes driven mostly by entorhinal inputs. Together, these findings suggest a mechanism by which the cognitive map adjusts to environments of different complexities.

ORIGINAL ARTICLE Sharif, F. et al. Subcircuits of deep and superficial CA1 place cells support efficient spatial coding across heterogeneous environments. *Neuron* <https://doi.org/10.1016/j.neuron.2020.10.034> (2020)

SYNAPTIC PLASTICITY

Curbing social cravings

Whether social deprivation induces cravings for interaction — similar to food deprivation inducing cravings to eat — is unknown. Here, 40 socially connected young adults were exposed to 10 hours of either social isolation or food deprivation and were then shown food images, images of people socializing or a neutral image. Functional imaging of midbrain dopaminergic regions showed higher activity following exposure to a cue of the deprived stimulus than of the non-deprived or neutral stimulus, and the response was proportional to the degree of self-reported craving.

ORIGINAL ARTICLE Tomova, L. et al. Acute social isolation evokes midbrain craving responses similar to hunger. *Nat. Neurosci.* **23**, 1597–1605 (2020)

NEURAL REPAIR

Sleeping off injury

Wounds and infection increase sleep. Here, Sinner et al. showed that, in *Caenorhabditis elegans*, epidermal injury activates innate immunity and promotes the upregulation of epidermal antimicrobial peptide (AMP) genes. Some AMP genes either directly or indirectly activate the sleep-active RIS neuron and increase sleep, revealing a cross-tissue mechanism by which peripheral injury induces protective sleep.

ORIGINAL ARTICLE Sinner, M. P. et al. Innate immunity promotes sleep through epidermal antimicrobial peptides. *Curr. Biol.* <https://doi.org/10.1016/j.cub.2020.10.076> (2020)

Credit: Jessica Florence/Getty



FRH was observed only during 'sleep-dense' periods and occurred during both rapid eye movement (REM) and non-REM sleep. Intermittent sleep deprivation during the period in which downward FRH was normally expressed prevented the decline in firing rate, indicating that sleep is necessary for downward FRH after ER. By contrast, the Hebbian plasticity-induced drop in firing rate that occurs immediately after MD was unaffected by sleep-wake state, suggesting that sleep is specifically required for homeostatic downward synaptic scaling.

This study provides in vivo evidence for the existence of

bidirectional synaptic scaling, as well further insight into the function of sleep. Previous findings have shown that upward FRH occurs exclusively during periods of wakefulness. These new data therefore suggest that upward and downward homeostatic mechanisms occur within different parts of the sleep-wake cycle, which the authors suggest may help to reduce interference or improve cooperation between these processes.

Katherine Whalley

ORIGINAL ARTICLE Torrado Pacheco, A. et al. Sleep promotes downward firing rate homeostasis. *Neuron* <https://doi.org/10.1016/j.neuron.2020.11.001> (2020)

viral-RNA-positive tissues. The various methods employed demonstrated broadly the same results. Immunohistochemistry revealed that SARS-CoV spike (S) protein was most prevalent in the olfactory mucosa, where it was found in epithelial-like cells and cells that morphologically resembled the olfactory sensory neurons (OSNs), which project dendrites into the nasal cavity and axons to the olfactory bulb. RNAScope in situ hybridization in formalin-fixed and paraffin-embedded tissues indicated the presence of SARS-CoV-2 RNA in the olfactory mucus and cells of the olfactory epithelium, a structure within the olfactory mucosa that includes various cell types, including OSNs and epithelial cells. Electron microscopy on some of the same tissue revealed intact CoV particles in the extracellular space of and within cells in the olfactory mucosa.

To explore further the cellular distribution of SARS-CoV-2 in the olfactory mucosa, the authors conducted immunofluorescence studies. They found perinuclear immunoreactivity for SARS-CoV S protein in cells

co-expressing neuronal cell markers. Together, the localization data provide further evidence suggesting that SARS-CoV-2 can enter the CNS at the neural-mucosal interface.

A recent clinical study reported thromboembolic events in the CNS in a small number of individuals with COVID-19. Here, the authors found a histopathological correlate of microthrombosis and acute brain infarcts in autopsy material from 6 of the 33 individuals. The endothelial cells in these infarcts were associated with higher levels of SARS-CoV S protein, suggesting that the virus may also use the blood vasculature system to enter the brain.

Together, these findings show that SARS-CoV-2 can be found in neurons of the olfactory mucosa and in the CNS endothelia and provide evidence for a possible route of entry of the virus into the CNS.

Darran Yates

ORIGINAL ARTICLE Meinhardt, J. et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat. Neurosci.* <https://doi.org/10.1038/s41593-020-00758-5> (2020)