

Sleep Oscillations

Sleep is one of the most fundamental functions of human life, and on average we spend more than a third of our life sleeping. As a consequence, not only well-characterized primary sleep disorders and sleep alterations secondary to other neurological diseases (such as depression and alcoholism), but even small abnormalities in the regular sequence of sleep stages during a single night sleep, lead to very serious problems in everyday life. Untreated sleep apnoea, for instance, costs the NHS £432 millions per year, with around 300,000 male sufferers in the UK (a figure similar to that for Type I diabetes and double that of asthma). Moreover, 20% of motorway accidents are due to excessive sleepiness, and the cost of sleep deprivation-related illnesses has been estimated to be \$41 billion a year in lost productivity and health-care bills in the USA. Against these high human and financial costs, our knowledge of the intricate mechanisms of human sleep is astonishingly poor. Indeed, whereas a minority of sleep disorders have a genetic origin (e.g. narcolepsy), the majority are still poorly understood.

In particular, the molecular, cellular and network processes that operate in thalamic and cortical neuronal ensembles (Fig. 1) to generate the different EEG rhythms that uniquely characterize each of the normal sleep stages in a night sleep are still mostly unknown. Within this scenario, it is not surprising that the majority of the sleeping pills we use today are still based on ill-defined mechanisms of action.

Thalamic and cortical network dynamics of sleep oscillations

The most fundamental cellular activity that permeates all stages of Non-Rapid Eye Movement (NREM) sleep in humans is the slow (<1 Hz) oscillation (Figs. 2 & 3). Thus, the classical sleep K-complex (of stage 2) is the EEG manifestation of a single cycle of the slow oscillation, and its depth EEG-positive and -negative phases simply reflect the DOWN state and the start of the UP state, respectively, of the oscillation. Sleep spindles, that are prevalent in the early stages of NREM sleep, most often occur immediately after the depth-negative peak of the EEG wave, i.e. on the UP state of the slow oscillation. As sleep deepens, the frequency of the slow oscillation, and thus that of K-complexes, increases until it develops into the slow waves of deep NREM sleep. From stage 2 to 4, therefore, the slow oscillation shows a relative increase in frequency (from around 0.03 to almost 1 Hz) and occupies an increasingly larger component of the EEG signal with clear periods of delta waves, that occur just before the negative peak of the depth EEG wave, becoming more frequent and longer.

A sequence of EEG waves with features that are extremely similar to those in humans also characterizes the progression of natural NREM sleep in many animal species, and it is well documented that the slow oscillation heavily permeates the EEG of these species during both light and deep anaesthesia, thus validating investigations of the slow oscillation under this experimental condition. However, although the use of certain anesthetics, and especially ketamine-xylazine and urethane, has greatly facilitated the investigations of the cellular correlates of the slow oscillation in intact animals, these drugs essentially ‘clamp’ the slow oscillation at particular frequencies and bring about an overall rhythm which considerably lacks the dynamic complexity of the EEG waves of natural sleep in humans and animals.

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OUR RESEARCH

Our work has significantly contributed to an increased understanding of the cellular and local network mechanisms of different sleep waves. In particular, our major findings in this field include:

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Ø characterization of the cellular mechanisms of the delta oscillation in thalamocortical neurons, and role of GABA-B receptors in different sleep stages

(see publications 23 and 27-29, below)

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Ø identification of the cellular mechanisms of the slow (< 1Hz) oscillation in thalamocortical (Figs. 2 & 3) and reticular thalamic nucleus (Fig. 3)

(see publications 1, 5, 6, 8-10, 13, 16, 18 and 22, below)

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Thus, we have proposed that full manifestation of this fundamental sleep oscillation is not simply dictated by a cortical slow rhythm, but requires the dynamic interaction of three independent oscillators: a mainly, but not exclusively, synaptically-based cortical oscillator and two intrinsic, conditional thalamic oscillators (Fig. 4). This scenario fully accounts for all available cortical and thalamic, in vitro and in vivo data on the slow oscillation.

(see publications 1, 9 and 10, below)

We are now investigating the intricate firing dynamics of large thalamic and cortical neuronal ensembles during different stages of non-REM sleep in naturally sleeping-waking animals, and dissecting the role of thalamic and cortical voltage- and transmitter-gated channels in different sleep stages.

Details of our discoveries in this field can be found in the following publications:

1. Crunelli, V. and Hughes, S.W. (2010). The slow (< 1Hz) sleep oscillation: a dialogue of three independent oscillators. *Nature Neuroscience*, 13, 9-17.
2. Lörincz, M., Geall, F., Bao, Y., Crunelli, V. and Hughes, S.W. (2009). ATP-dependent infra-slow (<0.1 Hz) oscillation in thalamic networks. *PLoS One*, 2, e4447.
3. Hughes, S. W., Lörincz, M., Cope D.W. and Crunelli, V. (2008). NeuReal: An interactive simulation system for implementing artificial dendrites and large hybrid networks. *J. Neurosci. Meth.*, 169, 290-301.
4. Blethyn, K.L., Hughes, S.W. and Crunelli, V. (2008). Evidence for electrical synapses between neurons of the nucleus reticularis thalami in the adult brain in vitro. *Thalamus Relat. Syst.*, 4, 13-20.
5. Destexhe, A., Hughes, S.W., Rudolph, M. and Crunelli, V. (2007). Are corticothalamic UP states fragments of wakefulness? *Trends Neurosci.*, 30, 334-42.
6. Blethyn, K.L., Hughes, S.W., Tóth, T.I., Cope, D.W. and Crunelli, V. (2006). Neuronal basis of the slow (<1Hz) oscillation in neurons of the nucleus reticularis thalami in vitro. *J. Neurosci.*, 26, 2474-2486.
7. Crunelli, V., Emri, Zs. and Leresche, N. (2006). Unravelling the brain targets of g-hydroxybutyric acid. *Curr. Opin. Pharmacol.*, 6, 44-52.
8. Zhu, L., Blethyn, K.L., Cope, D.W., Tsomaia, V., Crunelli, V. and Hughes, S.W. (2006). Nucleus- and species-specific properties of the slow (<1 Hz) sleep oscillation in thalamocortical neurons. *Neuroscience*, 141, 621-636.
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15. Emri, Z., Antal, K., Tóth, T.I., Cope, D.W. and Crunelli V. (2000). Backpropagation of the d oscillation and the retinal excitatory postsynaptic potential in a multi-compartment model of thalamocortical neurons. *Neuroscience*, 98, 111-127.
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