

clinical studies will be necessary to resolve this important question.

It is now clear that NSAIDs have a multitude of physiological effects. Some of the pathways that mediate these effects are COX-dependent, others COX-independent, and still others like angiogenesis, may involve both types of mechanisms. In the past 100 years of clinical NSAID use, we have learned that these drugs can produce beneficial or adverse outcomes on processes as diverse as inflammation, neoplasia or tissue integrity, and that all of the processes may be regulated by similar mechanisms. Overall, an improved understanding of NSAID function will improve the safety and efficacy of these drugs, as well other types of angiogenesis inhibitors that hold promise as major anti-cancer agents for the next century.

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Are thalamocortical rhythms the rosetta stone of a subset of neurological disorders?

Recent evidence indicates that “dysrhythmias” cause alterations in the normal function of the thalamocortical loop and lead to various types of neurological disorders. Will decoding this rhythm help us to understand the basis for movement disorders, chronic pain, and even neuropsychological dysfunction?

RHYTHMS CAN BE found in all aspects of life, including the mammalian nervous system. The generation of action potentials in single neurons is, after all, a type of membrane potential oscillation, and whenever large collections of these electrically active cells are connected, they have a pronounced tendency to generate network oscillations. The human brain is no exception to this rule, and since the discovery of the electroencephalogram approximately a century ago, investigators have related changes in this activity to brain function and dysfunction, including neuropsychiatric disorders¹.

Llinás, Jeanmonod and colleagues have attempted to take this analysis one step further^{2,3}. At the Society for Neuroscience 29th Annual Meeting in Miami (24 October 1999), and also in a paper that is in the press, they reported that the brain's gross electromagnetic fields, recorded with magnetoencephalography, are altered in patients suffering from a variety of disorders such as movement disorders (Parkinson disease), chronic pain, and even neuropsychological dysfunction (depression)^{2,3}. These results are interpreted in a broader hypothetical background of the normal and abnormal function of loops of activity between the cerebral

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cortex and an underlying structure, the thalamus.

Although it is convenient to think that brain structures communicate in a serial manner, in reality the brain operates through the functioning of dynamic loops. The cerebral cortex of the human brain can be viewed as a large sheet (about the size of a medium pizza), about 2 mm thick, with such massive interconnectivity (in loops) that the bulk of the brain is made up of axons. One of the most fundamental loops in the brain is that between the cerebral cortex and the thalamus—the thalamocorticothalamic loop (Fig. 1).

In the waking state, the operation of corticocortical and thalamocortical networks generates higher-frequency (30–80 Hz; the so-called gamma band) rhythmic activity. This activity is related to a large variety of parameters of network function, such as the state of the animal (such as aroused and attentive) as well as the sensory or motor conditions (such as active visual stimulation or the preparation of a movement). The generators of these higher-frequency oscillations may reside

either within the cells and networks of the cerebral cortex or perhaps within thalamocortical loops^{4–6}. Although it has been proposed that the higher-frequency oscillations may be representative of neuronal processes that ‘bind’ together diverse sensory information (such as the click, feel and look of a computer keypad) into a single percept (keyboard) and action (typing), this is still a controversial theory^{7,8}. In contrast to the waking state, during states of drowsiness or slow-wave sleep, thalamocortical networks generate lower-frequency rhythms (0.1–15 Hz) through the interaction of both the intrinsic properties of the cells themselves and their synaptic interconnectivity in networks^{9,10}. The role of these low-frequency oscillations in normal brain function remains to be discovered¹¹.

Could alterations in the normal functioning of this thalamocortical loop result in neurological disorders? Indeed, yes. The malfunction of corticocortical, thalamocortical and cortico-basal ganglia-thalamic activities may result in such diverse neurological disorders as some types of epileptic seizures and the tremor of Parkinson disease (both of which have large, rhythmic components)^{12,13}. Stimulation or lesion of the appropriate

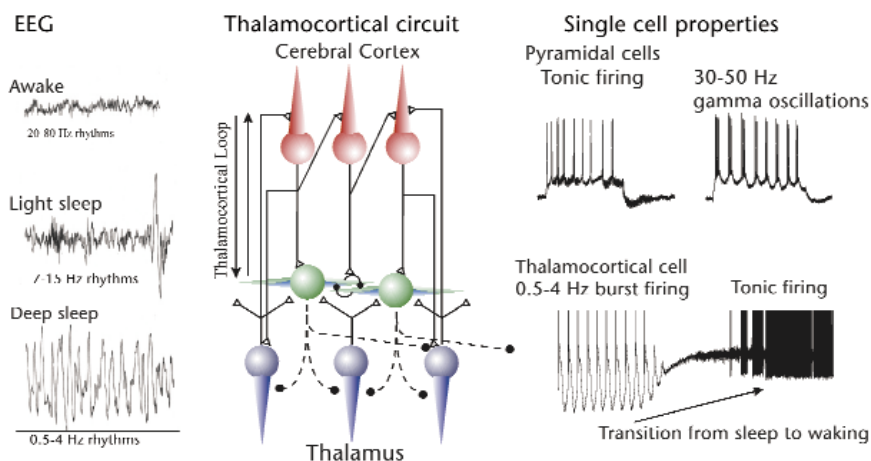


Fig. 1 Properties of activity in the thalamocortical circuit. The gross activity of the forebrain, as measured by the electroencephalogram, is characterized by higher-frequency oscillations in the waking state and lower-frequency rhythms during sleep. Likewise, thalamic and cortical neurons can also show different patterns of rhythmic activity. Thalamocortical neurons can generate slow rhythmic oscillations during deep sleep, and fire tonic trains of action potentials in waking. Most pyramidal neurons in the cerebral cortex generate only tonic trains of action potentials, although others presumably participate in the generation of higher-frequency rhythms through the activation of rhythmic bursts of spikes⁴. The thalamus and cerebral cortex are connected together in a loop (middle). Malfunction of the dynamics of this loop, and its interaction with other brain structures, may underlie some forms of neurological disorders.

portion of the thalamus (the ventral tier nuclei) is now a common method to alleviate movement tremor¹⁴, presumably through a disruption of the oscillatory network activities. Recordings of thalamic neurons have shown that abnormal activity in these cells may be present in neurological disorders that are not obviously rhythmic. For example, recordings of thalamic neurons in patients suffering from chronic pain as the result of sensory deafferentation also show the presence of abnormal rhythmic bursts of action potentials¹⁵, although it is still unknown if this abnormal thalamic activity is responsible for the perception of pain.

Where might these rhythmic bursts of activity come from? Thalamic cells, even as single entities, have two distinct firing modes: slow rhythmic burst firing at hyperpolarized membrane potentials, and tonic, repetitive spike activity at depolarized potentials (Fig. 1). In normal people, the slow rhythmic burst firing is typical only in non-rapid eye movement (non-REM) sleep, a time when cognitive abilities are at their lowest (thus this rhythmic burst firing is not interpreted as painful in the sleeping brain). In contrast, the generation of repetitive single spike activity is associated with either the waking or REM sleep state, when either the brain is active and cognitive, or dreams are their most vivid and dynamic. This dual state of thalamic neu-

rons is the result of their own intrinsic biophysical properties^{9,10,16}. Indeed, the precise cellular mechanisms for the generation of the diverse rhythmic activities of the forebrain are finally yielding to the experimenter's electrode^{6,9,10}.

The condition in which thalamocortical loops generate inappropriate rhythmic activity (such as slow rhythmic burst firing in the awake brain) has been called "thalamic dysrhythmia" by Llinás and colleagues². Thalamic "dysrhythmia" in this sense is a well-known feature of some forms of epilepsy and tremorgenic syndromes, both of which represent lower-dimensional (or simplified) states of the thalamocortical network accompanied by stereotyped behaviors (rhythmic hand movements in tremor or 3-Hz spike-and-wave oscillations in the electroencephalogram during generalized absence seizures). Could similar thalamocortical "dysrhythmias" underlie other disorders, including neuropsychiatric ones? At present, this interesting and provocative suggestion of Llinás and colleagues should be considered as strictly hypothetical, as it is based on only a small sampling of recordings and many factors have yet to be controlled. These authors suggest that the positive components of neuropsychiatric disorders may arise from the induction of abnormal patterns of higher frequency rhythmic activities in cortical and thalamocortical

networks at the edge of a central core region that is actively generating lower-frequency rhythms. These lower-frequency rhythms are hypothesized to result from the deafferentation or abnormal hyperpolarization of some portion of the thalamus, either through neurological damage or malfunction of a brain structure that projects to the thalamus. This hypothesis depends essentially on several assumptions: First, that the activation of abnormal patterns of higher-frequency activities in thalamocortical networks would have neuropsychiatric effects (for example, can abnormal oscillations make a person have paranoid delusions?); second, that abnormal patterns of higher-frequency rhythms can be generated in response to lower-frequency rhythms in thalamocortical networks; and third, that the relevant thalamocortical networks actually generate abnormal rhythms in neuropsychiatric conditions. Before undertaking risky neurosurgical procedures on the thalami of such patients, these assumptions should be carefully and adequately tested in both animals and humans.

Neurological and neuropsychiatric disorders have often been thought of in terms of abnormal neuronal connections, biochemistry or genetics. Whatever the primary cause for these disorders, they must all ultimately result in an abnormal pattern of activity in the neuronal networks of the brain. With the large advance in our understanding of forebrain (thalamocortical) networks in the mammalian brain during the last decade, neuroscience is now ready to begin to address the cellular basis underlying these disorders. These neurophysiological examinations promise to yield a new and in-depth understanding of human brain function and dysfunction, and may yield new diagnostic tools as well as therapeutic advances.

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Who's that lady?

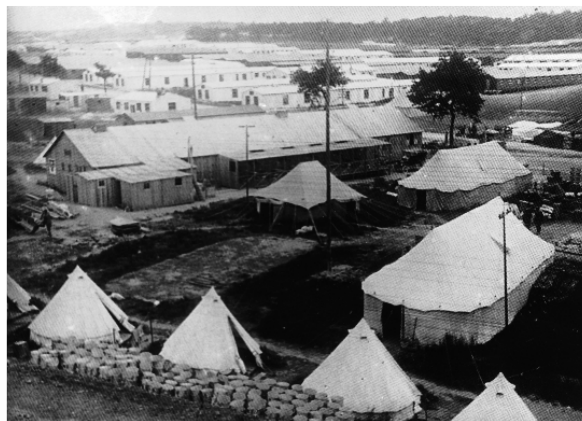
An analysis of scientific and social literature suggests that army bases located in France and the UK may be responsible for the worldwide distribution of the 'Spanish Lady' influenza pandemic of 1918.

THE 'SPANISH' INFLUENZA pandemic of 1918–1919 killed over 40 million people world-wide¹. But how could a virus spread throughout the world so rapidly? It seems inconceivable that a virus, even influenza, could be dispersed over such great distances in such a short time without an earlier 'seeding' of the virus. In this context, two rediscovered clinical and bacteriological descriptions are relevant. The first² reports a 1916 outbreak of 'purulent bronchitis' at an unidentified army base in France, whereas the second³ records another 1917 outbreak in the UK, at Aldershot Barracks.

We have reviewed the scientific and social literature published before 1918 for any indication of earlier outbreaks. This material includes medical war records at the Public Record Office (Kew), the British Library and the Imperial War Museum (all based in London, UK). We were prompted to undertake this search by a simple observation on the timings of deaths of the nine influenza victims who constitute, at present, the direct sources of clinical specimens and influenza A genes from that era. These victims were located in Fort Jackson (soldier; US)⁴, Camp Upton (soldier; US)⁵, Brevig Mission (Inuit woman; Alaska, US)⁵ and Longyearbyen (six Norwegian coal miners, Spitsbergen)⁶. Despite their wide geographical dispersion around the Northern Hemisphere, the dates of death of these victims are within a very narrow time period: late September–November 1918. Furthermore, influenza deaths at the same time were re-

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ported in regions as far apart as South Africa⁷, India⁸ and Indonesia⁹. In relation to the 'seeding' of the 'Great Influenza Pandemic of 1918', mortality figures for bronchopneumonia increased in the USA during the entire period of 1914–1918 (ref. 10). A similar review of records of bron-



France, 1918. General army hospitals at Etaples en route to Carniers.

chopneumonia deaths at the Royal London Hospital shows a peak in 1918 but substantial numbers between 1914 and 1917 (Fig. 1) whereas, on a national scale, there is clear evidence of spread of a virus from May 1918 (ref. 11) that showed enhanced lethality from June 1918 onwards¹².

Hammond *et al.*² reported that in 1916, large numbers of soldiers were admitted to a French base hospital, reportedly suffering from an acute respiratory infection,

high temperature and cough at a time when the recognized influenza was present. Despite the war and censorship at the time, we now have strong indications that the previously unidentified base hospital was at Etaples in Northern France, where one of the co-authors, T.H.G. Shore, was working. It was a large camp, with 100,000 soldier inhabitants at any time and many hospitals (Fig. 2). This 'outbreak' was further characterized by cyanosis and extremely high mortality.

Clinical examination showed, in most cases, signs of bronchopneumonia, and histology showed an acute purulent bronchitis. Our clinical microbiological review of the paper ranks the description as classic influenza being particularly similar to the extensive literature of deaths in 1918–1919 (ref. 12).

In the earlier literature, influenza was often described clinically as 'epidemic catarrhal fever'¹³. Essentially identical epidemic outbreaks of purulent bronchitis with bronchopneumonia, with cases showing a peculiar dusky heliotrope cyanosis and mortality rates of 25–50%, were described in Aldershot barracks in March 1917 (ref. 3). Furthermore, Abercrombie¹⁴ recorded: "Early in 1917 I had under my care in France a large number of (young) soldiers suffering from a grave form of purulent bronchitis proceeding in some cases to bronchopneumonia. The cases exhibited dyspnea, a heliotrope cyanosis, pyrexia and a high mortality".

Shortridge¹⁵ argues cogently that influenza A (H1N1) may have spread in China for 70 of the last 110 years, and that