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Infra-slow (<0.1 Hz) oscillations in thalamic relay nuclei: basic mechanisms and significance to health and disease states

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Abstract

In the absence of external stimuli the mammalian brain continues to display a rich variety of spontaneous activity. Such activity is often highly stereotypical, invariably rhythmic and can occur with periodicities ranging from a few milliseconds to several minutes. Recently there has been a particular resurgence of interest in fluctuations in brain activity occurring at <0.1 Hz, commonly referred to as very slow or infra-slow oscillations (ISOs). Whilst this is primarily due to the emergence of functional magnetic resonance imaging (fMRI) as a technique which has revolutionised the study of human brain dynamics it is also a consequence of the application of full band electroencephalography (fbEEG). Despite these technical advances the precise mechanisms which lead to ISOs in the brain remain unclear. In a host of animal studies, one brain region that consistently shows oscillations at <0.1 Hz is the thalamus. Importantly, similar oscillations can also be observed in slices of isolated thalamic relay nuclei maintained *in vitro*. Here, we discuss the nature and mechanisms of these oscillations, paying particular attention to a potential role for astrocytes in their genesis. We also highlight the relationship between this activity and ongoing local network oscillations in the alpha (α) (~8-13 Hz) band, drawing clear parallels with observations made *in vivo*. Lastly, we consider the relevance of these thalamic ISOs to the pathological activity that occurs in certain types of epilepsy.

Keywords

acetylcholine; metabotropic glutamate receptor; EEG; gap junctions; alpha rhythm; epilepsy; adenosine; astrocytes; GIRK channels

Introduction

Infra-slow oscillations (ISOs) in the human brain

In the absence of sensory input the unconstrained brain continues to exhibit a rich array of well-structured, spontaneous activity. Most commonly, this activity consists of prominent periodic signals which are generated by the rhythmic and synchronous discharge of large numbers of cortical neurons. Such signals have been traditionally examined using conventional scalp EEG recording and have been shown to occur within a multitude of overlapping frequency bands ranging from the ~0.5-4 Hz band that encompasses the slow waves of deep sleep (Crunelli and Hughes, 2010), to the gamma (γ) (30-80 Hz) band and

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beyond (>100 Hz) which contain oscillations that are salient to cognitive and attentional processes (Tallon-Baudry, 2009).

In recent years there has been an increasing interest in brain activities that take place on a much slower timescale than is generally recognised in traditional EEG bands; those which occur at <0.1 Hz and which are usually referred to as very slow or infra-slow oscillations (ISOs). Although the presence of such ISOs has been known about in animals for over 50 years (Aladjalova, 1957), one of the main reasons for the current surge of interest is the consistent finding from human fMRI studies that during the resting state the brain exhibits prominent fluctuations at <0.1 Hz in the BOLD signal (Damoiseaux et al., 2006, De Luca et al., 2006, Fox and Raichle, 2007, Mantini et al., 2007) (Fig, 1A). These fluctuations identify functional anatomical networks, termed resting state networks (RSNs), which are conserved across subjects (Damoiseaux et al., 2006, De Luca et al., 2006, Mantini et al., 2007). Although there is considerable debate regarding the precise relationship between such cerebral fluctuations and neuronal activity (e.g. see Lee et al., 2010, Leopold, 2010, Logothetis, 2010), it is now clear that at the very least they correlate closely with episodes of faster EEG oscillations in several well-defined, traditional EEG bands (Mantini et al., 2007). For example, activity in a well-characterised posterior RSN, that includes brain regions responsible for visual processing and which involves a significant participation of the thalamus (Mantini et al., 2007, Goldman et al., 2002, Moosmann et al., 2003, Feige et al., 2005), is well known to be correlated with changes in the amplitude of EEG α rhythms (Fig, 1B and C). Similar correlations with α band power have also been noted in other RSNs (Mantini et al., 2007, Laufs et al., 2003).

ISOs have also recently been identified in full band EEG (fbEEG) recordings from humans (Vanhatalo et al., 2004, Vanhatalo et al., 2005, Monto et al., 2008). Notably, as with activity in fMRI-defined RSNs, these ISOs are also coupled to conventional, faster EEG oscillations (Vanhatalo et al., 2004). Furthermore, and consistent with a role in modulating large-scale neuronal network excitability, they have been shown to regulate behavioural performance (Monto et al., 2008), organize electrophysiological sleep-related events and influence the precipitation of certain types of epileptic seizures (Vanhatalo et al., 2004). That cognitive performance, as well as the EEG signatures of sleep and epilepsy, can recur on an infra-slow timescale is of course not new. For example, generalized polyspikes in patients with the catastrophic Lennox-Gastaut syndrome (LGS) occur significantly more frequently during the active phase of the so-called cyclic alternating pattern (CAP) (Eisensehr et al., 2001), an ISO with a periodicity of ~20-40 seconds that participates in the dynamic organization of non-rapid eye movement (NREM) sleep EEG architecture (Terzano and Parrino, 2000). However, that such infra-slow fluctuations might occur because of underlying fluctuations in macroscopic excitability is important because it implies that rather than being simply an emergent property of the immediate neuronal networks under scrutiny, these fluctuations are likely to be driven by a more extrinsic source.

ISOs in the intact animal brain and their prominence in the thalamus

As alluded to above, ISOs were first described in the animal brain in a study published over 50 years ago detailing gross electrophysiological recordings from the neocortex of rabbits (Aladjalova, 1957). In this seminal study two main oscillations were described having periodicities of around 10 and 30-90 seconds, respectively (Fig. 2A). These oscillations were present at distinct cortical sites, were not synchronized between hemispheres and, in the case of the faster rhythm, could group periods of more conventional EEG oscillations as described above for humans. More recently, activity fluctuations at <0.1 Hz have also been identified in the visual cortex of the monkey (Leopold et al., 2003) as well as in both the visual and auditory cortices of the rat (Filippov, 2005, Filippov and Frolov, 2005, Filippov

et al., 2007, Filippov et al., 2008). Under certain conditions monkeys and rats also exhibit infra-slow fluctuations in the resting BOLD signal (Vincent et al., 2007, Lu et al., 2007).

Apart from the neocortex, ISOs, as evidenced in either local field potentials (LFPs) or neuronal activity, have also been observed in the hippocampus (Penttonen et al., 1999), basal ganglia (Ruskin et al., 1999a, Ruskin et al., 1999b, Hutchison et al., 2004, Zuo et al.) locus coeruleus (Filippov et al., 2004), dorsal raphe (Filippov et al., 2004) olivary pretectal nucleus (Szkudlarek et al., 2008) and, in particular, the thalamus (Albrecht and Gabriel, 1994, Albrecht et al., 1998, Filippov, 2005, Filippov and Frolov, 2005, Filippov et al., 2007, Lewandowski et al., 2000, He, 2003). For example, in sensory thalamic relay nuclei, ISOs at ~0.02-0.3 Hz have been noted in LFP recordings from both the rat lateral geniculate nucleus (LGN) (Filippov, 2005, Filippov and Frolov, 2005) and medial geniculate nucleus (MGN) (Filippov et al., 2007). In the cat LGN, an ISO is present in LFP recordings, with this oscillation being correlated with fluctuations in the amplitude of ongoing α waves (Fig. 2C and D), in a manner not dissimilar to that seen in the human EEG (Vanhatalo et al., 2004). At the cellular level, neurons in the LGN exhibit an ISO at ~0.01 Hz that is present in both freely moving and anaesthetized animals (Albrecht and Gabriel, 1994, Albrecht et al., 1998). This oscillation is readily observed in single unit recordings where it comprises episodes of robust firing interspersed with periods of neuronal silence (Fig. 2B). An ISO is also present in thalamic firing during the generation of so-called cyclic paroxysms (Steriade and Contreras, 1995). Cyclic paroxysms are experimental electrographic seizures in cats (Steriade and Contreras, 1995, Steriade and Contreras, 1998) which recur with a periodicity of ~40-60 seconds, involve a combination of slow (~2-4 Hz) spike/poly-spike wave (SW/PSW) complexes and fast (10-20 Hz) runs and are similar to the EEG activity that can occur in LGS in humans (Fig. 3A and B).

Taken together, evidence from both human and animal studies points clearly to the fact that oscillatory activity at <0.1 Hz is a fundamental trait of cerebral functioning. Furthermore, it is apparent from animal studies that ISOs are a particularly integral component of activity in the thalamus (Albrecht and Gabriel, 1994, Albrecht et al., 1998, Filippov, 2005, Filippov and Frolov, 2005, Filippov et al., 2007, Lewandowski et al., 2000, He, 2003). However, despite these obvious conclusions the mechanisms that might generate these oscillations remain poorly understood. More specifically, whilst the capacity of isolated neuronal circuits to generate oscillations at higher frequencies (e.g. 8-13 Hz α rhythms, Hughes and Crunelli, 2005, Hughes et al., 2004, Hughes and Crunelli, 2007, Lorincz et al., 2008, Lorincz et al., 2009b, and 20-80 Hz γ oscillations, Oren et al., 2006, Mann et al., 2005, Hajos et al., 2004, Fisahn et al., 1998, Cunningham et al., 2003, Cunningham et al., 2004, Jefferys et al., 1996) has been reasonably well characterised, their ability to display activities in the infra-slow (<0.1 Hz) range has not been extensively examined. In the remainder of this article we will describe the properties and mechanisms of an ISO that is present in isolated thalamic slices maintained *in vitro* (Lorincz et al., 2009a); see also (Leresche et al., 1991). As observed *in vivo* this thalamic ISO, i) is reflected in both the LFP and individual neurons, ii) coordinates regional oscillations in the α (~8-13 Hz) band, and iii) can be associated with cyclic paroxysms.

Properties and mechanisms of an ISO that is present in acute slices of thalamic relay nuclei maintained *in vitro*

Basic manifestation

Following moderate activation of either muscarinic acetylcholine receptors (mAchRs) and/or metabotropic glutamate receptors (mGluRs) with exogenous agonists, a manipulation that renders thalamic slices in a condition more akin to their natural state *in vivo*, between 10 and

30% of thalamocortical (TC) neurons in the cat LGN, MGN and ventrobasal (VB) thalamus (i.e. the somatosensory thalamus) exhibit a robust ISO at around 0.03-0.1 Hz (Fig. 4A) (Lorincz et al., 2009a). This ISO is evident in both extracellular single unit and intracellular recordings and consists of periods of waxing and waning action potential output that are separated by periods of neuronal silence or greatly diminished firing. These action potential epochs can comprise both single action potential firing and/or repetitive high-threshold (HT) bursting (Figs. 4A and 8C) (Hughes et al., 2004, Lorincz et al., 2008, Hughes et al., 2008). The ISO can be either highly rhythmic (e.g. Fig. 4A) or somewhat irregular (e.g. Fig. 5B) and once established in the slice can be apparent for several hours.

The thalamic ISO is a population rhythm and is sculpted by long-lasting hyperpolarizing potentials in individual neurons

Multiple unit extracellular recordings demonstrate that the ISO can be simultaneously present in small groups of closely situated neurons (Fig. 4B). Furthermore, because there can be a delay of several seconds in the peak of firing between these cells it appears that the ISO involves some form of slowly propagating wave-like phenomenon (Fig. 4B). The ISO can also be detected in LFP recordings (Fig. 4C and D). Unlike for other thalamic network oscillations where negative-going LFP deflections are associated with neuronal excitation, simultaneous intra- and extracellular recordings reveal that the ‘sharp’ negative deflections that make up the periodic LFP signal are actually coincident with the onset of stereotyped, long-lasting (~5-15 seconds) hyperpolarizing potentials (Fig. 4C and D). Thus, it appears that the ‘active’ phase of the ISO occurs in concert with a hyperpolarization of individual TC neurons. This also suggests that the LFP signal likely does not reflect the synchronous fluctuation of membrane currents in populations of thalamic neurons but rather some separate, non-neuronal process.

That the determining event of the ISO in individual neurons is a stereotyped long-lasting hyperpolarization is also supported by two additional lines of evidence. Firstly, examination of the development of the ISO over time in single TC neurons from a state of quiescence to a fully established oscillation shows that the emergence of the ISO is clearly associated with the progressive increase in the occurrence and rhythmicity of such hyperpolarizing potentials (Fig. 5A). Secondly, in cases where the ISO is not especially rhythmic, it is the hyperpolarizing phase of the oscillation that is highly conserved whereas the durations of constituent epochs of action potential firing are quite variable (Fig. 5B). In many cases long-lasting hyperpolarizing potentials exhibit a multiphasic nature, seeming to consist of two or more independent hyperpolarizing events which are temporally offset and superimposed (Fig. 5A and C). Again, this finding is indicative of a possible propagating wave-like process as being involved in the generation of the ISO.

Mechanisms underlying long-lasting hyperpolarizing potentials and the possible involvement of astrocytes

The ISO in TC neurons and its constituent long-lasting hyperpolarizing potentials are not blocked by agents that antagonize ionotropic glutamate receptors (Fig. 5C), $GABA_A$ or $GABA_B$ receptors (Fig. 4C), indicating a lack of dependence on conventional synaptic mechanisms and in particular that it is not due to the actions of GABA-releasing local circuit interneurons (Lorincz et al., 2009b). However, long-lasting hyperpolarizing potentials, and consequently the ISO in individual neurons, are reversibly abolished by barium (Ba^{2+}) when applied at 100 μM (Fig. 6A). At this concentration Ba^{2+} preferentially inhibits inwardly rectifying K^+ (Kir) channels (Yamada et al., 1998). Given that the ISO is a network phenomenon, this suggests that long-lasting hyperpolarizing potentials might be due to the opening of some type of Kir channels via the cyclic activation of a receptor complex on thalamic neurons to which these channels are coupled. Obvious contenders for such

channels are members of the G protein-coupled inwardly rectifying K^+ (GIRK/Kir3.x) channel family (Hibino et al., 2010). GIRK1, GIRK2 and GIRK3 (Kir3.1, 3,2 and 3.3) are all expressed at significant levels in thalamic relay nuclei (Karschin et al., 1996) where they are known to be responsible for the slow $GABA_B$ receptor-mediated inhibition of TC neurons (Crunelli and Leresche, 1991). Apart from $GABA_B$ receptors, which as noted above are not responsible for the ISO-related long lasting hyperpolarizing potentials in TC neurons, one of the other main receptor types that is known to be positively coupled to GIRK channels in these cells is the adenosine A1 receptor (Pape, 1992). In fact, the A1 receptor antagonist, DPCPX, fully blocks long-lasting hyperpolarizing potentials and the associated neuronal ISO (Fig. 6B). Interestingly, when assessed with extracellular single unit recordings DPCPX causes a progressive reduction in the silent period of the neuronal ISO without affecting its overall frequency (Fig. 6C). This is a critical finding because it shows that TC neurons are the recipients of a cyclic inhibitory influence which is clearly generated independently from these cells. Allied to this, DPCPX does not affect the presence of the ISO in the LFP (not illustrated) (Lorincz et al., 2009a), again indicating that the fundamental generation of the ISO occurs autonomously of TC neuron activity.

What is the source of adenosine that leads to phasic A1 receptor activation and probable GIRK channel opening in TC neurons? A possibility is that this adenosine results from the degradation of adenosine triphosphate (ATP) following its release from glial cells, along similar lines to the sequence of events that occurs in the retina whereby ATP released from Müller cells can lead to an eventual inhibition of neighbouring neurons (Newman, 2003). In support of this, the ecto-ATPase inhibitor, ARL 67156, which blocks the breakdown of ATP to adenosine, fully and reversibly abolishes the silent periods of the neuronal ISO (i.e. Fig. 6D). This shows unequivocally that the inhibitory phases of the ISO in TC neurons are due to the effects of ATP-derived adenosine.

In the thalamus the prime candidates for releasing ATP are astrocytes (Parri and Crunelli, 2002, Parri et al., 2001, Parri and Crunelli, 2001). On top of a general recognition that the ISO exists independently of neuronal activity, two main lines of indirect evidence support a role for these cells in producing this oscillation. Firstly, thalamic astrocytes exhibit spontaneous intracellular Ca^{2+} oscillations *in situ* (Parri et al., 2001) which can be both highly rhythmic (Fig. 7A) as well as somewhat irregular (Fig. 7A4) (Parri and Crunelli, 2001), and which occur within a virtually identical range of frequencies (0.003-0.1 Hz) to the ISOs in TC neurons (Fig. 7A4). Secondly, closely situated groups of thalamic astrocytes exhibit slowly propagating Ca^{2+} waves (Fig. 7B) (Parri and Crunelli, 2001) which, by virtue of the ability of Ca2+ increases in individual astrocytes to lead to ATP release (Guthrie et al., 1999), offers a reasonable explanation for the wave-like co-activation of different neurons (i.e. Fig. 4B) as well as the multiphasic nature of the long-lasting hyperpolarizing potentials in individual cells (i.e. Fig. 5A and C). In addition to these points, in neurons where an ISO is not present, one can be readily brought about by the application of the putative gap junction (GJ) opener, trimethylamine (TMA), whereas ISOs can sometimes be blocked by the putative GJ blocker, 18β-glycyrrhetinic acid (18β-GA). Whilst this may be due in part to an increase in GJ-mediated coupling amongst TC neurons (Hughes et al., 2002, Hughes et al., 2004, Lorincz et al., 2008; see also below) it can also be readily explained by an enhancement of such coupling between astrocytes leading to more pervasive and far-reaching intercellular calcium waves (Finkbeiner, 1992). Lastly, whilst the response of TC neurons to mGluR and/or mAchR activation is a sustained depolarization and instigation of tonic firing and/or HT bursting (Hughes et al., 2004, Lorincz et al., 2008, Hughes et al., 2008), the response of thalamic astrocytes to stimulation of these receptors is an increase in intra- and intercellular Ca^{2+} transients (Parri and Crunelli, 2003).

Association of the thalamic ISO with local alpha (~8-13 Hz) rhythms

In the LGN and VB, the sustained excitation of TC neurons brought about by mGluR and mAchR activation not only leads to depolarization and the appearance of tonic firing and HT bursting (Hughes et al., 2004, Lorincz et al., 2008, Hughes et al., 2008) but also to the appearance of network oscillations in the α (~8-13 Hz) band (Hughes et al., 2004, Hughes and Crunelli, 2005, Lorincz et al., 2008, Lorincz et al., 2009b). These oscillations are driven by the synchronized activity of groups of GJ-coupled, intrinsically rhythmic HT bursting neurons (Hughes et al., 2004, Hughes and Crunelli, 2005, Lorincz et al., 2008, Lorincz et al., 2009b). In the LGN, these neurons then rhythmically excite local circuit interneurons which, in turn, cyclically inhibit TC neurons which operate in a conventional relay-mode (Lorincz et al., 2009b). Some relay-mode TC neurons are also the recipients of direct GJ-mediated connections from HT bursting neurons (Hughes et al., 2002, Hughes et al., 2004, Lorincz et al., 2008, Lorincz et al., 2009b). Given that these α oscillations are a natural consequence of thalamic neurons occupying a tonically excited state, it is logical to expect that they might also be grouped by the ISO. Indeed, combined extracellular field and unit recordings in the LGN show (i) that the ISO in the LFP can be associated with changes in α rhythm amplitude (Fig. 8A), and (ii) that ISO-derived epochs of α rhythm-related HT bursting can drive synchronous firing in additional cells (i.e. Fig. 8B; see also Fig. 8C). In agreement with these findings, intracellular recordings of relay mode TC neurons reveal the presence of both burstlets (i.e. groups of spikelets which represent HT bursts that have been communicated via GJ coupling) (Fig. 8D) and rhythmic inhibitory postsynaptic potentials (IPSPs) (not illustrated) during the depolarizing phases of the ISO thereby demonstrating the functional electrical coupling of HT bursting TC neurons to other cells and the likely rhythmic engagement of local circuit interneurons, respectively.

The grouping of synchronized α oscillations by the ISO in the LGN slice is an important finding because we have identified a similar phenomenon in the cat LGN *in vivo* (i.e. Fig. 2C and D). Furthermore, as noted above, ISOs in several distinct human RSNs, some of which possess a substantial thalamic involvement, are linked to changes in α power (see Fig. 1B and C) (Mantini et al., 2007, Goldman et al., 2002, Moosmann et al., 2003, Feige et al., 2005, Laufs et al., 2003). Power in the EEG α band (as well as in other conventional EEG bands) is also modulated by the phase of the ISOs that are apparent in human fbEEG recordings (Vanhatalo et al., 2004).

Association of the thalamic ISO with cyclic paroxysms

In the state quiet of relaxed wakefulness, when α rhythms predominate, it is well known that susceptibility to several types of seizures is enhanced. In fact, in the case of the Rolandic μ rhythm, which is the equivalent of the classical occipital α rhythm in the somatosensory system and often presents as series of quite ‘spikey’ negative deflections in the EEG, there can be a co-localization with Rolandic epileptiform spikes (Niedermeyer, 1997, Hughes and Crunelli, 2005). With reference to this, in thalamic slices where mGluRs or AchRs are activated excessively (i.e. with high concentrations of exogenous agonists) there is both an increase in the prevalence of the ISO and a development of physiological α oscillations into cyclic paroxysmal activity consisting of recurring sequences of rhythmic spike wave (SW) and poly-spike wave (PSW) complexes at ~2-4 Hz that are occasionally mixed with fast runs at ~10-20 Hz (Fig. 9A). Whilst these paroxysmal events are also correlated with HT bursting in TC neurons, these HT bursts are considerably more powerful than those associated with normal α rhythms (compare Fig. 9A with Fig. 8B).

The cyclic paroxysms observed in thalamic slices are virtually identical to those previously described in the cat thalamus *in vivo* (Steriade and Contreras, 1995, Steriade and Contreras, 1998). This leads to the important and unavoidable conclusion that rather than simply

reflecting neocortical activity, the thalamus must play a considerably more active role in generating these paroxysms *in vivo* than had previously been acknowledged. An additional and no less important conclusion is that the type of bursting that is associated with SW/PSW complexes during paroxysmal activity is not mediated by conventional low-threshold Ca^{2+} potentials (LTCPs) (Llinas and Jahnsen, 1982, McCarley et al., 1983, Domich et al., 1986), but is due to HT bursts (Hughes et al., 2004, Lorincz et al., 2008, Hughes et al., 2008). In fact, upon reappraisal of the published thalamic recordings obtained *in vivo* it is quite clear that the TC neuron bursting associated with SW/PSW complexes is wholly incompatible with an LTCP-mediated origin, due to the presence of interspike intervals that are much too large (>10 ms) for LTCPs (e.g. Fig. 3B), but entirely reconcilable with an HT burst basis. One upshot of this is that, based on our previous work, we would expect the unusually powerful HT bursts that occur during cyclic paroxysms to be associated with a significant depolarization of TC neuron dendrites (Jahnsen and Llinas, 1984, Tennigkeit et al., 1998, Hughes et al., 2004, Hughes et al., 2008) and, consequently, a greatly elevated and potentially detrimental influx of Ca^{2+}. Were this to be the case, it might be envisaged that such excessive Ca^{2+} entry during aberrant neuronal bursting might play a key role in promoting the catastrophic cellular damage that occurs in certain types of malignant epilepsies such as LGS.

Concluding remarks

Physiological and pathological significance of ISOs in the thalamus

We have discussed the properties and mechanisms of an ISO that is present in acute slices of cat thalamic relay nuclei. In doing so, we have highlighted a potential key role for astrocytes in its generation. We have also identified two main similarities between the ISO that exists in reduced thalamic preparations with activity that occurs in the intact brain. Firstly, in both thalamic recordings from intact cats and those from acute slices, the ISO is linked to changes in the amplitude of local α rhythms. Whether there is any genuine mechanistic correspondence between ISOs in these two contexts remains to be seen but this is certainly addressable with the armoury of pharmacological tools available. On the other hand, it is not realistic to draw any meaningful conclusions about the relationship between ISOs in thalamic brain slices and the modulation of α band power by ISOs in humans. In particular, it would be remiss not to point out that whilst the ISOs described in thalamic slices are often highly rhythmic those observed in human BOLD and fbEEG signals are not. However, all that said, it remains difficult to ignore the fact that a phenomenon which ostensibly shares at least some characteristics with that which occurs in the whole brain can occur in a much more simplified preparation. Secondly, and unlike the ISO-related modulation of α power, where correspondence with *in vivo* activities is more difficult to assess, the thalamic ISO can be associated with cyclic paroxysmal episodes that are virtually identical to those described in the intact cat brain (Steriade and Contreras, 1995, Steriade and Contreras, 1998). In turn, these *in vivo* paroxysms are considered to closely resemble the electrographic signals that can occur in LGS in humans. As such, it is not unreasonable to suggest that this pathological form of thalamic activity may have genuine relevance to certain types of epileptic syndromes in humans. Finally, regardless of the significance of the *in vitro* thalamic ISO to activity present *in vivo*, the description of its properties and mechanisms given here provides several new insights into the basic physiology and rhythmogenic capacity of the thalamus.

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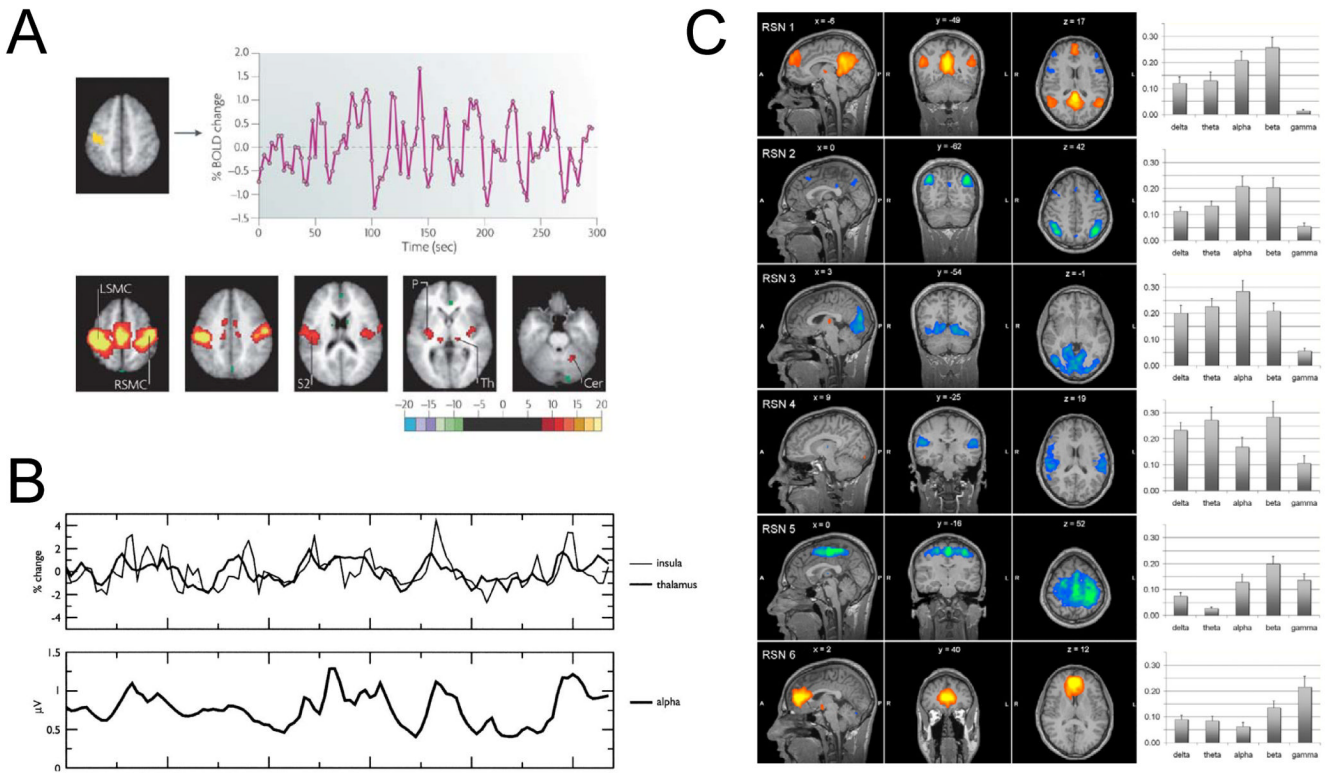

Figure 1. Infra-slow fluctuations in human brain activity as assessed with fMRI

A. Top: spontaneous fluctuations in human BOLD activity obtained during resting fixation (right) and taken from the seed region shown in the image to the left. Bottom: map showing voxels that were significantly correlated with the extracted signal shown above (LSMC and RSMC: left and right somatosensory cortex; S2: secondary somatosensory association cortex; Th: posterior nuclei of the thalamus; P: putamen; Cer: cerebellum) (reproduced with permission from Fox and Raichle, 2007). **B.** Simultaneous acquisition of the thalamic BOLD signal (top) and EEG α rhythm (convolved with a hemodynamic response function and plotted below) demonstrates a positive correlation between the two signals (reproduced with permission from Goldman et al., 2002). **C.** Association between EEG rhythms and resting state networks (RSNs). Several RSNs show correlations with α activity. The source of activity shown in **B** is likely to be RSN 3, a posterior network involving areas dedicated to visual processing, where there is both a clear involvement of the thalamus and a positive correlation between thalamic BOLD activity and the α rhythm (reproduced with permission from Mantini et al., 2007).

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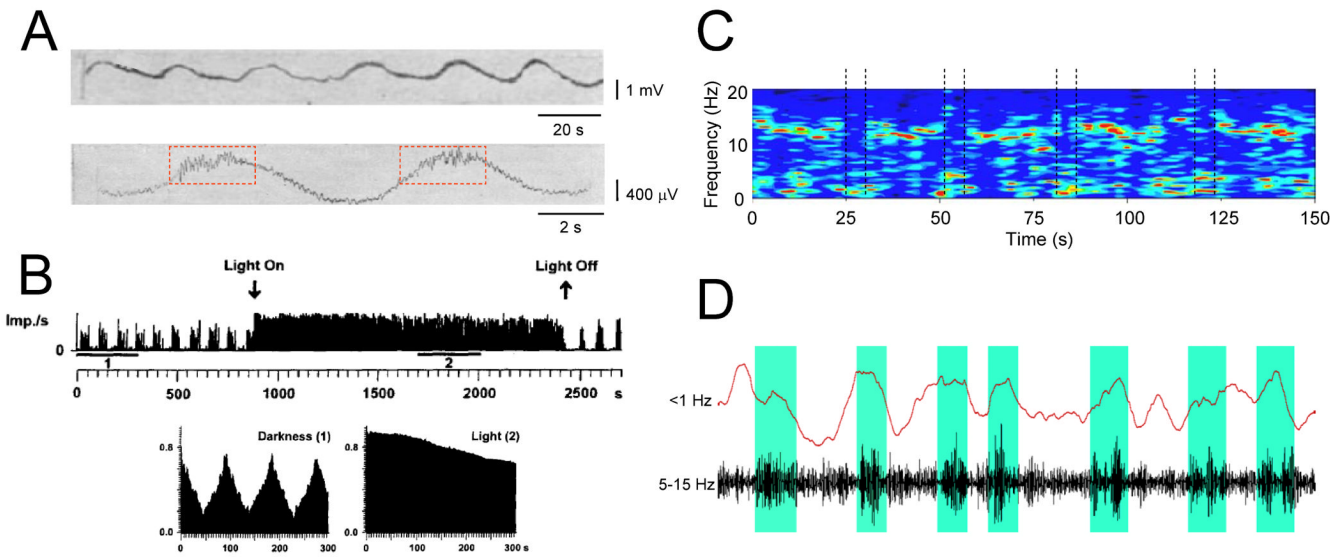

Figure 2. ISOs in the intact animal brain

A. ISOs recorded from the neocortex of the rabbit. The top trace shows an ISO occurring at ~0.05 Hz. The trace below shows a distinct ISO at ~0.1 Hz which is accompanied by faster oscillations during its most positive phases (see red boxes) (modified from Aladjalova, 1957). **B.** Activity of an LGN neuron in a urethane-anaesthetized rat. Note the presence of a clear ISO in unit activity and its abolition by light. Corresponding auto-correlograms are shown below (modified from Albrecht et al., 1998). **C.** Spectrogram showing the dominant frequency components of an LFP recording from a freely moving cat. Note how periods of α activity (at ~12 Hz) recur every 25-30 seconds and are separated by brief periods of activity at a lower frequency (between dotted lines) (modified from Hughes et al., 2004). **D.** LFP recording from the LGN of a freely moving cat filtered at <1 Hz (top, red trace) and 5-15 Hz (bottom, black trace). Note the presence of an ISO in the low-pass filtered trace and how periods of increased α activity are associated with positive-going deflections in this signal (green bars) and vice versa.

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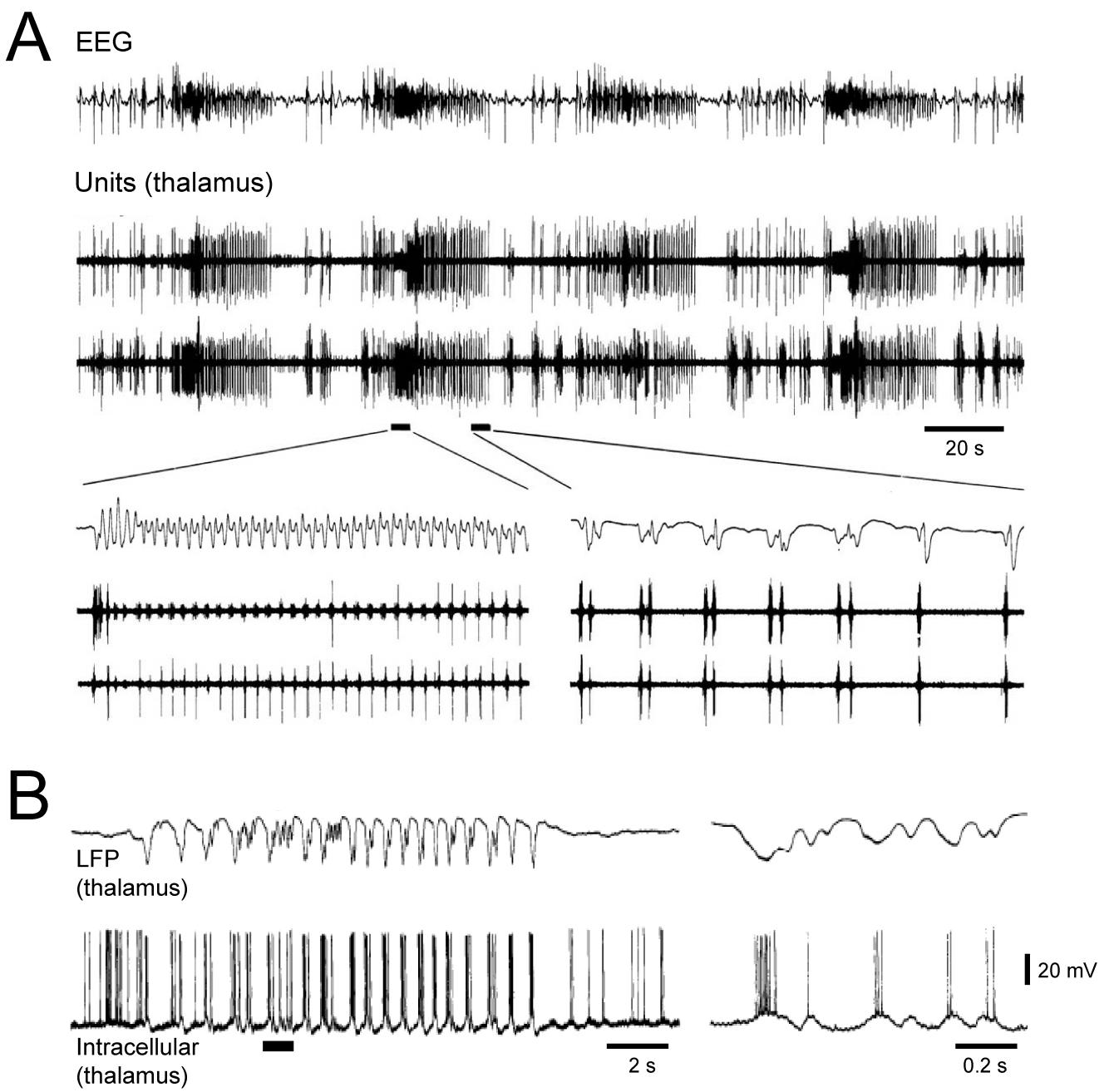

Figure 3. Cyclic paroxysms in the cat thalamus *in vivo*

A. Cyclic paroxysms induced by injection of bicuculline in the cortex of the anaesthetized cat. The top trace shows the depth EEG from the precruciate cortex whereas the two traces below are multiunit recordings from the thalamus. The enlargements further below illustrate the two main components of a paroxysm, namely fast runs at ~10 Hz (left) and SW/PSW complexes at 1.5-2 Hz (right) (modified from Steriade and Contreras, 1998). **B.** Simultaneous LFP recording and intracellular recording from a neuron in the ventral-lateral (VL) thalamus during a paroxysmal episode in the anaesthetized cat. The underlined section is enlarged to the right (modified from Steriade and Contreras, 1995).

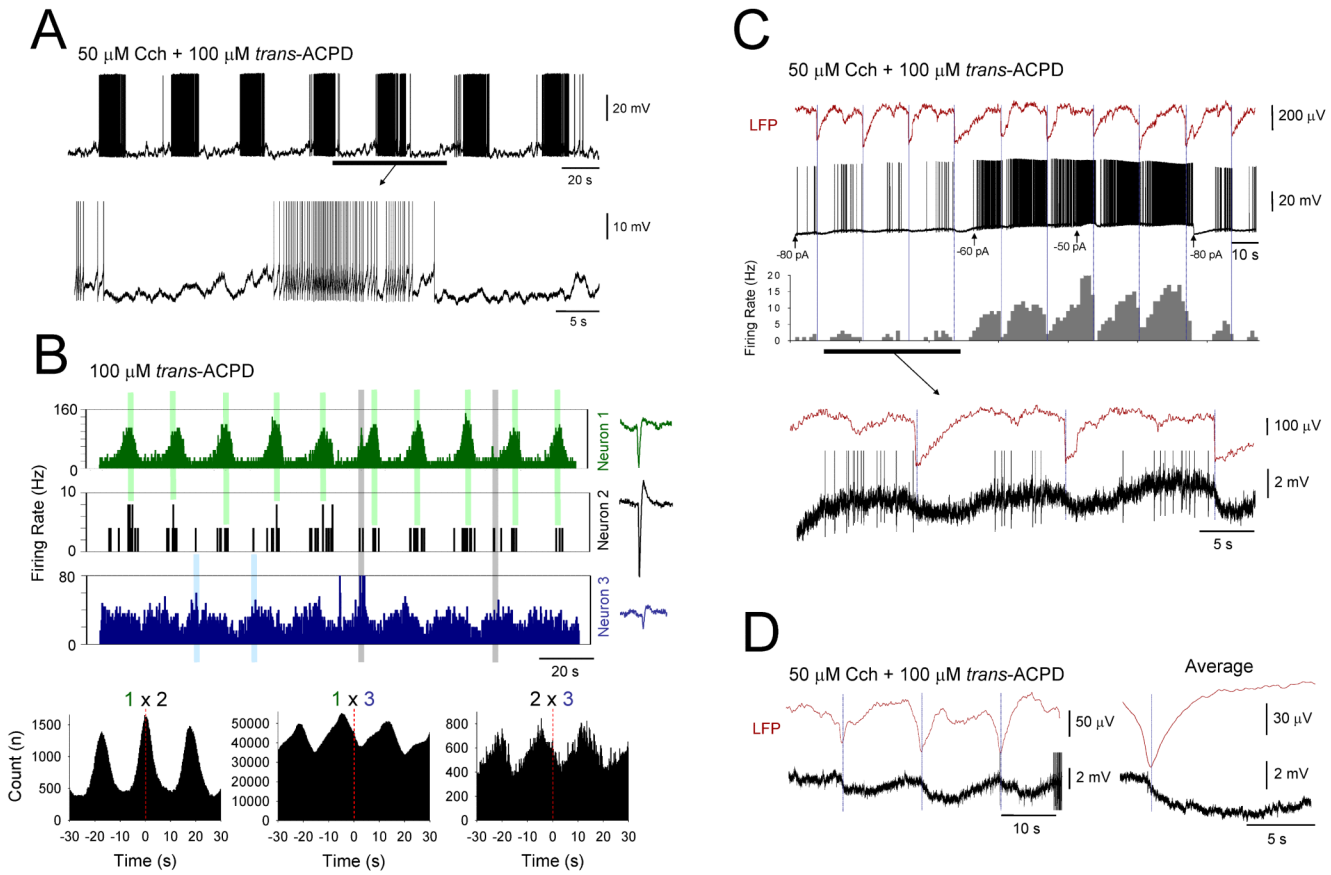

Figure 4. Basic properties of the ISO in acute thalamic slices

A. Intracellular recording of TC neuron from a cat LGN slice in the combined presence of the muscarinic AchR agonist, carbachol (Cch, 50 μM) and the non-selective mGluR agonist, *trans*-ACPD (100 μM). This neuron exhibits a stable, rhythmic ISO at ~0.025 Hz. **B.** Firing rate histograms for three distinct TC neurons simultaneously recorded from a slice preparation of the cat VB in the presence of 100 μM *trans*-ACPD. An ISO at ~0.05 Hz is evident in all three histograms. Note how the firing of neuron 3 (bottom plot, blue bars) peaks before that of neuron 1 (top plot, red bars) but that neuron 2 (middle plot, grey bars) seems to be directly linked to both cells (light red and light blue bars). The plots below show the corresponding cross-correlograms for the three neuron-neuron combinations. **C**. Simultaneous LFP and intracellular TC neuron recording of an ISO at ~0.06 Hz (dark red trace) in the cat MGN (black trace) at different levels of steady injected current as indicated. The corresponding firing rate histogram is shown immediately below. Shown further below is an enlarged section of the recording showing that the negative peaks of the LFP (blue vertical lines) are coincident with a hyperpolarization and suppression of firing in the TC neuron (in this experiment the $GABA_A$ receptor antagonist, SR95531, 10 μM, and the $GABA_B$ receptor antagonist CGP54626, 10 μM, were present in the recording medium). **D**. Different simultaneous LFP and intracellular TC neuron recording of an ISO at ~0.083 Hz (red trace) obtained from an LGN slice. The traces to the right show the LFP negative peak-triggered averages for the LFP and membrane potential. (All panels reproduced from Lorincz et al., 2009a with permission).

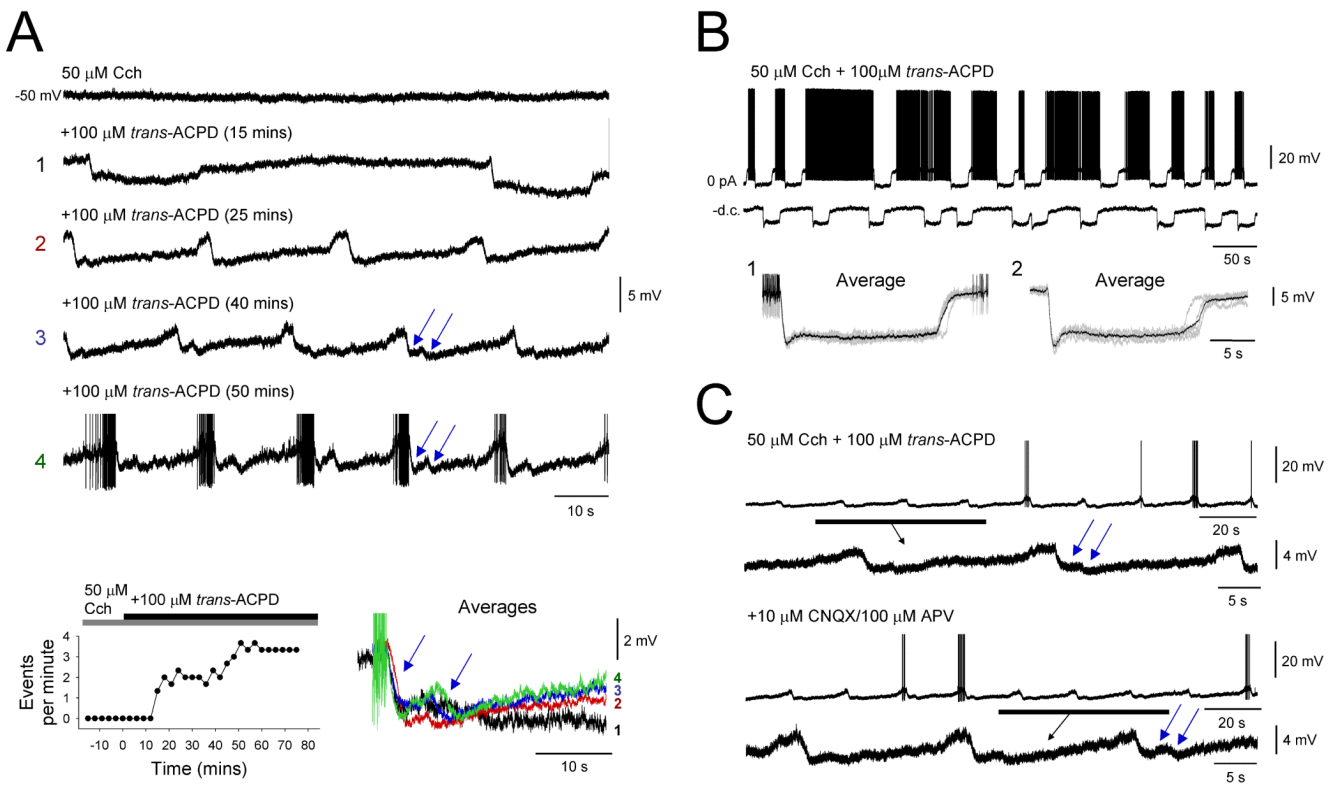

Figure 5. The ISO in thalamic slices is sculpted by stereotypical, long-lasting hyperpolarizing potentials

A. Intracellular recording of a TC neuron in the presence of 50 μM Cch which does not exhibit spontaneous firing (top trace). Following the additional application of 100 μM *trans*-ACPD the cell exhibits stereotypical long-lasting hyperpolarizing potentials which gradually increase in frequency (**1**-**3**) until an ISO with a stable frequency of ~0.05 Hz is established (**4**). The plot in the bottom left corner shows the time-course of these hyperpolarizing potentials following *trans*-ACPD application. The bottom right panel shows averages of the hyperpolarizing potentials at different stages of *trans*-ACPD application, as indicated. Note the biphasic nature of these events (as indicated by the blue arrows). **B.** ISO recorded intracellularly from a TC neuron in an LGN slice in the absence of steady injected current (top) and following the injection of a small amount of steady hyperpolarizing current (below). Although the ISO is irregular, the long-lasting hyperpolarizing potentials from which it is sculpted are conserved. This is further indicated by the averages (black traces) of these potentials which are shown below for the supra- (**1**) and subthreshold (**2**) case (the grey traces show the individual events used for constructing the average). **C.** Top traces: ISO at ~0.05 Hz recorded intracellularly in an LGN TC neuron. The underlined section is enlarged below and shows the stereotypical, biphasic nature of the constituent hyperpolarizing events. Bottom traces: these potentials, and therefore the overall ISO, are unaffected by 10 μM CNQX and 100 μM APV. (All panels reproduced from Lorincz et al., 2009a with permission).

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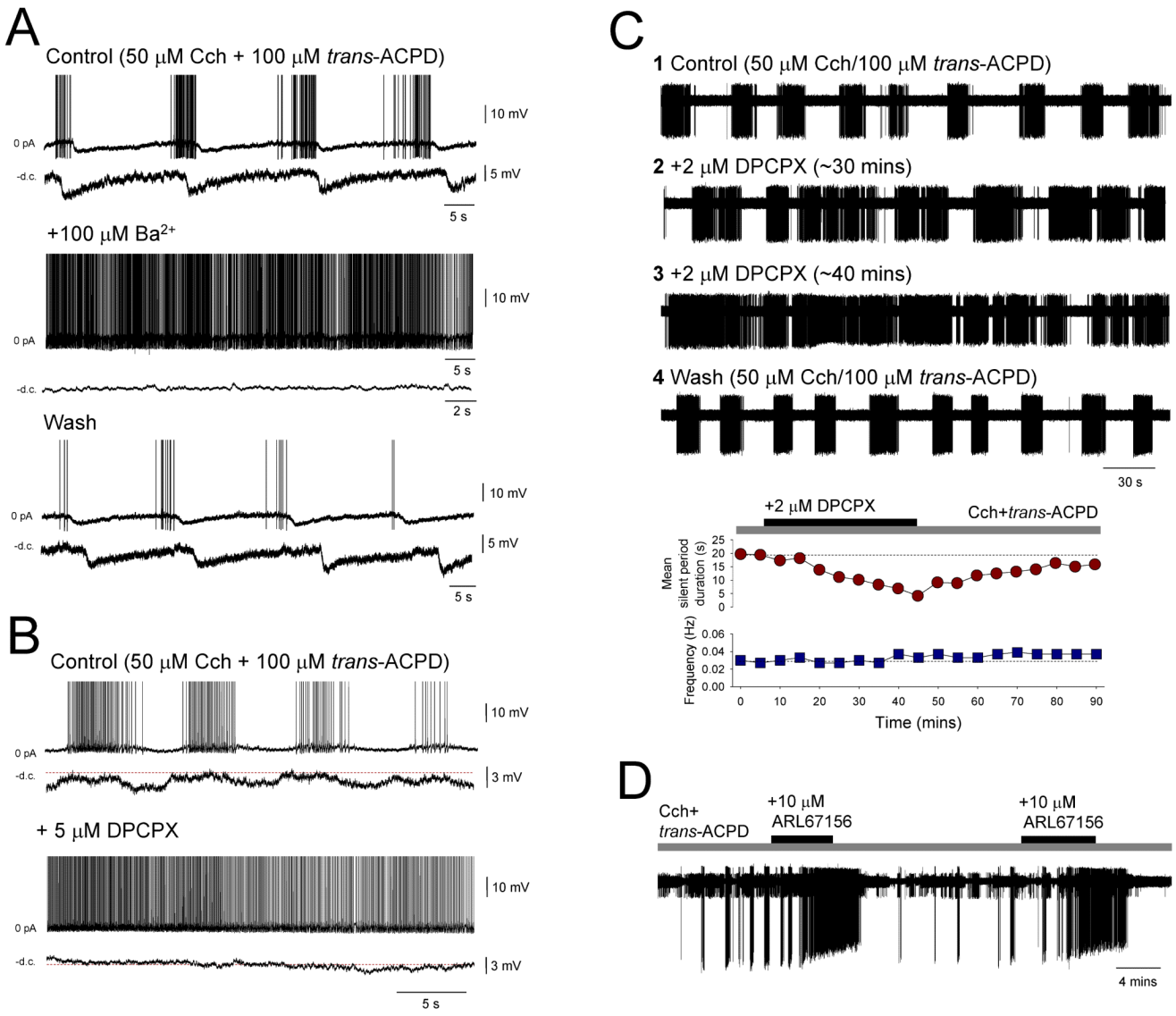

Figure 6. Evidence that long-lasting hyperpolarizing potentials result from GIRK channel opening by ATP-derived adenosine

A. Top panel: ISO recorded intracellularly in a cat LGN slice in the absence of steady injected current (top) and following the injection of a small amount of steady hyperpolarizing current (bottom). Middle panel: 100 μM Ba^{2+} abolishes the long-lasting rhythmic hyperpolarizing potentials that constitute the ISO. In the absence of steady inject current the neuron now exhibits continuous firing. Bottom panel: following removal of Ba^{2+}, hyperpolarizing potentials reappear and the neuron reverts to exhibiting an ISO. **B.** The ISO and constituent hyperpolarizing potentials in an LGN TC neuron are abolished by the A1 receptor antagonist, DPCPX (5 μM). **C.** Top: single unit extracellular recording in a cat VB slice showing the effect of DPCPX on an ISO observed in the presence of 50 μM Cch. Bottom: plots showing the effect of DPCPX on the mean duration of the silent period (top) and the overall frequency (bottom) of the ISO shown above. **D.** Extracellular single unit recording of a VB TC neuron exhibiting an ISO in the presence of 50 μM Cch. The ecto-ATPase inhibitor ARL67156 reversibly converts the ISO into continuous firing. (All panels modified or reproduced from Lorincz et al., 2009a with permission).

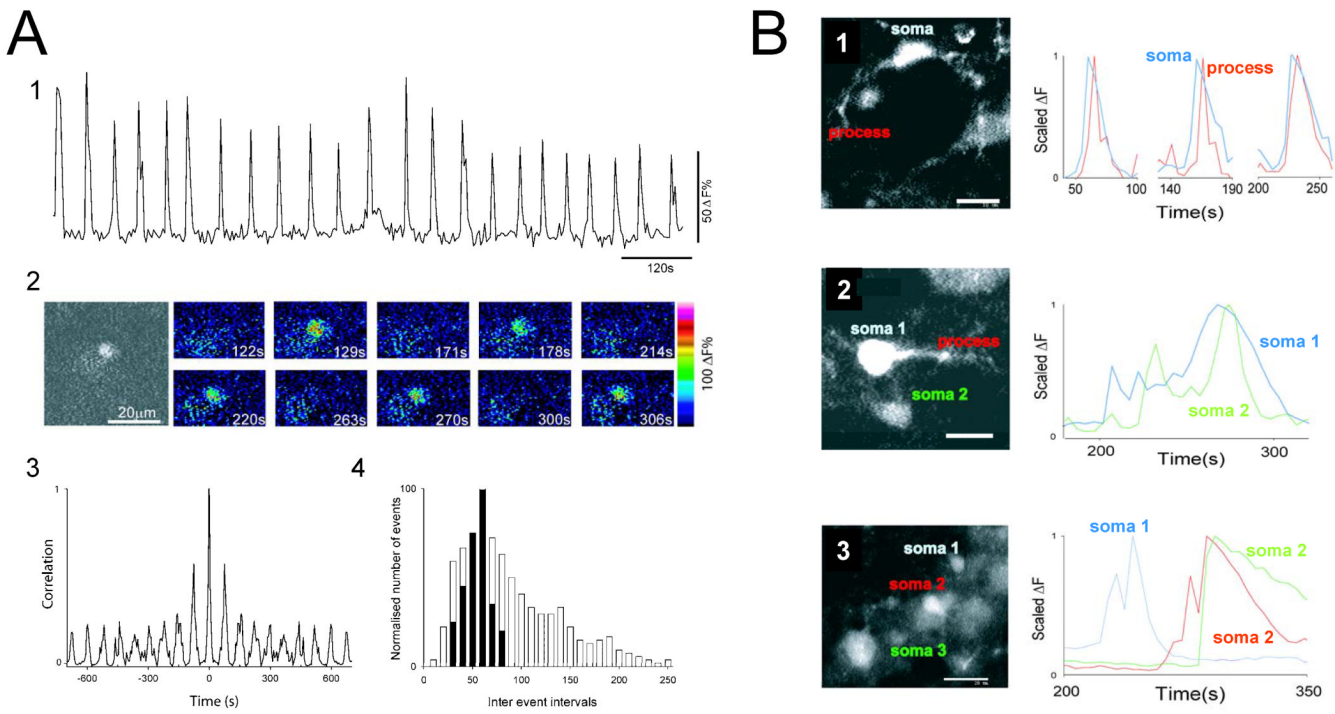

Figure 7. Rhythmic Ca^{2+} oscillations and intra- and intercellular Ca^{2+} waves in thalamic astrocytes

A. Rhythmic intracellular $[Ca^{2+}]_i$ oscillations recorded from an astrocyte in a rat VB slice (**1**), corresponding raw images (**2**) and associated auto-correlogram (**3**). The inter-event intervals for all rhythmically-active astrocytes are given by the filled bars in **4**. The empty bars in **4** represent the inter-event intervals for astrocytes that show spontaneous $[Ca^{2+}]_i$ oscillations that are non-rhythmic. Note how the rhythmic astrocytes appear to represent a specific subset of spontaneously active cells (reproduced from Parri and Crunelli, 2001 with permission). **B.** Propagation of $[Ca^{2+}]_i$ signals from the soma to a dendritic process in a thalamic astrocyte from the rat VB (1). Propagation of $[Ca^{2+}]_i$ between the somas of two dinstinct astrocytes (2). Propagation of $[Ca^{2+}]_i$ signal between the somas of three distinct astrocytes (3). In all three cases, note the appreciable delay of several seconds in the peak of the signal within and between astrocytes (modified from Parri et al., 2001).

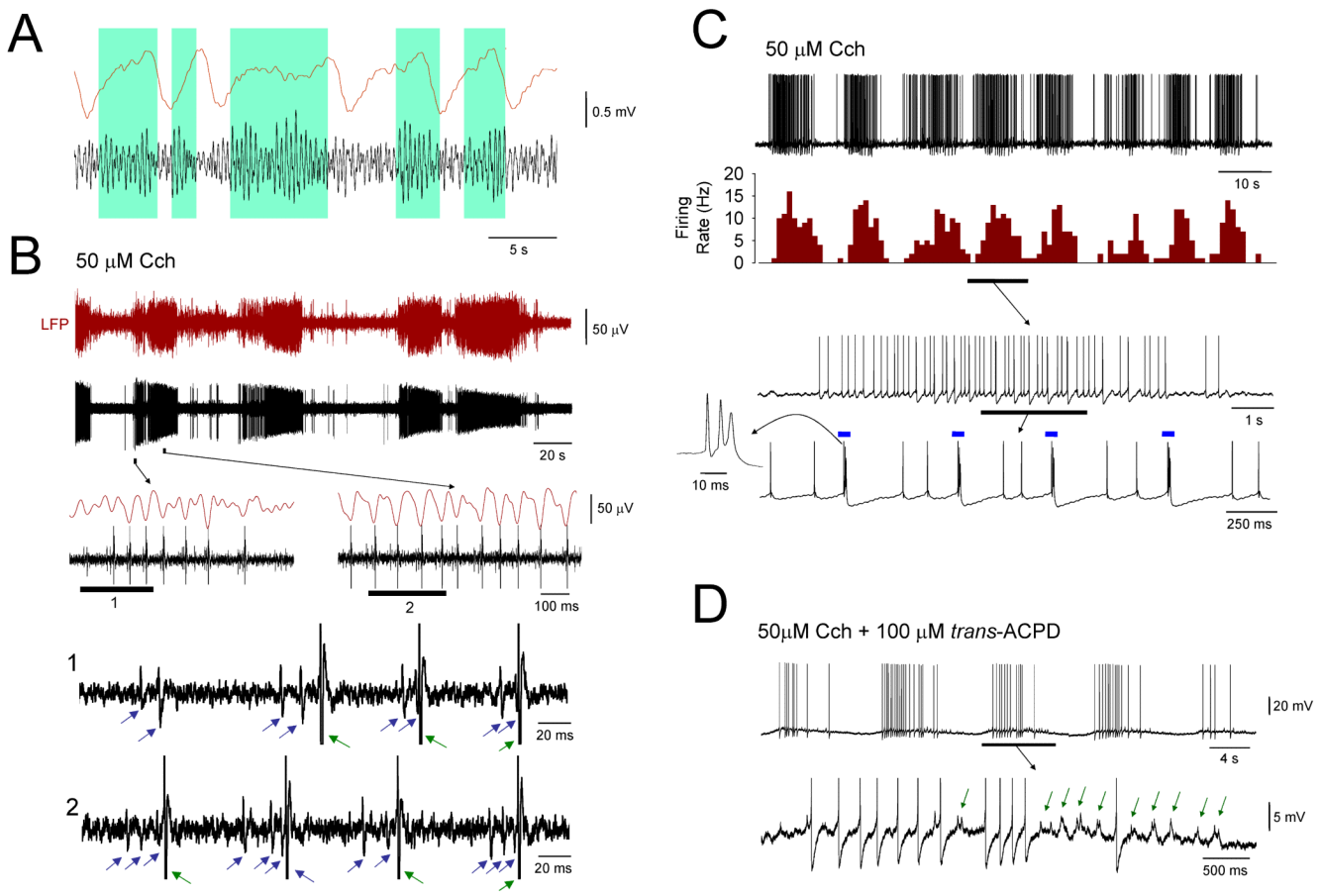

Figure 8. Modulation of network α oscillations and associated HT bursting by the ISO *in vitro*

A. LFP recording from the LGN of a freely moving cat filtered at <1 Hz (top, red trace) and 2-10 Hz (bottom, black trace). Note the presence of an ISO in the low-pass filtered trace and how periods of increased α activity are associated with positive-going deflections in this signal (green bars) and vice versa. **B.** Simultaneous LFP and multi-unit recording from the LGN in the presence of 50 μM Cch showing that the ISO in firing (bottom) is associated with a modulation of faster oscillations in the LFP (top). The labelled sections are expanded below and show that the ~13 Hz field oscillations are associated with HT bursts (blue arrows in expanded sections) that appear to drive activity in an additional tonic firing cell (green arrows in expanded sections). **C.** Intracellular recording of an LGN TC neuron which exhibits an ISO at ~0.075 Hz in the presence of 50 μM Cch. The corresponding firing rate histogram is shown immediately below. Enlarged sections are shown further below (HT bursts indicated by blue bars). **D.** ISO at ~0.1 Hz recorded intracellularly from an LGN TC neuron where the most depolarized phase of the oscillation is crowned not only by action potentials but also by a combination of spikelets and burstlets (green arrows in the enlarged section below). (All panels except **A** reproduced from Lorincz et al., 2009a with permission).

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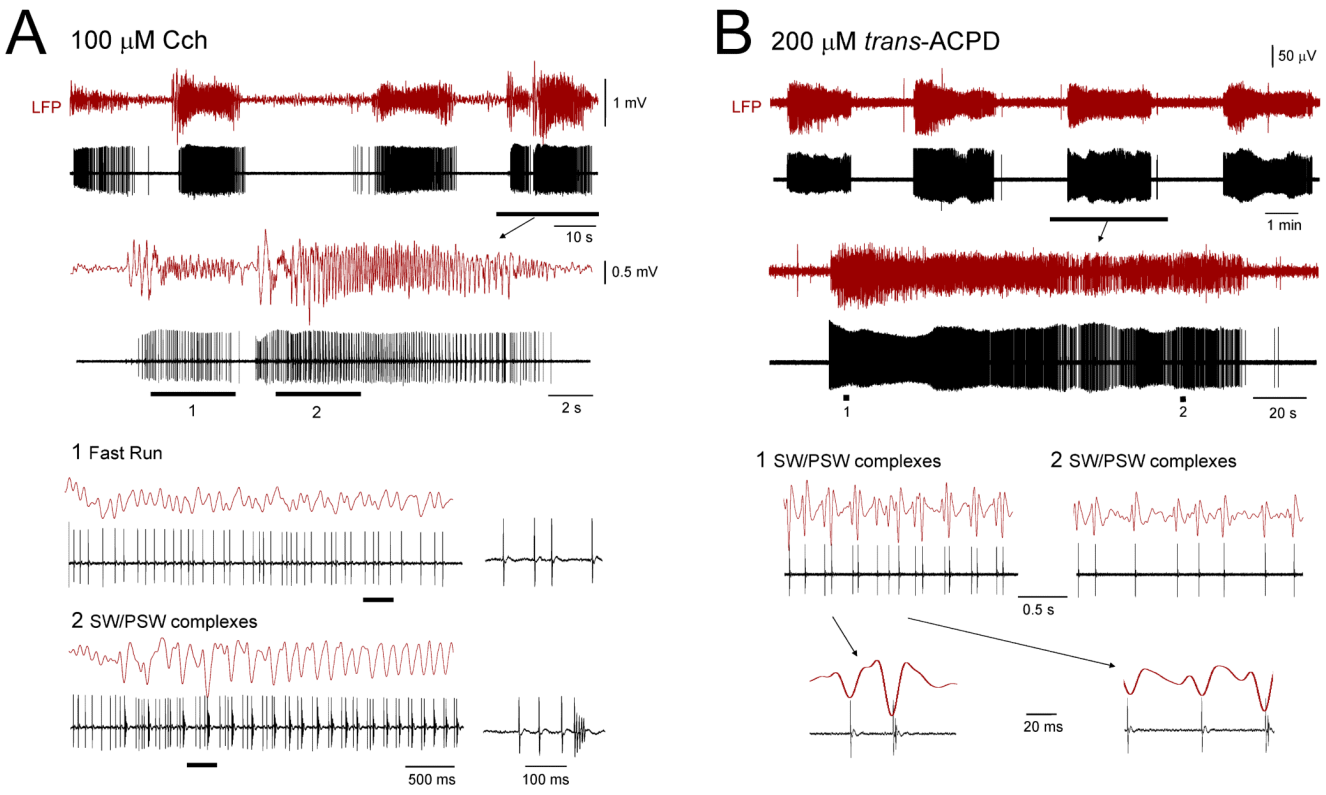

Figure 9. Excessive activation of mAchRs or mGluRs leads to ISO-derived cyclic paroxysms in the thalamic slice

A. LFP and unit recording from a cat VB slice in the presence of 100 μM Cch showing paroxysmal activity recurring with infra-slow rhythmicity at ~0.03 Hz. The underlined section is enlarged below. Additional enlargements of the sections marked **1** and **2** are shown further below and reveal that LFP activity consists of a mixture of fast runs at ~10 Hz that are related to periods of tonic firing (1), and rhythmic SW/PSW complexes at ~4 Hz (2) which are associated with powerful HT burst activity (cf. Fig. 3A). In **1** and **2**, the underlined portions are expanded on the right. **B**. LFP and unit recording from a cat LGN slice in the presence of 200 μM *trans*-ACPD, again showing paroxysmal activity recurring at at ~0.004 Hz. The underlined section is enlarged below. Additional enlargements of the sections marked **1** and **2** are shown further below, as indicated, and reveal that field activity consists of rhythmic SW/PSW complexes at ~3 Hz which are closely related to HT burst activity in the simultaneously recorded TC neuron. (All panels reproduced from Lorincz et al., 2009a with permission).

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