Altered Activity in the Central Medial Thalamus Precedes Changes in the Neocortex during Transitions into Both Sleep and Propofol Anesthesia

Rowan Baker,1,* Thomas C. Gent,1,* Qianzi Yang,1,* Susan Parker,1,2 Alexei L. Vyssotski,3 William Wisden,1 Stephen G. Brickley,1 and Nicholas P. Franks1

Departments of Life Sciences and Physics, Imperial College, South Kensington, London, SW7 2AZ, United Kingdom, and Institute of Neuroinformatics, University of Zurich/ETH Zurich, CH-8057 Zurich, Switzerland

How general anesthetics cause loss of consciousness is unknown. Some evidence points toward effects on the neocortex causing “top-down” inhibition, whereas other findings suggest that these drugs act via subcortical mechanisms, possibly selectively stimulating networks promoting natural sleep. To determine whether some neuronal circuits are affected before others, we used Morlet wavelet analysis to obtain high temporal resolution in the time-varying power spectra of local field potentials recorded simultaneously in discrete brain regions at natural sleep onset and during anesthetic-induced loss of righting reflex in rats. Although we observed changes in the local field potentials that were anesthetic-specific, there were some common changes in high-frequency (20–40 Hz) oscillations (reductions in frequency and increases in power) that could be detected at, or before, sleep onset and anesthetic-induced loss of righting reflex. For propofol and natural sleep, these changes occur first in the thalamus before changes could be detected in the neocortex. With dexmedetomidine, the changes occurred simultaneously in the thalamus and neocortex. In addition, the phase relationships between the low-frequency (1–4 Hz) oscillations in thalamic nuclei and neocortical areas are essentially the same for natural sleep and following dexmedetomidine administration, but a sudden change in phase, attributable to an effect in the central medial thalamus, occurs at the point of dexmedetomidine loss of righting reflex. Our data are consistent with the central medial thalamus acting as a key hub through which general anesthesia and natural sleep are initiated.

Key words: general anesthesia; midline thalamic nuclei; sleep

Introduction

Although significant progress has been made toward our understanding of how general anesthetics act at the molecular level (Rudolph and Antkowiak, 2004; Franks, 2008), much less is known about how anesthetics cause loss of consciousness at the level of neuronal networks (Alkire et al., 2008; Franks, 2008). Are some anatomical structures preferentially affected? Also, to what extent does anesthetic-induced loss of consciousness resemble natural sleep?

Almost all studies that have attempted to answer these questions have used imaging techniques and/or EEG measurements (mostly on humans). Key EEG signatures have been identified (Ku et al., 2011; Ni Mhuircheartaigh et al., 2013; Purdon et al., 2013) that are associated with loss of consciousness, and there is widespread agreement that functional connectivity between various parts of the brain is disrupted. However, there is no clarity as to which circuits are preferentially affected and which changes actually cause loss of consciousness (Velly et al., 2007; Boveroux et al., 2010; Mhuircheartaigh et al., 2010; Ku et al., 2011; Långsjö et al., 2012; Lewis et al., 2012; Schröter et al., 2012; Gómez et al., 2013; Jordan et al., 2013; Liu et al., 2013a, b).

A common feature of most, but not all, previous work is the use of a single anesthetic (propofol), which means that changes critical to loss of consciousness per se may be confounded by agent-specific changes. Similarly, rarely are the states of anesthetic-induced loss of consciousness and natural sleep directly compared during the same experiments. Finally, and perhaps most importantly, most previous studies have been limited, for technical reasons, in their temporal resolution, so that al-
though the states before and after loss of consciousness can be well characterized, what happens at the critical transition is harder to discern.

In this paper, we recorded local field potentials (LFPs) from four brain regions simultaneously in freely moving rodents during transitions into natural sleep and anesthetic-induced loss of righting reflex. Our use of Morlet wavelets to analyze these signals provided a far higher time resolution than is usually obtained by using Fourier Power spectra calculated from segments of data (typically $\approx 10$ s).

We measured from the barrel (BARR) cortex and the ventrobasal (VB) thalamus as representative of a first-order thalamocortical loop. We also recorded from the anterior cingulate cortex (CING) and the central medial thalamus (CMT), a higher-order (Sherman and Guillery, 2006; Jones, 2009) midline nucleus of the intralaminar complex, which projects widely to different cortical areas (Vertes et al., 2012), including the anterior cingulate.

Our data show strong similarities in the changes in the LFPs at high frequencies in the central medial thalamus at the point of anesthetic-induced loss of righting reflex, and following the transition into natural sleep. Moreover, for both natural sleep and propofol anesthesia, these changes occur significantly earlier than changes in the neocortex, suggesting that transition to loss of righting reflex is initiated by subcortical mechanisms.

### Materials and Methods

**Animals.** We used adult male Sprague Dawley rats (Charles River) weighing 320–360 g. All experiments were performed in accordance with the United Kingdom Home Office Animal Procedures Act (1986) with local ethical approval. We used a total of 22 animals. In many cases (13 of 22), the animals were used more than once (for sleep or anesthetic experiments), but for any given animal at least 7 d was allowed between experiments.

**Surgery and recording electrodes.** Surgical procedures were performed under either iso-flurane or ketamine/xylazine anesthesia, and animals were allowed at least 7 d to recover. Depending upon the experiment, we used either extradural stainless steel electrodes (J.I. Morris) to record cortical ECoG, or bipolar tungsten electrodes (1 M$\Omega$ impedance; MicroProbes) to record LFPs, or a combination of both. The coordinates of these electrodes are given in Table 1, and the nuclei chosen for LFP measurements are shown schematically in Figure 1A. In most experiments, an EMG electrode was imbedded in the trapezius muscles of the neck. Electrical signals were recorded on a wireless electronic recording device (Neurologger 2) at a sampling rate of 200 Hz as described previously (Pang et al., 2009; Vyssotski et al., 2009; Zecharia et al., 2012). The data recorded by the Neurologger were downloaded to a PC at the end of the experiment, and wave-

### Table 1. Coordinates of recording sites

| Bipolar electrodes | AP   | ML   | DV   |
|--------------------|------|------|------|
| CMT                | −3.2 | 0.0  | −6.5 |
| CING               | +3.0 | −0.8 | −2.3 |
| VB                 | −3.4 | −3.0 | −6.0 |
| BARR               | −2.5 | −5.0 | −3.0 |

*Coordinates of the recording electrodes relative to bregma: AP, anteroposterior; ML, mediolateral; DV, dorsoventral.

![Figure 1](image-url)

**Figure 1.** Recording of LFPs. **A,** The four brain sites from which we recorded LFPs (for the coordinates, see Table 1). Red dots indicate the electrode positions determined postmortem. **B,** Four representative brain sections verifying electrode placements (red arrows) for the CMT, CING, VB, and BARR deduced from the tracts. **C,** An example of LFPs recorded from the CING, CMT, BARR, and VB. These data were recorded from an animal under dexmedetomidine anesthesia. **D,** In experiments with anesthetics, a rat was placed in a rotating Plexiglas tube, and the electrical signals from the implanted electrodes were recorded on a small device that was plugged into a socket fixed to the animal’s skull. Anesthetics were introduced, when needed, via an implanted jugular vein catheter. **E,** Examples of Morlet wavelet power spectra from two of the LFP traces (for the central medial thalamus leading the LFP in the cingulate by $45^\circ$). **F,** Examples of phase plots for the cross-wavelet transform in E; for the two frequency domains with significant covariant power. In this example, the phase plots show that there is no significant phase relationship between the two LFP signals in the frequency range 20–32 Hz, but a high degree of phase coherence in the 0 range of frequencies of 1–4 Hz, with the LFP in the central medial thalamus leading the LFP in the cingulate by $−40^\circ$.
To standardize our recordings, we recorded LFPs during periods of waking state in the same orientation (medial-lateral) with the same nominal polarity. Representative of a higher-order thalamocortical circuit (Destexhe et al., 1999; Costa-Miserachs et al., 2003), we chose to record from the VB thalamus and BARR as representative of an individual rat showing a transition between the waking state and NREM sleep. The Morlet wavelet power spectra are shown for a dural electrode (ECoG) and four bipolar electrodes: the CMT, an imaginary and real parts of the cross-wavelet transform, which are time-scaled variants of a “Mother” wavelet. In general, the wavelet transform is defined as follows:

$$W(s, \tau) = \frac{1}{\sqrt{s}} \int x(t) \phi \left( \frac{t - \tau}{s} \right) dt$$

where $s$ and $\tau$ represent the scale and local center of the wavelet $\phi(s, \tau)$, and $x(t)$ is the LFP signal as a function of time $\tau$. We used the most commonly used Mother wavelet, the Morlet function, which is a complex sinusoid, windowed by a Gaussian:

$$\varphi_0(\eta) = \pi^{-1/4} e^{-\eta^2/2}$$

where $\eta$ is a dimensionless “time” parameter and $\omega_0$ is the dimensionless wavelet central “frequency,” which was set to 6 to satisfy the admissibility criterion (Farge, 1992). The Wavelet power spectra, which are given by the square of the wavelet transform, were calculated using MATLAB (MathWorks) with a script based on that of Torrence and Compo (1998). We investigated the relationship between LFPs from different electrodes by evaluating the cross-wavelet transform (Grinsted et al., 2004), $W_{xy}(s, \tau)$, which is calculated by multiplying the cross-wavelet transform of one signal, $x$, by the complex conjugate of the wavelet transform of a second signal, $y$. Thus:

$$W_{xy}(s, \tau) = W_x(s, \tau) \cdot W^*_y(s, \tau)$$

This cross-wavelet transform is large where both signals have high covariant power in both the time and frequency domains (Fig. 1F). The phase relationship between the two LFP signals can be calculated using the following:

$$\varphi(s, \tau) = \tan^{-1} \left( \frac{\Im \{W_{xy}(s, \tau)\}}{\Re \{W_{xy}(s, \tau)\}} \right)$$

where $\phi$ is the phase angle at scale $s$ and time $\tau$, and $\Im$ and $\Re$ are the imaginary and real parts of the cross-wavelet transform $W_{xy}$, respectively (Fig. 1G). For both the wavelet power spectra and the cross-wavelet transforms, a 95% confidence level was calculated assuming a red noise background (Torrence and Compo, 1998; Bédard and Destexhe, 2009). Only data that exceeded the 95% confidence level were included in the analysis.
In most cases, analyses of changes in power or phase angle during LORR involved following a fixed band of frequencies (e.g., δ oscillations between 1 and 4 Hz or θ oscillations between 5 and 9 Hz), for high-frequency oscillations; however, where there were large and continuous changes in frequency and power, the peak power and frequency at peak power were calculated at each time using a script in MATLAB that identified a peak within a broad band of frequencies (e.g., between 10 and 64 Hz) and followed peak power and frequency with time.

Results

Transitions into natural NREM sleep

To compare anesthetic-induced loss of consciousness with natural sleep, we first investigated the transitions from the waking state into NREM sleep. These experiments used rats (n = 9) housed in their home cages. In addition to recording LFPs from the individual thalamic nuclei and neocortical regions (CMT, CING, VB, and BARR; Fig. 1), we also measured ECoG signals using frontoparietal dural electrodes. These more global measurements of cortical activity are traditionally used, together with the EMG, to score an animal as being in WAKE, or sleeping in REM or NREM (Costa-Miserachs et al., 2003). Transitions into NREM are characterized by an increase in the ratio of δ to θ power, accompanied by a reduction in EMG power. During daytime, when NREM is at a maximum, rats typically had 8 periods of consolidated sleep, and we scored multiple WAKE-NREM transitions. Interestingly, following the abrupt WAKE-NREM transition identified using the EMG and ECoG, we could identify a transitional period of 10–20 s, immediately following the loss in muscle tone, before power in the δ band was fully established in the LFPs (Fig. 2). Immediately at the start of the “NREM onset”
with the most dominant feature being the $\theta$ oscillations at $\sim 8$ Hz, characteristic of moving rodents (Vanderwolf, 1969), and sporadic bursts of power at $\gamma$ frequencies ($\sim 40$ Hz). However, at $\sim 30$ s before LORR, there was a marked increase in power in the $\gamma$ frequency band and a coincident, gradual reduction in frequency (Figs. 4 and 5A). The frequency of the oscillations continuously reduced from $\sim 40$ Hz to $\sim 20$ Hz and then remained stable (Fig. 5A). The increase in peak power occurred in all four recording sites (CMT, CING, VB, and BARR) and reached a maximum at around LORR. This increase in power was characteristically different for the CMT compared with that seen in the other three regions, starting significantly earlier and with power reaching a peak at LORR but then subsiding somewhat (Fig. 5A). Half-times that characterized the changes in power and frequency in the high-frequency oscillations were obtained from data for individual animals. The half-times between the initial and maximum powers and minimal frequencies are shown in Figure 5B, C, where it can be seen that the power increases in the CMT significantly before the other three sites and the frequency changes in the CMT occur significantly earlier than changes in the VB and BARR.

In addition to the gradual changes in the power and frequency of the high-frequency oscillations, a striking additional feature in the LFPs was the sudden appearance of a strong oscillation $\sim 8$ Hz, more or less coincident with LORR (Figs. 4 and Fig. 5D). Power in this band of frequencies was not significantly above noise just before LORR but increased substantially following LORR (Fig. 5D). There was also an increase in power in the $\delta$ range (1–4 Hz) following propofol infusion (Fig. 5D), but this consisted of brief sporadic bursts of power, with no consistent phase relationships between the recording sites. We did note, however, that, following a period of propofol anesthesia, the eventual recovery and return to waking occurred from a state that resembled natural sleep with consistently high $\delta$ power, and was not simply a reversal of the changes observed during induction.

Transitions into dexmedetomidine-induced loss of righting reflex

Approximately 50 s after the $\alpha_2$-adrenergic receptor agonist dexmedetomidine (20 $\mu$g/ml) was infused at 20 $\mu$g kg$^{-1}$ min$^{-1}$ into the right jugular vein, rats placed inside the rotating cylinder lost their righting reflex after $48 \pm 3$ s (mean $\pm$ SEM; $n = 11$). Before LORR, the rats were able to maintain an upright posture and showed high power in the EMG (Fig. 4). For $\sim 20$ s after injection, the LFP power spectra showed little change,
7D) mirrored those observed between waking and NREM sleep (Fig. 3D).

Strong phase coherence was observed in the δ oscillations between the different recording sites that resembled those seen during NREM sleep (Fig. 3E). Once the δ oscillations had become established, the thalamic LFPs led the cortical LFPs by 110° (CMT-CING and VB-BARR), whereas the LFPs recorded between the cortical electrodes (CING-BARR) and between the thalamic electrodes (CMT-VB) were in phase (Fig. 7E). Immediately at LORR, however, there was a sudden phase change with the phase lead of the CMT decreasing by 45° with respect to the other three recording sites (Fig. 7E).

Discussion

We used multisite recording of LFPs in the brain and fast temporal analysis (Morlet wavelets) to investigate the controversy as to whether the neocortex or a subcortical region is the first to show changed activity at the boundary between the waking state and anesthetic-induced unconsciousness. Our principal finding is that, although there are changes in the LFPs that are anesthetic specific, altered activity in a band of high-frequency oscillations can be detected in a higher-order thalamic nucleus (CMT) significantly earlier than changes can be detected in the neocortex during transitions into natural sleep and propofol-induced loss of righting reflex. Our data with natural sleep identify a novel stage that precedes fully established NREM during which changes in the CMT are apparent with little change in a first-order thalamic nucleus, VB. Our most striking discovery with dexmedetomidine is that, in addition to it inducing a state similar to NREM, there is an abrupt phase change in the LFPs at δ frequencies in the CMT at the point of loss of righting reflex. We shall discuss each of these transitions in turn.

In rodents, NREM sleep is characterized by an increase in the ratio of δ to θ power in the EEG, and this was seen in the LFPs when NREM was fully established. However, before this point, there is a short transitional period where there is a large increase in power, and reduction in frequency, in the higher frequency oscillations recorded in the CMT, with smaller, or insignificant, changes in the other nuclei.

The changes that we observe in the CMT add weight to the proposal that such midline and intralaminar thalamic nuclei are hubs regulating cortical arousal and natural sleep (Glenn and Steriade, 1982; Van der Werf et al., 2002; Picchioni et al., 2014). At sleep onset, these nuclei receive a diminished input from the ascending reticular activating system (Siegel, 2004; Saper et al., 2010). Our observation that LFPs change in the CMT at the onset of NREM supports current thinking about the subcortical control of sleep states (Saper et al., 2010) and the observation that thalamic deactivation precedes a reduction in cortical arousal at sleep onset (Magnin et al., 2010). It seems clear that cortical changes, such as the breakdown in connectivity, observed during natural NREM sleep (Massimini et al., 2005), are initiated by subcortical neuronal mechanisms.

The α2 adrenergic receptor agonist dexmedetomidine initially causes a “sleep-like” sedative state (Kimibayashi and Maze,
changes in the LFPs observed in the transition into NREM. What was quite unexpected were the sudden changes that were also similar to those that occurred during the transition into LORR. This drop in frequency was accompanied by increases in power at low (≤1 Hz) frequencies, but we did not observe any other changes occur in the neocortex suggests a subcortical origin. Indeed, inactivation of thalamic inputs causes selective long-term elimination of fast (>10 Hz) oscillations in cortical LFPs (Lemieux et al., 2014). The thalamus receives dense innervation from brainstem nuclei, and some of these nuclei can generate γ oscillations (Simon et al., 2010; Kezunovic et al., 2011; Garcia-Rill et al., 2013) with the frequency reducing as the neurons become hyperpolarized. Most network models also predict that the frequency will drop as afferent synaptic input reduces (Whittington et al., 2000; Buzsáki and Wang, 2012; Economo and White, 2012). Although this latter consideration may account for the drop in frequency seen during the transitions into natural sleep and dexmedetomidine-induced LORR, an additional factor must come into play with propofol. All anesthetics acting on GABA_A receptors slow γ oscillations (Whittington et al., 2000; Dickinson et al., 2003), and this might cause a resonance with other networks, perhaps in subcortical structures, where the frequency has reduced due to a reduction in afferent input. This might account for the large increase in power as the γ band tunes down to the strong 20 Hz “beta” oscillations that we see just before propofol-induced LORR. Similarly, a resonance between cortical and thalamocortical oscillations has been proposed to account for the large increase in power at ~8 Hz occurring immediately following LORR (Ching et al., 2010). Another EEG signature observed in humans during propofol anesthesia (Ni Mhuircheartaigh et al., 2013; Purdon et al., 2013) is the steady buildup in power at low (<1 Hz) frequencies, but we did not observe this in the LFPs.

Our results highlight the pivotal role that higher-order thalamic nuclei might play during transitions into unconsciousness (Alkire et al., 2000, 2007; Liu et al., 2013a; Giacino et al., 2014). In contrast to first-order nuclei that are driven mainly by sensory input, the higher-order nuclei receive their main driving input from large areas of neocortex. Indeed, such nuclei may serve as the main relay of information from one neocortical area to another (Sherman and Guillery, 2006) so that disruption to this key hub would inevitably lead to a breakdown in cortical connectivity that seems to be a common feature of the unconscious state. Interestingly, the intralaminal models (Lytton et al., 1996) indicate that the oscillation frequency reduces as the hyperpolarization increases. Furthermore, as the frequency slows, the preferred phase of thalamocortical neuron firing with respect to cortical LFPs is retarded (Slezia et al., 2011). These observations would broadly explain the changes we see. We speculate that a coordinated reduction in ascending arousal causes a drop in δ frequency, which in turn leads to a phase retardation in the CMT with respect to the neocortex. Because information can be encoded by the phase in the LFP at which a neuron fires (Fries et al., 2007), a sudden phase change is likely to disrupt thalamocortical communication and could, therefore, be the cause rather than the consequence of LORR.

Propofol is the most widely used intravenous anesthetic with molecular targets, GABA_A receptors, quite distinct from dexmedetomidine’s. Nonetheless, for both anesthetics, we observed changes in the power and frequency of γ oscillations at, or before, LORR. With propofol, these oscillations grow in strength and drop in frequency ~30 s before LORR. The increase in power is most pronounced, and starts earlier, in the CMT, several seconds before any changes can be detected at the other sites. Similar changes in frequency and power can be seen in the human cortical EEG (Purdon et al., 2013) before loss of consciousness. Our observation of strengthening γ oscillations in the CMT before any other changes occur in the neocortex suggests a subcortical origin. Indeed, inactivation of thalamic inputs causes selective long-term elimination of fast (>10 Hz) oscillations in cortical LFPs (Lemieux et al., 2014). The thalamus receives dense innervation from brainstem nuclei, and some of these nuclei can generate γ oscillations (Simon et al., 2010; Kezunovic et al., 2011; Garcia-Rill et al., 2013) with the frequency reducing as the neurons become hyperpolarized. Most network models also predict that the frequency will drop as afferent synaptic input reduces (Whittington et al., 2000; Buzsáki and Wang, 2012; Economo and White, 2012). Although this latter consideration may account for the drop in frequency seen during the transitions into natural sleep and dexmedetomidine-induced LORR, an additional factor must come into play with propofol. All anesthetics acting on GABA_A receptors slow γ oscillations (Whittington et al., 2000; Dickinson et al., 2003), and this might cause a resonance with other networks, perhaps in subcortical structures, where the frequency has reduced due to a reduction in afferent input. This might account for the large increase in power as the γ band tunes down to the strong 20 Hz “beta” oscillations that we see just before propofol-induced LORR. Similarly, a resonance between cortical and thalamocortical oscillations has been proposed to account for the large increase in power at ~8 Hz occurring immediately following LORR (Ching et al., 2010). Another EEG signature observed in humans during propofol anesthesia (Ni Mhuircheartaigh et al., 2013; Purdon et al., 2013) is the steady buildup in power at low (<1 Hz) frequencies, but we did not observe this in the LFPs.

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A

Dexmedetomidine LORR

B

Frequency half-times

C

Delta frequency (Hz)

Figure 7. Spectral analysis for transition into dexmedetomidine anesthesia. A, Average data (n = 7 animals) showing changes in peak power, and frequency at peak power for higher frequency oscillations (20–40 Hz) between the waking state and the states just before and just after LORR. B, Half-times for γ-frequency decrease at dexmedetomidine LORR. C, Average data (n = 7 animals) showing the δ frequency before LORR and its reduction following LORR. *p < 0.05. D, Increases in power in the 1–4 Hz frequency band (open bars) and the 5–9 Hz frequency band (shaded bars) from WAKE to LORR (n = 7 animals). E, Phase relationships between the δ oscillations (1–4 Hz) before (top) and after (bottom) dexmedetomidine-induced LORR. Red arrows indicate the average phase angle (n = 7 animals) between the indicated thalamic nuclei or neocortical regions. Averages were taken over 10 s periods just before and just after LORR using only phases where the cross-wavelet transform was contoured above noise with 95% confidence. Gray areas represent the phase angle distributions for an individual animal. Error bars indicate SEM. p values are from paired t tests between the phase before and after LORR, and are shown where significant differences occurred.

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