Stimulus-Based State Control in the Thalamocortical System

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Neural systems operate in various dynamic states that determine how they process information (Livingstone and Hubel, 1981; Funke and Eysel, 1992; Morrow and Casey, 1992; Abeles et al., 1995; Guido et al., 1995; Mukherjee and Kaplan, 1995; Kenmochi and Eggermont, 1997; Wörgötter et al., 1998; Kisley and Gerstein, 1999). To investigate the function of a brain area, it is therefore crucial to determine the state of that system. One grave difficulty is that even under well controlled conditions, the thalamocortical network may undergo random dynamic state fluctuations which alter the most basic spatial and temporal response properties of the neurons. These uncontrolled state changes hinder the evaluation of state-specific properties of neural processing and, consequently, the interpretation of thalamocortical function.

Simultaneous extracellular recordings were made in the auditory thalamus and cortex of the ketamine-anesthetized cat under

several stimulus conditions. By considering the cellular and network mechanisms that govern state changes, we develop a complex stimulus that controls the dynamic state of the thalamocortical network. Traditional auditory stimuli have ambivalent effects on thalamocortical state, sometimes eliciting an oscillatory state prevalent in sleeping animals and other times suppressing it. By contrast, our complex stimulus clamps the network in a dynamic state resembling that observed in the alert animal. It thus allows evaluation of neural information processing not confounded by uncontrolled variations. Stimulus-based state control illustrates a general and direct mechanism whereby the functional modes of the brain are influenced by structural features of the external world.

Key words: *dynamic state; thalamocortical; spindles; oscillations; ketamine; alerting stimuli; burst mode; tonic mode*

A common dynamic state is characterized by widespread, synchronous neural activity in the thalamus and cerebral cortex. In particular, activity waxes and wanes across both structures at a rate of 7–14 Hz. This state occurs in sensory, motor, and association systems of many mammals, including humans, during various stimulus-driven and spontaneous epochs, and under diverse behavioral conditions (Moruzzi and Magoun, 1949; Chang, 1950; Andersen and Andersson, 1968; Steriade and Llinás, 1988; Buzsáki, 1991; Tiihonen et al., 1991; Eggermont, 1992; Morrow and Casey, 1992; Pfurtscheller, 1992; Steriade et al., 1993; Contreras and Steriade, 1996; Llinás et al., 1999; Cotillon et al., 2000). The oscillatory activity is imposed on the neuronal network by the inhibitory thalamic reticular and excitatory thalamocortical cells, which can fire in two distinct modes (Steriade and Llinás, 1988). The rhythmic or “burst” mode typifies drowsy or sleeping animals; the single-spike or “tonic” mode is more commonly seen in alert animals. In both awake and unconscious animals, however, random fluctuations between these modes occur (Livingstone and Hubel, 1981; Morrow and Casey, 1992; Mukherjee and Kaplan, 1995; Guido and Weyand, 1995). The fluctuations are, moreover, accompanied by changes in the response patterns and in the spatial and temporal receptive field properties of the neurons (Livingstone and Hubel, 1981; Funke and Eysel, 1992; Morrow and Casey, 1992; Guido et al., 1995; Mukherjee and Kaplan, 1995; Kenmochi and Eggermont, 1997; Wörgötter et al., 1998). Uncontrolled, these changes can severely hinder the evaluation of key aspects of neural processing.

The idea of intentionally altering or arresting such modes, i.e.,

dynamic state control, has a long history in central neurophysiology. The firing mode of thalamic cells, and therefore the thalamocortical state, is responsive to electrical, chemical, and surgical manipulation (Moruzzi and Magoun, 1949; Steriade et al., 1985; Steriade and Llinás, 1988; McCormick and von Krosigk, 1992). Whereas these traditional manipulations alter thalamic network properties, they are nonspecific and may have widespread and sometimes devastating effects on the brain. Previous studies suggest, however, that such extreme methods are not essential to modulate thalamocortical state, and an external stimulus with the appropriate qualities might suffice (Moruzzi and Magoun, 1949; Pompeiano and Swett, 1962; Tiihonen et al., 1991). A stimulus with these qualities would be defined, with reference to the behavioral correlates of a burst-to-tonic mode change, an “alerting stimulus” (Tennigkeit et al., 1996).

Clearly, not all stimuli are sufficient to prevent the oscillatory mode, because 7–14 Hz rhythms can be elicited or entrained by traditional clicks and tones, light flashes, mechanical pinches, and synchronous electrical stimulation (Chang, 1950; Pompeiano and Swett, 1962; Andersen and Andersson, 1968; Eggermont, 1992; Pfurtscheller, 1992; Contreras and Steriade, 1996; Dinse et al., 1997). We develop a candidate alerting stimulus for the auditory modality, the “dynamic ripple”, whose spectrotemporal properties are motivated by the cellular and network mechanisms that regulate thalamocortical state changes. We then determine whether the dynamic ripple stimulus affects the oscillatory dynamic state and how its effects differ from traditional stimuli.

MATERIALS AND METHODS

The dynamic ripple stimulus (Escabí et al., 1998) is an elaboration of the static and the moving ripple sounds (Schreiner and Calhoun, 1994; Kowalski et al., 1996). It is a temporally varying broadband sound composed of 230 sinusoidal carriers (500–20,000 Hz) with randomized phase. The magnitude of any carrier at any time is modulated by the spectrotemporal envelope, consisting of sinusoidal amplitude peaks (“ripples”) on a logarithmic frequency axis that change through time. Two parameters define the envelope: the number of peaks per octave, or ripple density, and the speed and direction they are sweeping, or temporal frequency modulation (FM). Both ripple density and temporal FM rate were varied randomly and independently during the 20 min, nonrepeating stimulus. Ripple density varied slowly (maximum rate of change, 1 Hz) between 0 and 4 cycles per

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Figure 1. Summary of the experimental procedure. Simultaneous extracellular recordings were made in layers III/IV of primary auditory cortex and in the ventral division of the medial geniculate body. Spike trains were sorted off-line. Thalamocortical temporal relations and dynamic state were assessed with cross-correlograms and coherence measures. *AI*, Primary auditory cortex; *MGB-V*, medial geniculate body, ventral division; *SSG*, suprasylvian gyrus; *LGN*, lateral geniculate nucleus; *HC*, hippocampus.

octave; the temporal FM parameter varied between 0 and 100 Hz (maximum rate of change, 3 Hz). Both parameters are statistically independent and unbiased within those ranges. This statistical stimulus quality has relevance for deriving receptive fields with the reverse correlation method (Aertsen and Johannesma, 1980) (see also Kowalski et al., 1996). The modulation depth of the spectrotemporal envelope was 45 dB. Mean intensity was set ~ 20 –30 dB above the pure-tone threshold of the neuron. Pure-tone stimuli were used to test the effects of traditional stimuli on the oscillatory dynamic state. Six hundred seventy-five tones were presented at a rate of 2–3 Hz in pseudorandom order at various frequencies and intensities covering the excitatory region of the receptive field of the neuron, usually several octaves with a 70 dB intensity range. Each tone was 50 msec in duration, with a 5 msec linear rise/fall envelope.

Young adult cats ($n = 4$) were anesthetized with Nembutal (15–30 mg/kg) during the surgical procedure and maintained thereafter in an unreflexive state with a continuous infusion of ketamine–diazepam. All procedures were in strict accordance with the University of California at San Francisco Committee for Animal Research and the guidelines of the Society for Neuroscience. Simultaneous extracellular recordings (Fig. 1) were made in layers III/IV of the primary auditory cortex (AI) and in the ventral division of the medial geniculate body (MGBv). All recordings were made with the animal in a sound-shielded anechoic chamber (IAC, Bronx, NY), with stimuli delivered via a closed, binaural speaker system. Electrodes were parylene-coated tungsten (Microprobe, Potomac, MD) with impedances of 1–2 M Ω or 3–5 M Ω tungsten electrodes plated with platinum black. Localization of thalamic electrodes, placed stereotactically, was later confirmed with Nissl- or neutral red-stained sections. Spike trains were recorded on a Cygnus Technology (Delaware Water Gap, PA) CDAT-16 recorder and sorted off-line with a Bayesian spike-sorting algorithm (Lewicki, 1994). Dynamic states assessed with single and multi-units were indistinguishable, and results from both were therefore combined.

Thalamocortical state was assessed by the degree of synchronous oscillations in the thalamus and cortex in the 7–14 Hz range. This frequency band was chosen because, as described in the introduction, 7–14 Hz spindle-like oscillations are a paradigmatic manifestation of burst mode. Slower oscillations (< 7 Hz), also characteristic of natural sleep, were observed too rarely to afford a comprehensive analysis. The dynamic state was compared across three stimulus conditions: for spontaneous activity (silence), pure-tone stimulation, and dynamic ripple stimulation. All of the data analysis was performed in Matlab (Mathworks, Natick, MA). Auto- and cross-spectra were computed using the Welch periodogram method, in which the spike trains were binned at 1 msec resolution. The degree of synchronous oscillations was quantified by the coherence among neural spike trains. Coherence is a form of normalized cross-spectrum between unit pairs, giving a measure of the association between the spike trains, as a function of frequency. Coherences, their significance values, and their

Figure 2. The oscillatory thalamocortical state is apparent in cross-correlograms under spontaneous conditions. On the diagonal are depicted the autocorrelograms for two thalamic and two cortical neurons, recorded simultaneously. Cross-correlograms among the four units are off the diagonal. There is strong oscillatory synchrony within the thalamus, within the cortex, and across the thalamocortical system. The oscillations are manifest as side peaks with a temporal lag of ~ 120 msec and thus have a frequency of ~ 8 Hz. They are generally in phase across the entire network, with a typical small (~ 0 –15 msec) thalamic phase lead over cortex. Dashed lines indicate 95% confidence under an independent, Poisson assumption.

significant differences among stimulus conditions were computed (Rosenberg et al., 1989). Only coherences whose contributing spike trains had > 500 spikes were used. Neuronal pairs whose spontaneous (null) condition showed no evidence of thalamocortical oscillations, as judged by a peak coherence < 0.05 in the 7–14 Hz range, were discarded. All significance values were set to 95% confidence. Percentage of change in coherence was computed only for those frequencies within 7–14 Hz that were significantly different across stimulus conditions. Thus, some fraction of valid unit pairs were further analyzed: 392 of 1590 pairs for pure-tone versus spontaneous, 248 of 954 pairs for ripple versus spontaneous, 167 of 565 for ripple versus tuning curve, and 171 of 522 pairs for comparisons across all three conditions. The remaining pairs did not show significant coherence differences, usually because the variability in the data were too high to determine a difference or because there were no detectable oscillations. The peak coherence criterion, however, was kept at 0.05 to avoid biasing the sample toward units with very strong effects. Only the coherences from intrathalamic and thalamocortical pairs were included in the analysis, because input layer (III/IV) corticocortical pairs are probably much less reliable in reflecting dynamic state. This is attributable to their lack of low-threshold calcium dynamics and their long-lasting depolarization during the thalamic silent phase of the oscillations (Grenier et al., 1998).

RESULTS

The dynamic state of the thalamocortical system was assessed with simultaneous extracellular single-unit and multi-unit recordings in AI and the MGBv. Cross-correlation analysis shows an oscillatory dynamic state under spontaneous (silent) conditions in the anesthetized animal (Fig. 2). Strong oscillatory behavior is expressed as large side peaks in the correlograms. The position of the side peaks along the delay axis indicates that most of the energy of these oscillations is located ~ 8 Hz. The widespread and synchronous quality, the frequency range (7–14 Hz), and the thalamic/cortical phase relationship of these oscillations all indicate that the thalamocortical system is in burst mode (Andersen and Andersson, 1968; Steriade and Llinás, 1988; Contreras and Steriade, 1996), the most common mode during quiet sleep.

The dynamic ripple: a candidate alerting stimulus

For a stimulus to effect a state change, namely from an oscillatory to a non-oscillatory mode, it should satisfy certain conditions based

Figure 3. The dynamic ripple stimulus satisfies a principled conception of an “alerting stimulus.” The spectrogram representation of one short segment is shown. Regions of high spectrotemporal energy are represented by red, and regions of low energy are represented by blue. The dynamic ripple is a wideband sound with spectral peaks whose spacing and frequency modulations are varied randomly and independently over ~20 min. The stimulus mimics many elements of natural sounds, including the temporal modulations and depth or contrast distribution of the modulations. Whereas there is a degree of correlation across the spectral axis of the sound, also in imitation of many natural and communication sounds, the dynamic ripple is devoid of any large-scale correlations or long silent periods. Spectral and temporal modulations are bounded to match the preferred range of thalamic and cortical cells, and acoustic energy moves about rapidly and randomly, assuring a highly asynchronous drive across populations of neurons.

on the underlying cellular and network mechanisms. As detailed in Discussion, such an alerting stimulus could prevent the widespread oscillatory mode through two basic means: depolarization and desynchronization of the thalamocortical cells. Specifically, stimulus features would include a generally persistent excitatory effect on most cells, a relative lack of long silent or hyperpolarizing epochs, and an asynchronous spatiotemporal quality.

The dynamic ripple (Fig. 3) fulfills these conditions for disrupting coherent oscillations. In addition, the formal aspects of its frequency-amplitude statistics permit its use in the reverse correlation method for constructing the spectrotemporal receptive field of a neuron (Aertsen and Johannesma, 1980) (see also Kowalski et al., 1996). With respect to depolarizing influences, the dynamic ripple stimulus is designed to drive thalamic and cortical neurons very well, because the range of spectral peak densities (Fig. 3, along the vertical axis) and temporal (along the horizontal) modulations was selected to match the global preferences of these cells. In a system in which responses are dominated by phasic onsets, such as the auditory thalamocortical network, a sustained increase in activity is best elicited by repeated excitatory drives within the range of preferred spatiotemporal modulations. As intended, ripple stimulation typically increased the activity of thalamocortical cells above the spontaneous firing rate. This contrasts with constant Gaussian white or colored noise, which are poor excitatory stimuli for the lemniscal thalamocortical auditory system; because the rates of spectral and temporal modulations in these noises are much too high, they tend to inhibit many neurons. Additionally, silent or hyperpolarizing influences in the dynamic ripple stimulus, unlike repeated click or tone presentations, tend to be brief (average, 35 msec).

The asynchronous spatiotemporal nature of the dynamic ripple stimulus is also apparent in its spectrogram representation (Fig. 3). Although there is a degree of local correlation across time and frequency, in imitation of many natural and communication sounds (Nelken et al., 1999), large-scale correlations are entirely absent. This is reflected in an impulsive autocorrelation function of the stimulus (data not shown). Randomly changing spectral peak spacing and frequency sweeps assure that regions of slightly different receptive field preference will be excited asynchronously. By con-

Figure 4. Correlograms and coherences reveal suppression of the oscillatory state with ripple stimulation. Four thalamocortical neural pairs are shown. *a*, Spontaneous thalamocortical correlograms from Figure 1 are plotted in red. Correlograms under the ripple-driven condition are in blue. The oscillatory activity is markedly suppressed by ripple stimulation. Moreover, evidence for short-time functional thalamocortical correlations (peak lag time, ~3 msec) under the ripple condition is either absent or greatly obscured by large-scale oscillations under the spontaneous condition. All correlograms are normalized to the firing rates of the contributing neurons, for comparison across conditions. *b*, Coherences for the same units. The robust suppression of the oscillatory dynamic state with the ripple stimulus is seen as a clear reduction in the size of the peak (clockwise from top left, 496, 474, 122, and 135% reduction). Vertical green bars demarcate the 7–14 Hz region of analysis.

trast, traditional stimuli such as bursts of pure tones, white noise, or clicks deliver spectrally limited or temporally highly synchronous excitation. Hence, unlike traditional experimental stimuli, the dynamic ripple coincides well with a principled idea of an alerting stimulus. These features include a generally persistent excitatory effect on most cells, a relative lack of long silent or hyperpolarizing epochs, and an asynchronous spatiotemporal quality.

Effects of dynamic ripple and traditional stimuli on oscillatory dynamic state

As the formal aspects of the dynamic ripple would suggest, its real effects on the auditory thalamocortical dynamic state are dramatic (Fig. 4). Thalamocortical correlograms (Fig. 4*a*) are compared for spontaneous (red) and ripple-driven (blue) conditions. For the spontaneous condition, strong oscillatory behavior in the 7–14 Hz range can again be seen as large side peaks in the correlograms. In most cases, ripple stimulation suppressed these synchronous oscillations completely. Coherences for the spike trains (Fig. 4*b*) quan-

Figure 5. For all thalamo-thalamic and thalamocortical pairs, the percentage of change in 7–14 Hz coherence is shown across the three conditions: pure-tone, dynamic ripple, and spontaneous. In the histograms, pairs are binned to the left of zero if there is a suppression of 7–14 Hz coherence (oscillatory energy) from the one condition to the other and to the right if there is an exacerbation of the coherence. *a*, Pure tones tend to have ambivalent effects on spontaneous thalamocortical oscillatory synchrony (mean, 54% exacerbation). *d*, The dynamic ripple sound, in contrast, robustly and consistently suppresses the oscillations (mean, –535%). Similar effects are seen when comparing dynamic ripple to pure tone stimulation (*c*) (mean, –886% suppression). (In the histograms, striped endbins indicate values beyond that end of the abscissa; the lowest bin in *c* is truncated from value 57 for clarity). The scatter plot (*b*) compares, for the same pairs, effects in *a* directly to those in *d*. Circles in quadrant one (*top right*, $n = 2$) indicate that both the ripple sound and pure tones exacerbated the oscillatory synchrony; those above the diagonal line indicate that the pure tone exacerbated the coherence even more than the dynamic ripple. Quadrant two (*top left*, $n = 77$) contains those pairs in which the dynamic ripple suppressed but the pure tones exacerbated the coherence. Circles in quadrant three (*bottom left*, $n = 92$) indicate that both the dynamic ripple and pure tones suppressed the 7–14 Hz coherence; those above the diagonal line ($n = 80$) indicate that the pure tone suppressed the coherence less than the ripple. Finally, quadrant four (*bottom right*, $n = 0$) would contain those pairs in which the dynamic ripple exacerbated, but the pure tones suppressed the oscillations.

tify the degree of association between the two signals, as a function of frequency; it is therefore a highly appropriate assay for the degree to which the thalamocortical network is engaged in the oscillatory (7–14 Hz) dynamic state. Under ripple stimulation, the coherence peak of ~8 Hz is markedly suppressed for all pairs shown (Fig. 4*b*), ranging in reduction from 122 to 496%.

To demonstrate the effectiveness of the dynamic ripple stimulus relative to other sounds in suppressing oscillations, we tested the influence of more traditional stimuli on the thalamocortical state. One of the most common experimental stimuli in auditory neurophysiology are sequentially presented bursts of pure tones. Figure 5 shows the population effects on oscillatory state for dynamic ripple and for the traditional pure-tone stimulation, each compared to the spontaneous condition. Pure-tone stimulation (Fig. 5*a*) had ambivalent effects on 7–14 Hz oscillatory synchrony, occasionally suppressing the coherence, occasionally exacerbating it, and on average leaving it virtually unchanged from the spontaneous case (54% exacerbation). The dynamic ripple, on the other hand (Fig. 5*d*), clearly and consistently suppressed the oscillatory state, by an average of 535%. A direct comparison between pure-tone and dynamic ripple stimulation shows an even greater disparity (Fig. 5*c*), with an average relative suppression of 886%. Finally, the

effects on a given unit pair are plotted for both the pure-tone versus spontaneous and the dynamic ripple versus spontaneous conditions (Fig. 5*b*). The distribution is generally unbiased across the horizontal midline but highly skewed to the left of the vertical midline. This ensures that the effects in Figure 5, *a* and *d*, apply to all unit pairs, not just different subpopulations. Therefore, in probing the receptive field properties of neurons, pure tones may drive the thalamocortical network further into or out of the oscillatory state, whereas the dynamic ripple maintains a constant non-oscillatory state resembling the alert animal. That is, unlike traditional stimuli, the dynamic ripple effectively controls the dynamic state of the thalamocortical system.

DISCUSSION

Mechanisms of state control and the design of an alerting stimulus

The specific qualities of an alerting stimulus can be derived with some confidence, because the mechanisms regulating thalamocortical state fall into two closely related categories: depolarizing and desynchronizing influences. Depolarizing influences occur at the cellular level, where a mode change can be elicited by a small fluctuation in resting membrane potential; sustained depolarization induces tonic mode by inactivating the low-threshold Ca^{2+} channel, a key element in rhythmic firing (Steriade and Llinás, 1988). Depolarization from high rates of input or simply increased activity in the circuit itself can drive the system into tonic mode (Andersen and Andersson, 1968; McCormick and Feese, 1990; McCormick and von Krosigk, 1992). In contrast, a sustained hyperpolarization, either spontaneous or stimulus elicited, can deactivate the low-threshold Ca^{2+} current and prepare the thalamic network for widespread spindle oscillations (McCormick and Feese, 1990; Contreras and Steriade, 1995), a paradigmatic feature of burst mode.

In addition to persistent depolarization, an alerting stimulus could also modulate dynamic state by effectively desynchronizing the thalamocortical network. The cellular effects are similar to those described above: asynchronous barrages of afferent EPSPs transiently disrupt rhythmic firing by maintaining the low-threshold Ca^{2+} channel in its inactive state (Andersen and Andersson, 1968; McCormick and Feese, 1990). On a network level, moreover, synchronization mediated by the thalamic reticular nucleus is important for the entrainment of spindles (Steriade et al., 1993), and network desynchronization contributes to their abolition (Andersen and Andersson, 1968).

The functional profile of an alerting stimulus thus includes a persistent excitatory effect, the relative absence of long silent or hyperpolarizing epochs, and an asynchronous spatiotemporal quality. The dynamic ripple stimulus satisfies all these conditions. Its spectral and temporal modulation rates are chosen to persistently excite neurons in the thalamocortical network. Its hyperpolarizing features tend to be brief (average, 35 msec)—much too brief to readily enable the deactivation of the thalamic low-threshold Ca^{2+} current. Finally, it has a broadband, smoothly varying, asynchronous spatiotemporal quality that contributes to network desynchronization. Evidently, these qualities are sufficient to control thalamocortical state.

Although sufficient, however, perhaps not all the structural features of the dynamic ripple are necessary to control the state, and some more impoverished stimulus could also consistently alter firing mode. Many other stimuli, however, prove insufficient to suppress the oscillatory activity, including repeated tones presented at the characteristic frequency of the units (Dinse et al., 1997), tones of various frequencies presented for long (4 sec) times (deCharms and Merzenich, 1996), click trains (Eggermont, 1992), and amplitude-modulated (AM) noise (Eggermont, 1994). Both click trains and, especially, AM noise approximate the dynamic

ripple as they are broadband and temporally modulated. Yet, they both lack spectral structure or frequency modulations and consist of highly synchronous onsets and offsets, which are virtually absent in the dynamic ripple. It thus appears that in addition to any depolarizing effects, some approximation of the asynchronous spectrotemporal modulations of the dynamic ripple are essential for controlling dynamic state.

As mentioned in the introductory remarks, the thalamocortical firing state may be manipulated through many means. Stimulus-based state control, observed with the dynamic ripple but not traditional pure-tone stimuli, differs from electrical, chemical, and surgical methods by acting through primary afferent pathways rather than through direct or indirect mimicry of mesencephalic, hypothalamic, and basal forebrain modulatory systems. Its precise biophysical effects would also differ from the naturally alert state because the typical cast of neuromodulators is presumably not engaged. Several of these modulators drive the thalamocortical system from the oscillatory into the tonic mode by reducing the leak potassium current in thalamic neurons, thereby depolarizing them (Lee and McCormick, 1997). In our case, we surmise that the dynamic ripple stimulus suppresses burst mode via afferent (colliculo-thalamic) ionotropic excitation that persistently depolarizes thalamic cells and consistently interrupts and desynchronizes the lengthy hyperpolarizations essential for repeated burst firing. Another, mutually compatible possibility is that the stimulus produces state change through massive corticothalamic feedback, which in concert with fast EPSPs could reduce the leak potassium current and depolarize cells via metabotropic glutamate receptors (McCormick and von Krosigk, 1992; Lee and McCormick, 1997).

The interpretive dilemma of variable dynamic state

Thalamocortical dynamic state control is essential to understand how information is processed at this neural juncture so crucial for perception, action, and cognition. Without such control, the processing properties of the thalamocortical neurons are constantly and randomly changing, rendering exceedingly difficult any analysis of state-dependent aspects. The interpretive dilemma presented by a variable dynamic state extends at least to traditional spatial and temporal receptive fields (Livingstone and Hubel, 1981; Morrow and Casey, 1992; Guido et al., 1995; Mukherjee and Kaplan, 1995; Kenmochi and Eggermont, 1997; Wörgötter et al., 1998), to fine temporal correlation properties (Abeles et al., 1995), and perhaps to plasticity (Weinberger, 1995). For instance, fine temporal correlation properties can change with dynamic state, indicating that neurons may be differentially engaged in functional circuits. Similarly, if memory consolidation or topographical map rearrangement occurs preferentially during certain brain states, then to understand changes in neural responses it would be crucial to know which state is manifest. Some mechanism must be invoked to isolate these state-dependent properties or to mitigate the effects of unpredictable firing mode fluctuations, and care should be taken to reinterpret previous studies which did not control for dynamic state.

Stimulus-based state control addresses this problem by maintaining a particular dynamic state, while probing the representational properties of the system. Insofar as it fixes the network in a processing mode, it bears directly on issues of neural coding. Moreover, given the common mechanisms of this state change throughout the thalamocortical system, alerting stimuli could presumably be devised for other modalities as well. It is noninvasive, so it may be used in awake, sleeping, or anesthetized species, including humans under both normal and pathological conditions (Llinás et al., 1999). Indeed, comparative studies in awake, asleep, and comatose humans suggest that suppression of an analogous oscillatory state corresponds to cortical engagement in a task (Pfurtscheller, 1992). Because of the ubiquity of its underlying mechanisms, stimulus-based state control is a phenomenon with direct implications for neural processing in many modalities across the thalamocortical network.

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