Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

A Thalamic Origin to the Electro cortical Patterns Associated with Transitions into Anesthetic-Induced Loss-of-Consciousness

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Review of Baker et al.

The neuronal mechanisms that mediate anesthetic-induced loss-of-consciousness are unknown. A major focus of current research is to identify the brain regions that mediate the changes in electrocortical activity that are associated with loss-of-consciousness during general anesthesia (Rudolph and Antkowiak, 2004). Importantly, an early “deactivation” of the thalamus has been identified during anesthetic-induced loss-of-consciousness in several brain imaging studies (Franks, 2008). Brain imaging techniques, however, are not ideally suited to identify alterations in subcortical activity and/or offer indirect indices of neuronal activity and poor temporal resolution (Menon and Kim, 1999; Franks, 2008; Mishra et al., 2011). Moreover, there is accumulating evidence that indicates a more complex role for the thalamus, beyond a basic reduction in signaling, during loss-of-consciousness elicited by general anesthetics (Ching and Brown, 2014).

A recent study by Baker and colleagues (2014) has further highlighted the primacy of the thalamic response to general

anesthetics and provides new insight on the nature of this response and how it relates to the naturally occurring patterns of neuronal activity identified during sleep. Using multisite local field potential recordings and Morlet wavelet analysis, Baker et al. (2014) identify alterations in neuronal population activity at a high temporal and spatial resolution. Specifically, population signaling in the central medial thalamus, ventrobasal complex, anterior cingulate cortex, and barrel cortex was recorded during transitions into natural sleep and propofol- or dexmedetomidine-induced loss-of-righting reflex (a well established index for loss-of-consciousness; Franks, 2008) in rats. The spectral composition of neuronal activity was then analyzed using continuous wavelet analysis with a complex Morlet wavelet, which provides a finer temporal understanding of spectral changes than the more commonly used fast Fourier transform.

Neuronal population activity during transitions into natural sleep was characterized first, because some of the patterns of electrocortical activity that emerge during loss-of-consciousness with certain general anesthetic agents resemble those that are associated with non-rapid eye movement (NREM) sleep (Franks, 2008). A novel transition state was identified when rats switched from waking to NREM sleep. This transitory state was characterized by an increase in the amplitude of high-frequency (20–40 Hz) oscillations with a concomitant shift to a lower

dominant frequency (i.e., peak power occurred at a lower frequency) in this high-frequency band. Importantly, this spectral signature manifested first in the central medial thalamus. Thalamic sites were also found to lead neocortical sites in delta (1–4 Hz) oscillations during NREM sleep, consistent with other reports that have also implicated a role for the thalamus in mediating electrocortical delta activity during NREM sleep (David et al., 2013; Mesbah-Oskui et al., 2014).

A similar increase in high-frequency amplitude and shift to a lower dominant frequency in this frequency band was identified during transitions into propofol-induced loss-of-righting reflex and, as with transitions into NREM sleep, these changes occurred first in the central medial thalamus. Importantly, however, unlike transitions into NREM sleep where thalamic sites led neocortical sites in delta oscillations, there were no measurable phase associations between delta oscillations at the different recording sites during transitions into loss-of-righting reflex with propofol. Furthermore, propofol uniquely elicited a sharp increase in 8 Hz electrocortical signaling at loss-of-righting reflex. The coherent increase in 8 Hz activity is of particular interest given the growing number of reports that identify a similar phenomenon upon anesthetic-induced loss-of-consciousness in humans (Ching and Brown, 2014). Moreover, modeling studies have identified that alterations in thalamic signaling can generate this coherent

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increase in 8 Hz activity during loss-of-consciousness with propofol (Ching and Brown, 2014).

To determine whether the neuronal activity patterns seen with propofol also occur with other anesthetic/sedative agents, transitions into loss-of-righting reflex with dexmedetomidine were also examined. The same alterations in high-frequency activity were again observed during transitions into loss-of-righting reflex with dexmedetomidine. Importantly, however, with dexmedetomidine the increase in high-frequency power and shift to a lower dominant frequency in this frequency band did not appear first in the thalamus, as it did during transitions into propofol-induced loss-of-righting reflex and NREM sleep, but instead was seen at the same time at all recording sites. Moreover, unlike propofol, dexmedetomidine did not elicit any measurable effects on 8 Hz signaling. Additionally, transitions into dexmedetomidine-induced loss-of-righting reflex were associated with a coherent increase in delta signaling, with thalamic sites leading neocortical sites in delta oscillations, which resembles the pattern of delta activity identified during NREM sleep but is unlike the pattern identified during transitions into propofol-induced loss-of-righting reflex where delta oscillations exhibited no phase associations across the recorded brain regions. Importantly, Baker et al. (2014) also identified an abrupt reduction in the delta phase lead of the central medial thalamus following dexmedetomidine-induced loss-of-righting reflex, which was not seen during NREM sleep.

The study by Baker et al. (2014) identifies early recruitment of the central medial thalamus during transitions into the electrocortical and behavioral patterns that characterize NREM sleep and propofol-induced loss-of-righting reflex in rats. What are the possible factors that could sensitize central medial thalamic neurons to these state changes? Anatomically, the central medial thalamus is well positioned to respond to state-driven subcortical input and exert a significant influence on cortical activity, receiving inputs from subcortical sleep regulatory regions such as the supramammillary nucleus and pedunculopontine tegmental nucleus, and projecting diffusely to limbic and sensorimotor structures of the rostral forebrain, including the anterior cingulate cortex (Vertes et al., 2012). Electrophysiological studies in cats and primates further support a role for the central medial thalamus in mediating the electrocortical patterns associated with arousal. Specifically, low-frequency stimulation of

intralaminar/midline thalamic regions elicits slow-wave electrocortical activity and somnolence, whereas high-frequency stimulation promotes patterns of electrocortical activity that are associated with arousal (Van der Werf et al., 2002). Importantly, reductions in excitatory subcortical input to the central medial thalamus accompany transitions into both NREM sleep and anesthesia elicited with anesthetics that target GABA type A receptors (GABA_ARs; Franks, 2008). Baker and colleagues (2014) reasonably posit that such a mechanism could account for the progressive decrease in the dominant frequency of the 20–40 Hz band that manifested first in the central medial thalamus.

A positive correlation between arousal and inhibitory reticular input to limbic projecting thalamic nuclei, which include the central medial thalamus, was also recently identified (Halassa et al., 2014). This association is seemingly at odds with the generalized increase in GABA_AR activity associated with propofol anesthesia and NREM sleep. Importantly, however, the inhibitory input to limbic projecting thalamic nuclei that was associated with increased arousal did not typically exceed 20 Hz. Thus, it is possible that at even higher firing rates, like the 20–40 Hz rhythm identified by Baker and colleagues (2014), input from the thalamic reticular nucleus to limbic-projecting thalamic nuclei exerts an opposing effect on arousal. Indeed, the emergence of a voltage-dependent, ~40 Hz rhythm in reticular thalamic signaling has been reported under urethane anesthesia in rats, which effectively recruited thalamocortical neurons into the same rhythm of activity (Pinault and Deschênes, 1992). Such a mechanism could account for the increase in high-frequency power identified by Baker et al. (2014) at thalamic sites followed by neocortical sites, the latter triggered via thalamocortico-corticothalamic signaling, during transitions into NREM sleep and loss-of-righting reflex with propofol. This explanation, however, cannot account for why changes in thalamocortical activity manifest first in the central medial thalamus and not simultaneously across all thalamic nuclei, save for a preferential recruitment of limbic projecting thalamic reticular nucleus neurons. Therefore, alterations in the complex of other inputs to the central medial thalamus and/or differences in channel/receptor expression might position the central medial thalamus to respond to these state changes before other thalamic nuclei.

Propofol and dexmedetomidine differ in their primary molecular targets, with propofol targeting GABA_ARs and dexmedetomidine acting on α_2 -adrenergic receptors. Importantly, α_2 A adrenergic receptors of the locus ceruleus mediate hypnosis with dexmedetomidine in rats (Mizobe et al., 1996). Moreover, the rat thalamus exhibits very sparse expression of the α_2 A-adrenergic receptor subtype (Scheinin et al., 1994). Thus, the profile of adrenergic receptor expression in the thalamus coupled with the identified role of the locus ceruleus, which heavily innervates both the thalamus and neocortex, in mediating dexmedetomidine-induced hypnosis could explain why the spectral changes in power elicited with dexmedetomidine occurred simultaneously across the thalamic and neocortical sites recorded by Baker et al. (2014) (Jones and Moore, 1977). The authors also found that the delta phase lead of the central medial thalamus decreased abruptly following dexmedetomidine-induced loss-of-righting reflex and posit that this phase change could trigger loss-of-consciousness by disrupting thalamocortical communication. This hypothesized role for altered delta coupling between thalamic and neocortical sites in triggering loss-of-consciousness is not readily supported by existing data. Indeed, delta oscillations exhibited no coupling across the thalamus and neocortex during induction of loss-of-righting reflex with propofol, indicating that disrupted delta coupling between thalamic and neocortical sites occurs before propofol-induced loss-of-consciousness. Moreover, while alterations in the temporal coupling of neuronal population signaling in different brain regions has been linked to cognition and information processing, its ability to trigger loss-of-consciousness is not established (Fell and Axmacher, 2011); thus, the functional significance of the delta phase change in the central medial thalamus at dexmedetomidine-induced loss-of-righting reflex requires further investigation.

The findings of Baker et al. (2014) indicate a subcortical origin to the changes in electrocortical activity that are seen during propofol and dexmedetomidine-induced loss-of-righting reflex. Most importantly, this study indicates that the breakdown in cortical connectivity that occurs during anesthetic-induced loss-of-consciousness is not triggered by an inactive thalamus, but may rather be linked to the emergence of an intrinsic thalamocortico-corticothalamic loop whose activity resonates under maintained hyperpolarization, a condition that can be met during both anesthesia and NREM sleep. Moreover, it is

possible that the 20–40 Hz signaling described above is directly related to the emergence of alpha (8–12 Hz) activity seen after propofol-induced loss-of-righting reflex, given the apparent thalamic origin of both rhythms, their association with anesthetic-induced loss-of-consciousness, and the decrease in the dominant frequency of the 20–40 Hz band during transitions into loss-of-righting reflex (Ching and Brown, 2014). Characterizing the temporal profile of spectral changes in reticular thalamic activity during transitions into NREM sleep and anesthetic-induced loss-of-righting reflex will further our functional understanding of the changes in thalamic and neocortical activity that were identified by Baker and colleagues (2014).

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