

Central lateral thalamic nucleus stimulation awakens the cortex via modulation of cross-regional, laminar specific activity during general anesthesia.

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Experiments identify cortical layer specific effects during induced arousal from general anesthesia. Redinbaugh et al. (2020) find evidence that central lateral thalamic nucleus electrical stimulation reactivates the cortex by restoring deep layer firing rates and modulating feedforward and feedback connectivity.

Theoretical considerations, direct experimentation, and clinical evidence have long suggested a key role for the central lateral (CL) nucleus of the thalamus in supporting consciousness in the mammalian brain. Prior studies considered the privileged role of CL in forebrain arousal and control of cortico-cortical communications via selective modulation of intra-columnar and inter-regional interactions (Larkum et al. 1999, Llinas et al. 1998, Purpura and Schiff, 1997, Steriade et al. 1996). However, no *in vivo* experiments had directly examined the specific causal influence of CL projections within and across cortical layers while controlling level of consciousness. In the current/recent issue, Redinbaugh et al. provide evidence that CL supports consciousness through modulation of neocortical intra-columnar and inter-regional interactions. As discussed below, although the experiments examine a restricted range of recovered arousal this provides an advantage to isolate a key transition in inter-regional and intra-columnar neocortical activity at the point of initial emergence from coma induced by anesthesia (Brown et al. 2010).

Using an innovative experimental model, changes in neuronal firing rates and local field potential (LFP) activity were measured in frontal eye field (FEF), lateral intraparietal area (LIP) and CL in two rhesus monkeys comparing four states of arousal: stable general anesthesia, emergence from anesthesia induced by electrical stimulation of CL, natural sleep, and awake states. Electrical stimulation through 16 small (25 micrometer diameter) microelectrode recording/stimulation contacts embedded in the central thalamus, and centered on the CL nucleus, restored arousal during both isoflurane and propofol anesthesia. In FEF and LIP, employing the same type of microelectrodes allowed identification of superficial, middle and deep cortical layers through use of a passive auditory paradigm. Comparison of experimental effects across stimulation contacts identified CL as primarily responsible for producing emergence from anesthesia.

Comparing the four arousal states showed changes in neuronal firing rates, LFP power, and LFP coherence within and across electrode contacts (Figure 1). General anesthesia and natural sleep demonstrated selective depression of deep cortical layer neuronal firing rates in FEF and LIP compared with wakefulness. General anesthesia also sharply increased cortico-cortical coherence across layers at delta frequencies (<4Hz) within FEF and LIP and reduced coherence at higher frequencies. Effective CL stimulation restored deep layer firing rates in LIP and modulated inter-regional coherence of LFPs within different laminar components of FEF and LIP: stimulation increased 'alpha' (8-15Hz) coherence in feedback connections from the deep layers of FEF to superficial layers of LIP and increased alpha and gamma (30-60Hz) coherence in feedforward connections from deep layers of LIP to the superficial and middle layers of FEF.

Taken together, these observations suggest a key role for the Layer V pyramidal neurons that reach their apical dendrites into the superficial cortical layers (Larkum et al. 1999, Jones 2009). Jones (2009) had reasoned that connectivity between Layer V pyramidal neurons and the intralaminar nuclei, including CL, might shift of level of consciousness and control transitions from sleep to wake or the adjustment of levels of wakeful vigilance or directed attention. The observed coherence modulation is consistent with earlier proposals that CL activation of Layer V pyramidal neurons acts to synchronize activity within the cortical column (Llinas et al. 1998, Larkum et al. 1999). Prior *in vivo* studies in intact awake cats (Steriade et al. 1996) demonstrated that CL participates in prominent ~40Hz coherent oscillations across LFPs obtained from cortical regions homologous to FEF and LIP and that power spectra similarly show sharp

oscillatory features at the same frequencies (as seen in the present monkey experiments in the awake state, Figure 1 panels E-H). It is clear, however, that the arousal state produced with CL stimulation during anesthesia does not restore these key features of the background power and coherence observed in wakefulness (Figure 1, A-D).

Power and coherence spectra obtained from human wakeful EEG and monkey cortical LFPs typically reveal peaks at alpha and beta (~15-25Hz) or gamma frequencies as seen in this study (Figure 1E-H, Redinbaugh et al.; cf. Giacino et al. 2014, Baker et al. 2014). Most human subjects with early evidence of recovery of consciousness after coma, either in minimally conscious state (MCS) or confusional state (characterized by communication but disorientation, see Giacino et al. 2014 for review) demonstrate restoration of much of the wakeful background activity at the cortical level seen in the EEG (setting expectations for LFPs more consistent with Figure 1 Panels E-H “Wake” shaped spectra, than panels A-D “Stim” shaped spectra). The lack of restoration of either background resting features of the wakeful power or coherence spectra (Figure 1) from either LIP or FEF support the inference that the limited behavioral changes measured are well-calibrated to the states on the lower end of recovery of arousal.

As in human studies, drawing inferences that further recovery of consciousness existed would require measured behavioral evidence. The clinically inspired arousal index used can be compared with clinical diagnostic categories to calibrate the level of arousal restored in the experiments (Figure 1, see Giacino et al. 2014 for review). The dichotomized 10 point scale used separated fully unresponsive states consistent with stable anesthesia or coma (Arousal Score 0-2) from a range of limited graded behavioral responses. At the highest level of the scale these responses would correspond with the lower range of MCS, ‘MCS-’, (Giacino et al. 2014). For example, an arousal at the top end of the scale of 10 would reflect an eyes open state with jaw movements, full reaches, and large truncal movements. Similar findings would place a human subject the level of MCS -, requiring reliable contingent sensorimotor associations to follow commands to reach the higher level of this category (MCS+). Eye opening alone would only satisfy the level of arousal recovery seen in the vegetative state which clinically is not considered evidence of consciousness.

Emergence from anesthesia in humans also has several stages that can be compared to the continuum of changes observed with recovery from coma associated with changes in the anterior forebrain mesocircuit linking CL to fronto-parietal network interactions (Brown et al. 2010). Graded activity within this network is identified with levels of recovery in human subjects with disorders of consciousness, with frontal regions remaining strongly underactivated (Giacino et al. 2014). In the present study the clear distinction of CL stimulation effects on LIP compared with FEF are consistent with the graded restoration of the anterior forebrain mesocircuit in humans (deep layer firing rate increases only reach significance for LIP, and similarly, broadband coherence changes are specific to LIP). Deep layer LIP firing increases may account for the observed feedforward/feedback coherence changes during stimulation.

The findings of Redinbaugh et al. have implications for use of CL electrical stimulation to support impaired consciousness and cognitive function following structural brain injuries (Baker et al. 2016, Schiff 2016). Clinical deep brain stimulation in the central thalamus (CT –DBS) focuses on CL and aims to restore arousal regulation sufficient to support communication in MCS or restore executive cognitive function in patients with moderate to severe cognitive dysfunction (Schiff 2016). In awake monkeys, co-activation of CL and its adjacent fiber tract, the medial dorsal tegmental tract, show the strongest effects of behavioral facilitation (Baker et al. 2016). The identification of cell bodies in CL as underlying the

primary effects of CT-DBS in this study independently confirms these observations. In studies of awake animals and humans, stimulation frequency ranges of 100-200Hz have been found to be optimal (Baker et al. 2016, Schiff 2016); this intermediate range of higher frequencies was not explored by Redinbaugh et al. who found only stimulation at 50Hz (but not 200Hz) demonstrated emergence from anesthesia. In awake behaving monkeys, 150-225Hz CL stimulation induced modulation of LFP frontal cortical beta and gamma frequencies which was linked to behavioral facilitation (Baker et al. 2016). An interesting possibility is that 100-200Hz stimulation in non-anesthetized states allows for the integrative effects within the Layer V pyramidal neurons to contribute to the overall arousal state. Frequencies above 130Hz permit various forms of dendritic electrogenesis such as back-propagating action potentials to emerge (Larkum et al. 1999). The sharpening of activity within the beta and gamma range of the power spectrum of frontal cortical regions linked with behavioral facilitation produced by CT-DBS in alert non-human primates suggests that further recruitment and synchronization within and across columns may play a role. Prior theoretical work emphasized the possibility that cortico-cortical information flow could be modulated by CL in the gamma frequency range in the form of persistent activity (Purpura and Schiff 1997).

This new experimental model suggests further exploration of range of arousal between MCS- and fully recovery (Figure 1) with measurement of effects at intra-columnar and across cross-layer inter-regional levels. In humans, more organized but disoriented behaviors often arise prior to the full restoration of wakefulness, a condition known as 'emergence delirium' (Brown et al. 2010). Experimentally capturing such further graded levels of recovery may allow for more detailed investigation of the impact and mechanisms of CT-DBS. Overall, what is particularly exciting about this new report is the ability to frame such questions based on these measurements.

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