MODELING WAKEFUL UNRESPONSIVENESS: CHARACTERIZATION AND MICROSTIMULATION OF THE CENTRAL THALAMUS.

Nicholas D. Schiff*, Andrew E. Hudson, and Keith P. Purpura. Department of Neurology and Neuroscience, Weill Medical College of Cornell University, 1300 York Ave, New York, New York, 10021

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MOTIVATION

Experimental and clinical studies indicate an important role for the central thalamus in attentive visuomotor behaviors (Schlag and Schlag-Rey 1984, Matsumoto et al. 2000, Minamimoto and Kimura 2002, Kinomura et al. 1996, Paus 1997, Purpura and Schiff 1997, Schiff et al. 2001). Physiological and anatomical studies demonstrate that regions in the paramedian thalamus receive multiple afferents from brainstem arousal systems and are active in supporting different patterns of forebrain integration within arousal states (Steriade et al. 1997).

We have modeled a study of focused attention in human normal subjects by Roland and colleagues (Kinomura et al. 1996) in the non-human primate (Schiff et al. 2001). In their studies, subcortical contributions to the short-term focusing of attention were examined with fPET during performance of a reaction-time task (Kinomura et al. 1996). They identified strong activation of both the rostral (CL) and caudal (Cm-Pf) intralaminar thalamic nuclei during the sustained attention component of the behavior. These thalamic nuclei co-activated with the tegmental mesencephalon, consistent with previously demonstrated bi-directional monosynaptic connections between these structures (Steriade and Glenn, 1982). Regional cerebral blood flow in the cerebral cortex showed a diffuse elevation (~3-4ml/100g/min) coincident with the increases to these subcortical structures.

Here we report our characterization of the neuronal responses in the central thalamus using this behavioral paradigm and develop a microstimulation paradigm as a first step toward modeling wakeful unresponsiveness (WU) in the non-human primate. Several neurological disorders demonstrate global or focal symptoms of WU. The vegetative state and akinetic mutism are the most profound global examples, while hemispatial unawareness and the unresponsiveness seen with other forms of the 'neglect' syndrome represent more isolated disturbances. In addition to large cortical injuries, small bilateral (global disorders) or unilateral (focal disorders) injuries to the central (paramedian) thalamus may reproduce these conditions (Schiff and Plum 2000). The ultimate goal of modeling WU is to develop a neurophysiological foundation for novel neuromodulation strategies aimed at improving the general cognitive function of brain-injured patients. Selective stimulation of intralaminar thalamic nuclei has been proposed as an open loop DBS strategy for treating patients with acquired cognitive disabilities (Schiff et al. 2000, 2002). Appropriate stimulation parameters for achieving such goals are unknown. *In vitro* slice preparations (Llinas et al. 2002) have demonstrated that electrical stimulation of intralaminar neurons can strongly induce cortical microcircuit activity in the 30-50 Hz frequency range, similar to what is seen in the EEG and LFP during attentive behaviors (Steriade et al. 1996). To further develop open- and closed-loop strategies, primate experimental models of WU using reversible inactivation methods and deep brain stimulation techniques along the lines of the MPTP model in Parkinson's Disease will be required.

EXPERIMENTAL METHODS

Spike Recordings:

We recorded extracellular potentials simultaneously from the central thalamus and striate/extra-striate visual cortex (V1-V4) in the occipital lobe, of a rhesus monkey. Central thalamic sites were identified utilizing 3-dimensional MRI reconstruction and attachments to guide electrodes to central thalamic sites. Action potentials were sorted on-line using two different methods: a multi-window discriminator (Tucker-Davis Technologies) and a neural-network template-matching algorithm implemented on a computer card (MEXv5).

Local field potential recordings:

We recorded local field potentials from high impedance electrodes (~3MΩ, FHC) used for simultaneous single-unit recordings low-pass filtered at 300Hz (Tucker-Davis Technologies). Simultaneous recordings from two electrodes were obtained from central thalamic sites and striate/extrastriate cortices in 108 separate experiments. In addition, a small number of recordings were obtained from striatal neurons.

Eye movements: Eye movements were monitored using an infrared camera (ASL 5000)

Electrical brain stimulation: A recording microsyringe (Crist Instruments Co.) delivered electrical current to central thalamic sites previously characterized using high impedance electrodes. In pilot experiments, constant current stimulation (FHC Co. Model Pulsar 6bp) in the range 200-500µA was applied as a brief train of 5 biphasic stimulation pulses (50µsec/phase) at a stimulation of frequency of 50Hz (chosen to reflect the middle range of elevated high frequencies identified in local field potential recordings in the characterization experiments).

Spectrograms (Thomson and Chave 1991, Mitra and Pesaren 1999):

$$M(t,f)=\frac{1}{K}\left|\sum_{k=0}^{K-1}X_k(f)v_t^{(k)}\right|^2$$

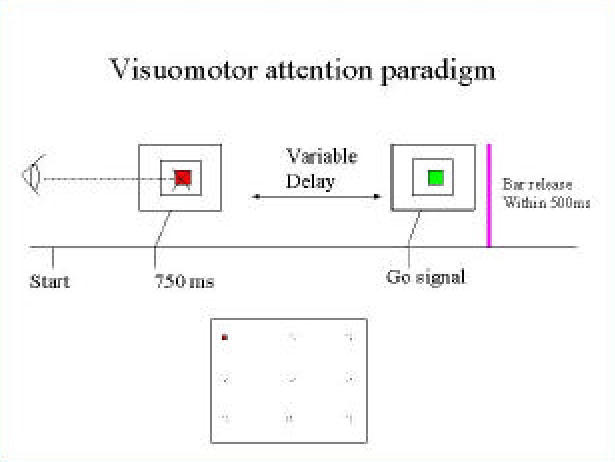
K is the number of tapers specified by relation $2WT$-1=K (Percival and Walden 1993), and v is the kth Slepian taper at time t. If X_k is the kth eigenspectrum, then $M(t,f)$ is a calculation of the time-frequency spectrum at time t and frequency f.

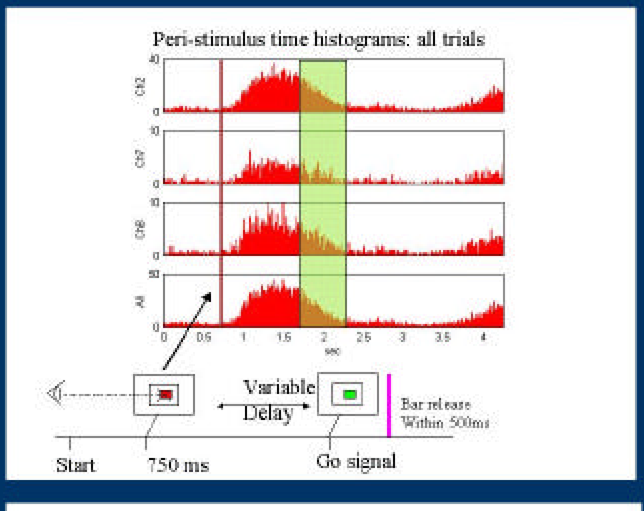
Estimation of variance (Delete-one jackknife on a logarithmic transformation of the spectrum estimate):

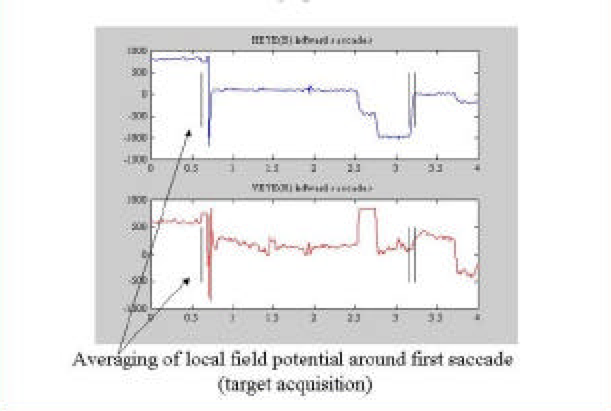
$$\ln\hat{M}_j=\ln\left(\frac{1}{N-1}\sum_{\substack{i=1\\ i\neq j}}^{N}\hat{M}_j\right)\qquad \ln\hat{M}_{.}=\frac{1}{N-1}\sum_{j=1}^{N}\hat{M}_j$$

$$\hat{\sigma}^2=\mathrm{var}\{\ln M\}=\frac{N-1}{N}\sum_{i=1}^{N}(\ln M_j-\ln M_{.})^2$$

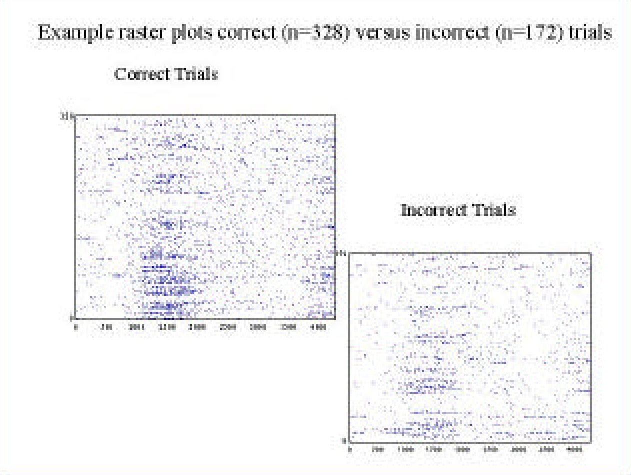
BEHAVIOR TASK AND CHARACTERIZATION OF THALAMIC ACTIVITY

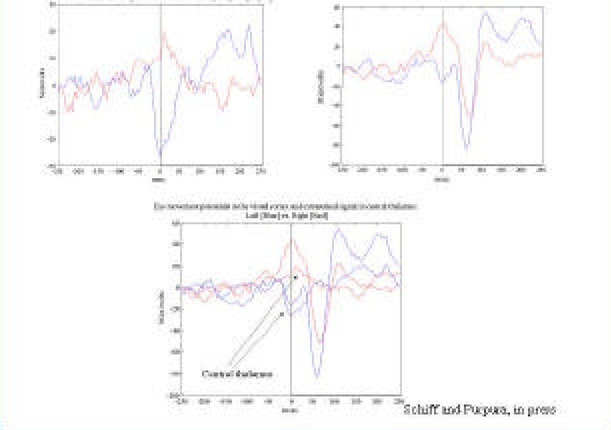

Visuomotor attention paradigm


Peri-stimulus time histograms: all trials

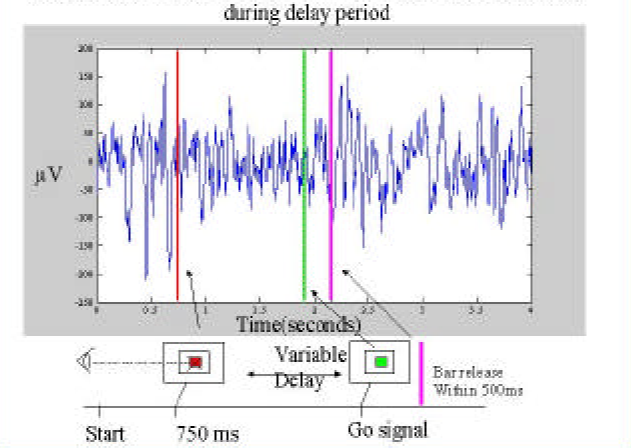

Horizontal and vertical eye positions for a correct trial

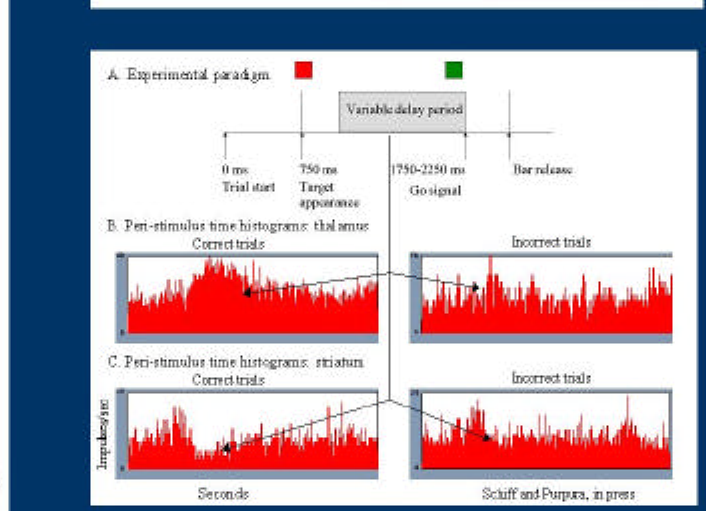
Averaging of local field potential around first saccade (target acquisition)


Example raster plots correct (n=328) versus incorrect (n=172) trials

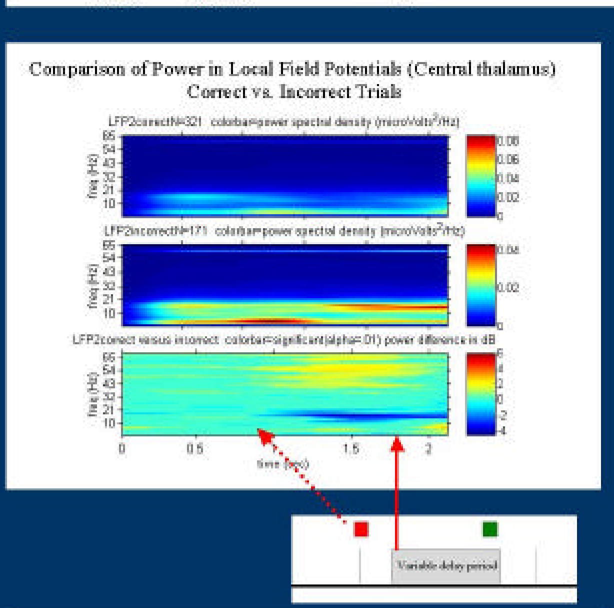


Schiff and Purpura, in press


Single-trial LFP for correct performance: high frequency activity during delay period



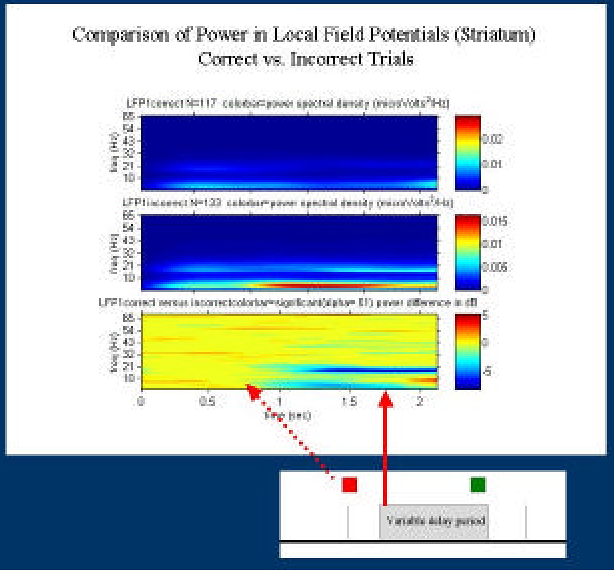
Schiff and Purpura, in press


Comparison of Power in Local Field Potentials (Central thalamus) Correct vs. Incorrect Trials

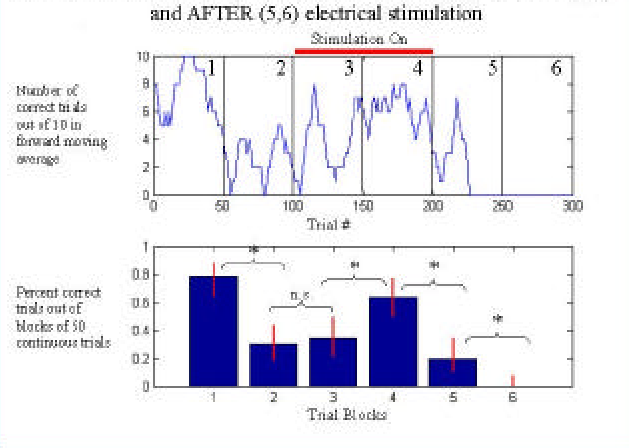
Characterization of thalamic recording sites	#/total	%
Number of single units with significant* elevation in firing rate during delay period	32/135	24%
Number of simultaneously recorded local field potentials from populations with single unit response during delay period with saccade related potentials	24/26	92%
Number of simultaneously recorded local field potentials from populations with significant† differences in population activity during delay period of correct trials compared with incorrect trials	18/26	69%

- Significant by Wilcoxson Rank-sum test (p<0.05)

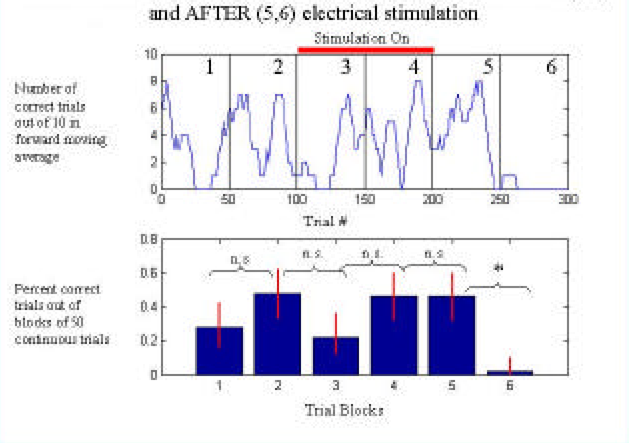
† Significant by jackknife comparison of population variance (p<0.01)

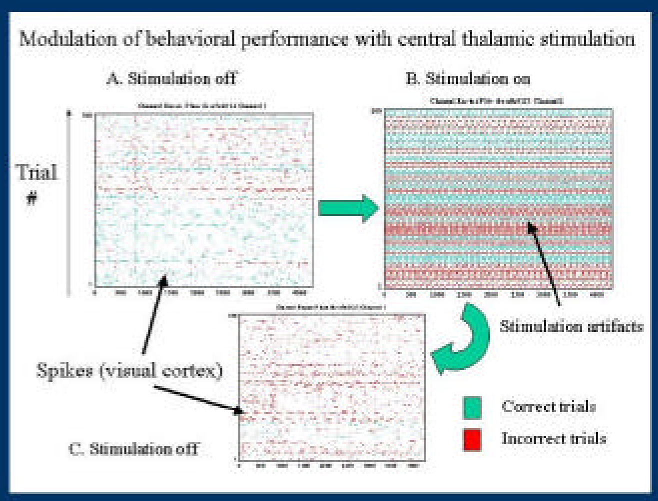

Comparison of Power in Local Field Potentials (Striatum) Correct vs. Incorrect Trials

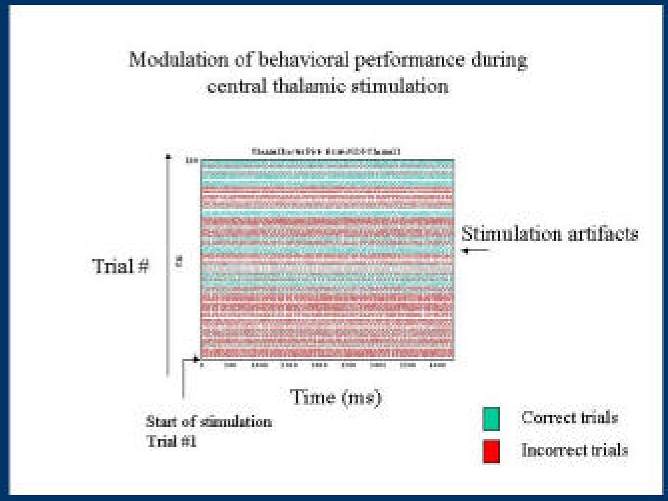
ELECTRICAL STIMULATION OF CENTRAL THALAMIC NEURONS


Evaluation of behavioral performance BEFORE (1,2), DURING (3,4) and AFTER (5,6) electrical stimulation

Stimulation On: 500µA, 50Hz, continuous during trials 100:200


Evaluation of behavioral performance BEFORE (1,2), DURING (3,4) and AFTER (5,6) electrical stimulation


Modulation of behavioral performance with central thalamic stimulation


Modulation of behavioral performance during central thalamic stimulation

HYPOTHESIS FOR MODULATION OF WAKEFUL UNRESPONSIVENESS

Hypothesis: deep brain stimulation of central thalamic structures may mediate extension of distributed sustained activity envelopes

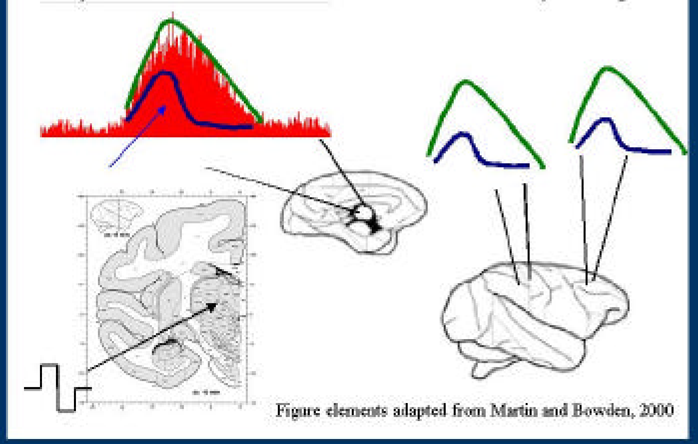


Figure elements adapted from Martin and Bowden, 2000

CONCLUSIONS

- Central thalamic neurons participate in the formation of internally organized states (Steriade, 2000) that reflect sustained attention.
- Most local populations recorded simultaneously with single-units that demonstrated delay period elevation show modulation of field potentials around the time of the saccade. This modulation typically is directionally selective.
- The observation of saccade-related modulation supports the localization of these central thalamic neurons in subpopulations known to signal saccade parameters which have been identified in the central lateral (CL)/paracentralis (Pc) components of the anterior intralaminar nuclei (Schlag and Schlag-Rey 1984) or in the paralaminar regions of the median dorsalis nucleus (Leichnetz and Goldberg 1981)--an area classified by Jones as an extension of CL based on dense representation of 'matrix' neurons (Jones 1998).
- The saccade-related response in these recordings suggests that direction of moment-to-moment intention may also play a role in establishing the necessary behavioral set facilitated by these central thalamic neurons (Schiff and Purpura, in press).
- Selective enhancement of high frequency (30-70Hz) activity in the central thalamus during sustained attention is consistent with similar shifts of spectral activity observed in cortical areas during attentional processing (Fries et al. 2001) and working memory (Pesaran et al. 2002).
- Electrical stimulation of the central thalamus at a stimulation rate consistent with the high frequency range observed in LFPs during the delay period of correct trials may briefly extend behavioral performance at the end of a training session.
- A reliable model of wakeful unresponsiveness, however, will require more robust and less variable behavior control to demonstrate effects of stimulation.

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