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Gating of attentional effort through the central thalamus

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Schiff ND, Shah SA, Hudson AE, Nauvel T, Kalik SF, Purpura KP. Gating of attentional effort through the central thalamus. *J Neurophysiol* 109: 1152–1163, 2013. First published December 5, 2012; doi:10.1152/jn.00317.2011.—The central thalamus plays an important role in the regulation of arousal and allocation of attentional resources in the performance of even simple tasks. To assess the contribution of central thalamic neurons to short-term adjustments of attentional effort, we analyzed 166 microelectrode recordings obtained from two rhesus monkeys performing a visuomotor simple reaction time task with a variable foreperiod. Multiunit responses showed maintained firing rate elevations during the variable delay period of the task in ~24% of recording sites. Simultaneously recorded local field potentials demonstrated significant decreases in power at ~10–20 Hz and increases in power at 30–100 Hz during the delay period when compared against precue baselines. Comparison of the spectral power of local field potentials during the delay period of correct and incorrect trials showed that, during incorrect trials, similar, but reduced, shifts of spectral power occurred within the same frequency bands. Sustained performance of even simple tasks requires regulation of arousal and attention that combine in the concept of "attentional effort". Our findings suggest that central thalamic neurons regulate task performance through brief changes in firing rates and spectral power changes during task-relevant short-term shifts of attentional effort. Increases in attentional effort may be reflected in changes within the central thalamic local populations, where correct task performance associates with more robust maintenance of firing rates during the delay period. Such ongoing fluctuations of central thalamic activity likely reflect a mix of influences, including variations in moment-to-moment levels of motivation, arousal, and availability of cognitive resources.

intralaminar nuclei; arousal regulation; corollary discharge; corticothalamic pair-recordings; phasic alerting

PERFORMANCE OF EVEN SIMPLE tasks repeatedly over time requires a sustained cognitive engagement that has been characterized as "attentional effort" (Sarter et al. 2006). Simple reaction time tasks with variable foreperiods are optimal for eliciting fluctuations in performance that typically result from a mix of contributions of factors, such as variations of arousal level, motivation, distraction, boredom, and psychological stress (Langer et al. 2010; Parasuraman et al. 1998; Steinborn et al. 2008; Tucker et al. 2009). Among neuronal systems identified to play a role in the regulation of attentional effort, experimental studies across species and clinical investigations have consistently identified a key role for central thalamic neurons in maintaining a state of vigilance and adjustments of arousal level (Bogousslavsky et al. 1991; Castaigne et al. 1981; Kinomura et al. 1996; Moruzzi and Magoun 1949; Paus et al. 1997; Schiff and Plum 2000; Steriade and Glenn 1982; Van der Werf et al. 1999). The neurons distributed within the central thalamus share anatomical and physiological specializations that support such an important role (Gronewegen and Berendse 1994; Jones 2007; Llinas et al. 1994; Minamimoto and Kimura 2002; Plum 1991 Purpura and Schiff 1997; Steriade 2000; Steriade et al. 1993, 1996; Van der Werf et al. 2002). Evidence from human neuroimaging studies specifically demonstrates that increased activity within the central thalamus is linked to widely distributed activation of cortical regions and the striatum during brief state changes associated with attentional effort, shifts in baseline vigilance/arousal level, and increased cognitive demands (Chee and Choo 2004; Kinomura et al. 1996; Nagai et al. 2004; Naito et al. 2000; Paus et al. 1997; Portas et al. 1998). Few studies, however, have directly examined the response profiles of central thalamic neuronal populations during controlled attentive behaviors in alert nonhuman primates (Matsumoto et al. 2001; Minamimoto and Kimura 2002; Schlag and Schlag-Rey 1971, 1984; Schlag-Rey and Schlag 1984; Wyder et al. 2003, 2004).

Here we measure single-unit activity (SUA), multiunit activity (MUA), and local field potentials (LFP) from the monkey central thalamus during performance of a forewarned simple reaction time task with a variable time duration of wait time prior to a "GO" signal. Such simple manipulations of attentional resources and sensorimotor associations provide a basis for many more complex behaviors, and a similar task structure underlies the basis of many other studies that have characterized the role of the central thalamus in supporting goal-directed behaviors (Burk and Mair 1998; Kinomura et al. 1996; Mair et al. 1998; Matsumoto et al. 2001; Minamimoto and Kimura 2002; Schlag and Schlag-Rey 1971, 1984; Schlag-Rey and Schlag 1984; Wyder et al. 2003, 2004). We identify a population of central thalamic neurons (~24% of our sample) that demonstrate marked increases in firing rates during the variable delay component of correctly performed trials. Incorrect performance of the task correlates with specific shifts of spectral activity in the background activity recorded in the central thalamic LFP and consequent drops in MUA firing rates, implicating a role for the changing level of input to central thalamic neurons in overall behavioral performance.

METHODS

Physiological preparation. All work was performed in strict accordance with the National Institutes of Health Guidelines for Use of Animals in Research and under an approved protocol from the Weill Cornell Medical College Institutional Animal Care and Use Committee. Following behavioral training to establish performance levels of at least 80% on simple visually guided tasks, two male rhesus monkeys (*Macaca mulata*) received implants of recording chambers (Crist) and a head holder using sterile surgical technique under deep gas anesthesia (Purpura et al. 2003). Recordings were obtained in

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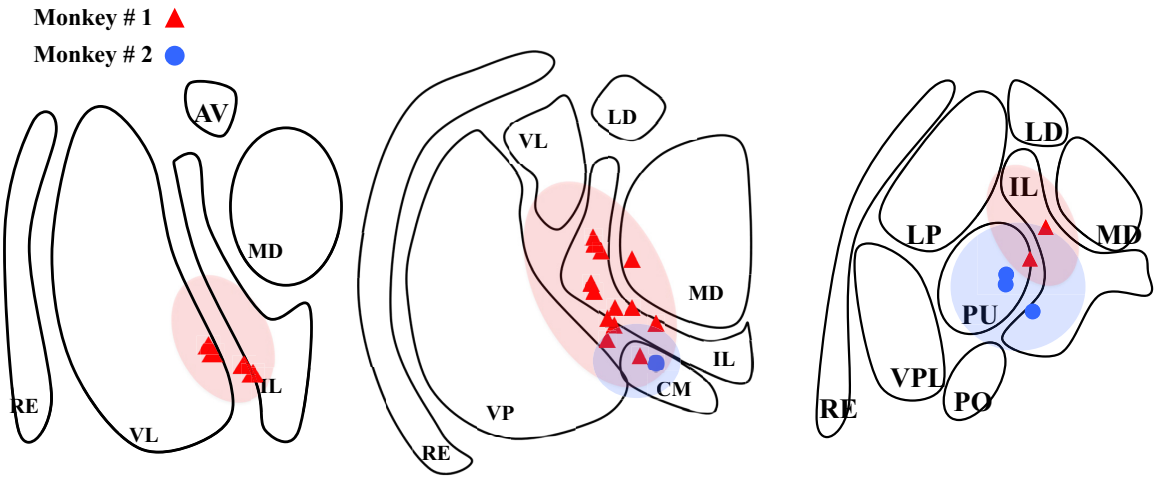

Fig. 1. Recording locations (*left-right* coronal slices: rostral to caudal). Figure shows locations of recording sites for *monkey 1* (M1; red shaded region) and *monkey 2* (M2; blue shaded region). Local populations with increased activity during delay period of task are individually marked (red triangle, M1; blue circle, M2). CM, centromedian nucleus; IL, intralaminar; LD, lateral dorsalis nucleus; MD, medial dorsalis nucleus; PO, posterior nucleus; PU, pulvinar nucleus; VL, ventral lateral nucleus; VP, ventral posterior nucleus; VPL, ventral posterior lateral nucleus; RE, reticular nucleus; AV, anteroventral nucleus; LD, laterodorsal nucleus.

monkey 1 (M1) from two chambers positioned over the right hemisphere occipital and parietal regions, and in *monkey 2* (M2) from a left parietal lobe chamber. The parietal chambers were used for gaining access to the central thalamus. A plastic grid system (Crist Instruments) allowed consistent electrode guide tube placement from day to day. Chamber placement was confirmed by MRI and compared with a standard atlas for localization of targets (Paxinos et al. 1999; see Fig. 1). Physiological methods for experiments involving *monkey 3* (M3) are reported in Smith et al. (2009); analyses of task performance from M3 presented in RESULTS are derived from these previously reported experiments.

Experimental protocol. We used a modification of a standard variable foreperiod simple reaction time task ("S1–S2," or "phasic alerting" paradigm, cf. Posner 1978, and Luce 1991); see Fig. 2. The structure of this task is a simple reaction time task initiated by a cue signal (S1) and followed by a variable foreperiod prior to the arrival of the imperative stimulus (S2), the "GO" cue. The temporal uncertainty present in this task produces sensitivity to arousal effects in human studies of this general paradigm (Steinborn and Langner 2012). Similar paradigms have demonstrated selective activation of the central thalamic neuronal populations of interest here in human subjects using functional positron emission tomography, ^{15}O-PET imaging, and functional magnetic resonance imaging (Hulme et al. 2010; Kinomura et al. 1996; Naito et al. 2000; Paus et al. 1997). Our specific behavioral paradigm (Fig. 2) consisted of the following: a fixation target appeared (small red rectangle) in one of nine predetermined locations on the visual display chosen at random from the location set on each trial. The monkeys were required to maintain their gaze within a 2.5–3.5° window centered on the target within 100 ms of the target's appearance in order for the trial to proceed. The monkeys were then required to restrict their gaze to within the fixation window until the appearance of the "GO" signal. The GO signal was a change in the color of the fixation target from red to green. The monkeys were required to maintain fixation on the red fixation target for a variable delay period (uniform normal distribution with mean 1,350 ms and standard deviation of 350 ms). In the experiments reported here, the target could appear either on a uniform gray background or on a flashing checkerboard background. Finally, the monkey had to release a bar within 1 s of the GO signal to receive a liquid reward. The monkeys needed to have their hands on the bar from the start of the delay period in order for the bar release trigger to be armed. Typically, the monkeys placed their hand on the bar almost immediately after release at the end of the previous trial. Response times for the correct behavior ranged from 280 to 350 ms following the GO signal.

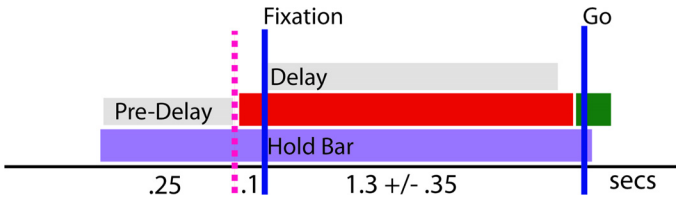

Fig. 2. Experimental paradigm. Dashed pink line indicates trial start; blue line indicates fixation. Task begins after animal grabs bar (purple). A red square appears in 1 of 9 locations on screen. The animal acquires fixation within 100 ms. After a variable delay period (normal distribution with mean = 1.3 s and SD = 350 ms), the color of the square changes to green. Color change to green square provides cue to release bar and receive reward if successful. Gray bars indicate epochs used for data analysis.

We focus here on manipulations aimed at lowering the animals' performance from a baseline (Parasuraman et al. 1998). The paradigm was designed to tax the animal's vigilance as repeated trials were completed over time (Paus et al. 1997). Thus we imposed a modest attentional load, short intertrial intervals, and spatial uncertainty of the initial cue, as these are all manipulations that increase demands on sustained attention (Parasuraman and Davies 1977). Despite these efforts, only one monkey showed a relatively low percentage of correct trials (average 70–75% correct) across all recording days; the second monkey maintained a high average percent correct performance (90%). Such variance in rhesus monkey task performance is well known and previously characterized (Fuster and Uyeda 1962).

Behavioral experiments were programmed and implemented using a computer control system (TEMPO, Reflective Computing, St. Louis, MO, running under DOS 6.0; Microsoft, Redmond, WA). Trial data (behaviorally relevant events, eye movements, and electrophysiological data) for M1 and M2 were collected within short files acquired via the computer control system. For behavioral data from M3 shown in RESULTS, all data types were continuously streamed and stored for further analyses.

Initial localization and histological confirmation of electrophysiological recording sites. Central thalamic recording sites were initially localized in M1 utilizing a three-dimensional MRI reconstruction and attachments built from computer-aided design models, developed using the in situ geometric relationship of the implanted Crist chamber and the thalamus to guide electrodes to the central thalamus. In M2, we localized chamber placements using an MRI-compatible stereotaxic device (Kopf) prior to and during implantation surgery. Recording sites were referenced to the each animal's MRI images and compared with standard rhesus monkey atlas coordinates (Ilinsky et al. 2002; Paxinos et al. 1999; Fig. 1). For each animal, the anterior intralaminar nuclei (central lateral, paracentralis) and related parala-

minar regions of the median dorsalis nucleus were targeted. Presaccadic evoked potentials were recorded in 83% of sites reported here and, in combination with imaging guided placement of guide tubes, provided an initial physiological confirmation of targeting of central oculomotor regions of the thalamus (Schlag-Rey and Schlag 1984; Schlag and Schlag-Rey 1984).

After the completion of the recording experiments in each animal, we inserted electrodes painted with Di-I using stereotaxic guidance. After a waiting period of 1 h, the animals were deeply anesthetized with propofol (5–10 ml) and perfused (4% paraformaldehyde; EMS, Hatfield, PA) in phosphate-buffered saline. A block of brain tissue from each animal containing the Di-I electrode tracks was then removed and allowed to sink in 10%, 20%, and 30% sucrose solution in 4% paraformaldehyde. For M1, frozen sections were then cut parallel to the Di-I electrode tracks, mounted, and stained for Nissl in thionin staining solution (1%, Sigma-Aldrich, St. Louis, MO). Slides were also stained for glial fibrillary acidic protein to identify course of electrode tracks from experiment (done in laboratory of Dr. Daniel Herrera, Harvard University). For M1 (majority of recordings were obtained from this animal), recording sites were localized to the following regions of the central thalamus: central lateral/parafascicularis nuclei, medial regions of the ventral lateral nucleus, posterior lateral median dorsalis nucleus, parafascicularis/centromedian nucleus, and inferior medial pulvinar (see Fig. 1). For M2, gross histological confirmation indicated that the location of most of the recordings remained within the region of the parafasicularis-centromedian nucleus and posterior aspect of the central lateral nucleus with some recording sites in the medial aspect of the inferior pulvinar.

Electrophysiological recording methods. We recorded extracellular action potentials and LFPs from the central thalamus of two monkeys (M1, M2). The extracellular recordings were obtained using epoxy insulated tungsten microelectrodes (FHC, Bowdonham, ME), with nominal impedance of 1–4 MΩ. All of the recordings were monopolar, with the ground tied to a partially exposed skull screw. The same indifferent was used for both microelectrodes in the dual recordings from thalamic sites. The signals from each electrode were separated into LFP and spike channels (Tucker-Davis, Tech., Gainesville, FL). After filtering (low-pass filtered at 1 kHz), the LFPs were downsampled at 200 Hz (gain of 6,000), and the 1- to 10-kHz spike channels were sorted for shapes (gain of 3,000) with either matched template filters or neural network classifiers (Chandra and Optican 1997). Up to four channels of SUA were isolated online using the MEX spike-sorting system (Laboratory of Sensorimotor Research of the NEI, National Institutes of Health). An additional threshold triggered hoop discriminator channel (Tucker-Davis Technologies) allowed a total of up to five channels to be simultaneously recorded from each of two chambers.

Eye tracking. Each monkey was positioned with its head fixed 114 cm from the video monitor (Cambridge Systems). Eye position measurements were recorded using the horizontal and vertical analog outputs from a E5000 infrared video eye tracking system fitted with a telephoto lens (ASL, Bedford, MA). The animal's gaze position was calibrated each day before experiments began and then whenever necessary to ensure the accuracy of the calibration. Horizontal and vertical eye position signals were processed to determine the occurrence of a saccade, its amplitude, velocity, direction, and positions of fixation. Fixation was considered to be broken if the recorded eye position left a 2.5–3.5° window around the fixation target. The eye tracker has a resolution of ~1.3° of visual angle and a latency of signal acquisition between 25 and 29 ms, consistent with the nominal specification from the factory and the 5-ms resolution of the behavioral computer control system (TEMPO, Reflective Computing, St. Louis, MO, running under DOS 6.0, Microsoft, Redmond, WA).

Analysis of spike recordings. We recorded MUA from 166 separate locations in the central thalami of M1 and M2. Online analysis of the microelectrode recordings yielded 196 neurons identified as single units from within these multiunit clusters by hoop discrimination and matched filters (Chandra and Optican 1997). However, as the recorded single units typically showed similar profiles to the population's MUA obtained with threshold discriminator, we chose here to carry out all analyses on the 166 MUA recordings from the separate sites to be conservative in our conclusions as online streaming and storage of waveforms for later analysis were not available. For each neuronal population we computed rate functions (RF) by averaging the neuronal responses for each set of trials. RFs were examined for task-related changes in firing rate. A multiunit cluster was considered to show a selective activation during the delay period if a statistically significant increase in firing rate was present during the delay compared with the preceding baseline firing rate. The baseline period refers to an interval of 750 ms prior to the appearance of the fixation target, which is illuminated 50 ms after the start of the trial. Firing rates during the delay period were computed for the interval 1,000 ms $\leq t <$ 1,750, beginning 250 ms after the appearance of the fixation target. Significance of a change in firing rate was initially evaluated using a nonparametric Wilcoxon rank-sum test and by comparing jackknifed standard error estimates of the mean of the firing rate during the baseline and delay periods. Using the jackknifed standard error of the difference between population means, we computed confidence limits for the difference in mean firing rates for the two time intervals.

RFs were obtained by fitting a quadratic polynomial to spike event times by local regression (Loader 1999), shown in Fig. 3. The local regression formulation has better convergence properties and less bias than spike density function approaches (Loader 1999). We compute 95% confidence limits obtained from the resulting marginal rate estimates by jackknifing over the RFs computed by leaving one trial out of the ensemble in turn (Hudson et al. 2009). The bandwidth used includes the larger of 150 nearest-neighbors spikes or 15% of the data with the result that regions of high firing rate have a narrower

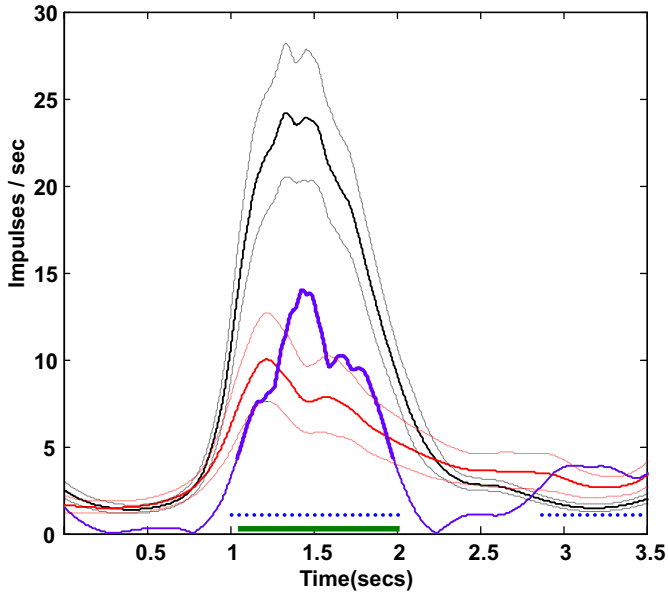

Fig. 3. Comparison of rate functions (RFs) from sample correct and incorrect trials using statistical difference test. *1*) The differences at each data point in the RF between correct trials, $n = 325$ (black solid line), and incorrect trials, $n = 175$ (red solid line), are first compared against differences obtained from shuffled trials (i.e., random population of two groups of 325 and 175 trials, repeated 1000 times) at each data point. The data points with significant difference (*t*-test) are indicated with blue dots. The $-\log$ of the *P* values is plotted in the purple curve. *2*) The *P* values are then corrected for the false discovery rate (Benjamini Hochberg method), and the data points that pass this correction are represented by a thickening of the purple line (superimposed on the $-\log P$ curve). Data points corresponding to those passing the full sequence of statistical difference test are represented by the thick green line on the *y*-axis of the figure (as also seen in Figs. 4 and 7). For this data, the cutoff for *P* values was 0.011.

temporal bandwidth than those with low firing rates. These algorithms are publicly available in the Locfit library (Loader 1999) as a part of the Chronux project (http://www.chronux.org). We compare firing rates between baseline and delay periods and around specific task-related events and compare firing rates during the delay periods from correct trials and incorrect trials.

Statistical evaluation of RFs. To determine the statistical significance of differences between RFs for various trial designators, such as correct and incorrect trials, we compared the original difference value (correct − incorrect trials) to difference values determined from surrogate data sets. A surrogate set was formed by shuffling together trials from both correct and incorrect trials; for each surrogate set, a new difference value was computed. This process was repeated to produce 1,000 difference values for each time point. The significance of the observed difference at each time point was computed by comparison to the surrogate distribution by a *t*-test; see Fig. 3. The *P* values found to be significant using this approach were then corrected for the false discovery rate (Benjamini and Hochberg, 1995). Values that pass the false discovery rate test are considered to represent time points where the original RFs differ (marked in green along the *x*-axis in plots of RF comparisons below).

Spectral analyses. We characterized the LFP by its power spectrum and its time-varying analog, the spectrogram. These quantities were calculated via the multitaper method (Mitra and Pesaran 1999; Thomson 2002), as implemented in Chronux (http://www.chronux.org). An initial assessment of the time-evolving changes in spectral content of the LFPs observed across task performance (from correct and incorrect trials) used the method of high-resolution spectrograms (Thomson 2002) to identify characteristic features of time-varying shifts of frequency content during trial performance. To compare spectra (e.g., baseline vs. delay period, or correct vs. incorrect trials), we used the two-group test, which includes a correction for unequal sample size (Bokil et al. 2007).

RESULTS

Multiunit recordings reveal thalamic subpopulations with increased activity during delay period. Recordings of MUA were obtained from 166 (131 M1) central thalamic locations. In 46 of these sites (27.7%), MUA firing rate during the delay period (1,000 to 1,750 ms after the start of the trial) differed significantly ($P < 0.05$) from baseline (750 ms prior to the start of the trial); we focus on these sites. The large majority of these recordings were from M1 ($n = 42$). Of these 46 sites, most showed firing rate increases with peak firing rates (range ~10–100 spikes/s) falling within the variable delay period of the trial ($n = 39/46$, 84.7%, 35 M1). A small number of recording sites showed activity after the delay period, revealing late post-bar release elevations in firing rate ($n = 6/46$, 13%). One recording site demonstrated a clear delay period suppression in firing rate.

Figure 4 shows four examples of RFs of MUA (correct and incorrect trials separated) from central thalamic recording sites with significant maintained elevations of firing rate during the variable delay period of the task. Each set of recordings also shows a significant difference (green line along abscissa) between MUA during correct and incorrect trial performance (see Fig. 3 and METHODS). As seen in Fig. 4, *A–D*, the onset of firing rate elevation differs among the multiunit populations, as does the period of sustained discharge and time of peak firing rates. In the majority of recordings with MUA firing rate elevations during the delay period, the onset of increased firing occurred between 0.5 and 1.5 s into the task during the delay period (cf. Fig. 4, *A*, *B*, and *D*). The earlier RF modulation in Fig. 4*C* may reflect saccade-related activity, since saccades can be made in the interval just prior to the start of the delay period [100 ms after onset of the fixation target, marked as blue (correct trials) and red (incorrect trials) asterisks on Fig. 4].

As seen in Fig. 4, *A–D*, each set of recordings shows a significant difference between MUA during correct and incorrect trial performance. For the majority of recording sites that showed significant RF increases during the delay period, MUA from incorrect trials showed RF amplitudes during the delay period that did not reach the peak amplitudes of correct trial RFs (for example, as seen in Fig. 4, *A–D*); incorrect trial MUA RFs typically declined back to pretrial baseline activity before the MUA rate declined in correct trials (31/39, 88% showed significant differences). In some cases (5/39, 12.8%), correct and incorrect MUA RFs remained statistically indistinguishable in their peak firing rate and across the duration of a maintained elevation above baseline.

While we observed weak correlations between firing rate elevation and the timing of sensory and motor events of the trial, this was not prominent. To assess the potential relationship of the observed delay period firing rate elevations to the sensory and motor events of the trial, we separately assessed the relationship of the MUA to the appearance of the red target at trial onset, the initial saccade to the red target, and the GO signal to release the bar (results not shown). We realigned RFs of MUA to these separate events in the trials. In all recording sets, realignment of RFs around each trial-related event resulted in shifting the peak of the firing rate, which typically remained well past the time of the initial saccade onto the red target. The relationship of MUA to the appearance of the GO signal varied considerably. Although some recording location's MUA show a clear peak prior to the appearance of the GO signal, the majority of recordings showed no clear relationship of MUA firing rates to the appearance of the GO signal. In our sample, we found no example of an abrupt drop in firing of the MUA at the onset of the GO signal. Similar results were obtained by realigning RFs across the entire population of MUA recordings with significant delay period firing rate elevations, suggesting that the rise in firing rate seen in the MUA population recording in our data set is not strongly timed-locked to the behavioral cues in the trial structure. We also examined the possible contribution of gaze position to the maintained firing rate elevations. Elevations of mean firing rate appeared to be generally independent of direction of gaze across the populations recorded in our database (results not shown).

Behavior errors during the variable foreperiod ("delay" period) of the task. Data acquisition for task performance in M1 and M2 began after an initial saccade was made onto the red fixation target. In the comparisons of correct and incorrect trials from these animals, only errors made after the initial target fixation are included in the "incorrect trial" comparisons. Both M1 and M2 made consistent errors during continuous task performance, but the performance rate in M1 typically averaged ~70–75% during the first hour of task performance (see Smith et al. 2009, Fig. 1), whereas M2 performed the task at a consistent rate of ~90% correct. Figure 5 shows a compilation of correct and incorrect trials from M1 and a third monkey, M3, which also carried out this task with similar performance characteristics to M1 (reported in Smith et al. 2009). The data from M3 were continuously streamed to disk and thus allowed for a more complete assessment of trial performance characteristics for this monkey to compare with

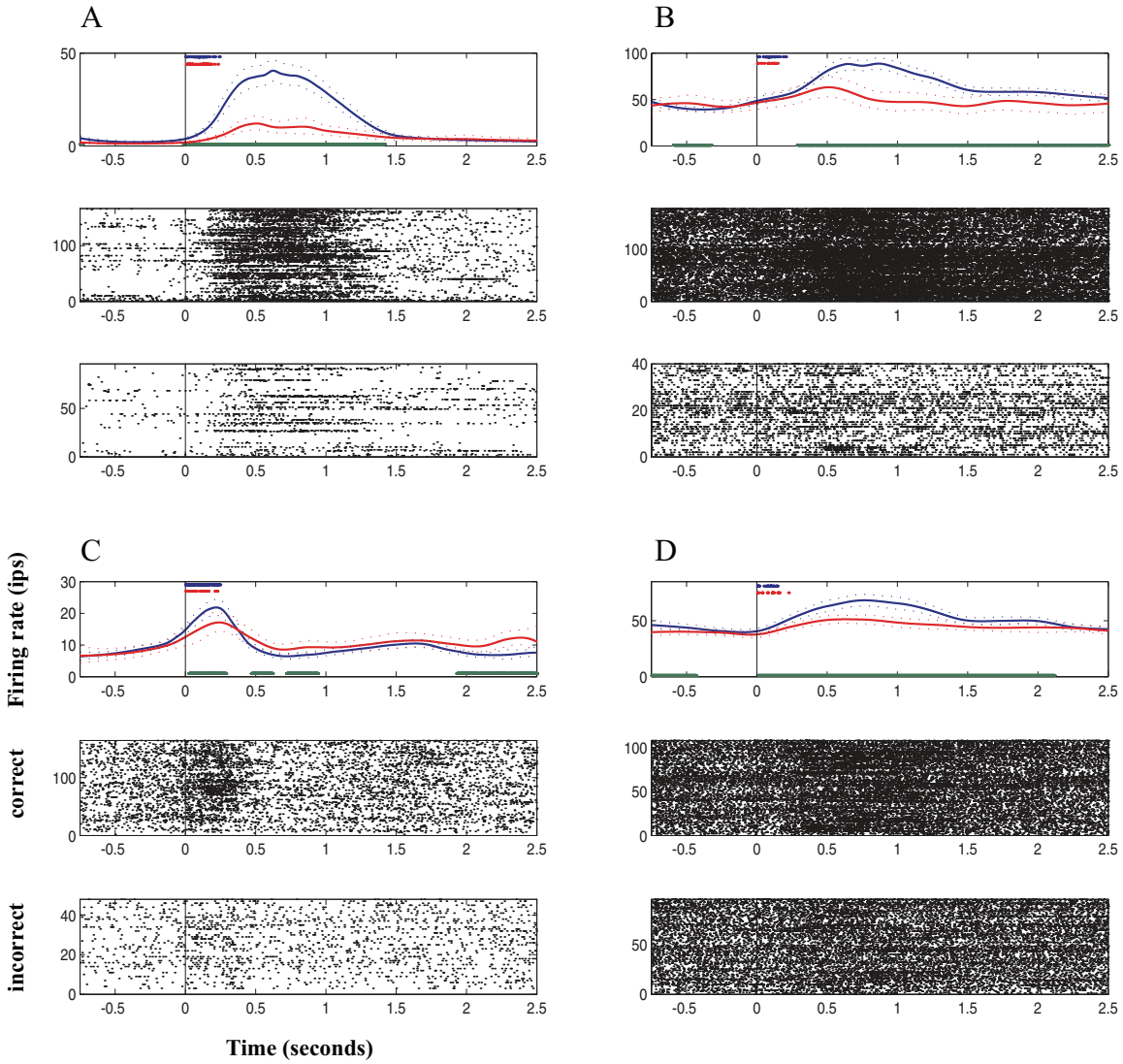

Fig. 4. *A–D*: RF. *A*, *B*, and *D*: RFs of multiunit activity (MUA) from central thalamic recording sites that showed significant maintained elevations of firing rate during the variable delay period of the task (3 M1). Each set of recordings shows a significant difference (green line) between MUA during correct (blue) and incorrect (red) trial performance. Asterisks on the *top* of each plot, aligned to start of delay, represent saccades for correct (blue) and incorrect trials (red).

M1. As shown in Fig. 5, M3 also acquired the target in the majority of incorrect trial performances. Both monkeys show similar behavioral profiles for their performance in correct and incorrect trials. In most incorrect trials, initial fixation is evident in Fig. 5. The lack of green GO signals in incorrect trial plot from M3 reflects a difference in data acquisition methods (GO time for trial not recorded in incomplete trials), and the presence of saccade marks (asterisks) for both M1 and M3 during delay period in some trials reflects the presence of fixational eye movements during the delay period that are more frequent for M1 than M3. These fixational eye movements were not large enough in amplitude to trigger abortion of the trial. We quantified the error types for a randomly selected set of 23 experiments in M3 (6512 trials) and found that 769/3,490 incorrect trials in M3 occurred due to failure to make an initial fixation of the target, with the majority of other errors occurring during the delay period. The majority of errors occurred during the delay period of the trial, 2,304/3,490 early bar releases often with fixational breaks, and 66/3,490 breaks in fixation without a bar release. In the comparisons of correct and incorrect trial performance for M1 and M2 above and below, we average over all error types which reflect failures to perform the task after an initial fixation onto the red target.

LFP recordings show characteristic changes in power during delay period. Our MUA results raise the question of whether the background activity in the LFP, which reflects the summed excitatory and inhibitory potentials near the electrode tip (Henrie and Shapley 2005), differs during the delay period and for correct vs. incorrect trial performance during the delay period. To address this, we measured the time-varying frequency content of the LFP across the baseline and delay period of the task. To begin this analysis, a first stage of evaluation of the LFP used high-resolution spectrograms developed by Thomson (2002). This analysis method (Purpura et al. 2003) indicated structure in the time-evolving LFP signal in most recordings containing elevated MUA firing rate during the delay period. Figure 6 shows the spectrograms of LFP signals from all trials obtained during one recording session from a representative site [321 correct trials (*top*), 171 incorrect trials (*middle*), and power difference (*bottom*)]. The *bottom* panel

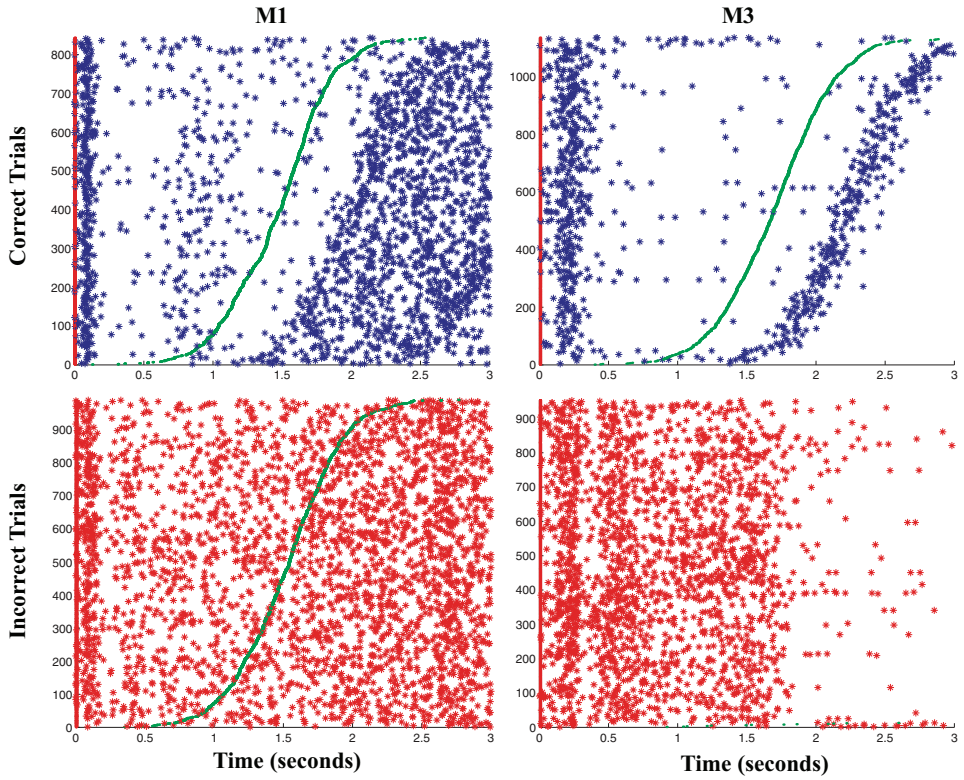

Fig. 5. Comparison of saccades during correct vs. incorrect trial performance. Comparison of saccades (asterisks) made during correct and incorrect task performance in two monkeys, M1 and M3, show similar behavioral profiles with initial acquisition of red square target with saccade. Correct trials show fixation through variable delay times (green line indicates GO signal). Saccades marked within fixation period of correct trials reflect sensitivity of post hoc saccade identification algorithm. In both animals, brief fixations can be seen to occur after the initial saccade onto the red target in most incorrect trials. Saccades marked within delay period of task reflect fixational eye movements (more frequent in M1) that did not trigger trial abortion. Green GO signal was not recorded for incorrect trials in M3 that did not continue through appearance of the behavioral event.

shows the power difference spectrogram which here compares the two populations of spectrograms at a 99% confidence interval for statistical significance and quantifies the significant power differences on a decibel scale (Purpura et al. 2003). There are two prominent differences in the spectrograms of the correct and incorrect trials: *1*) a suppression (−4 dB) of frequencies in the 10- to 20-Hz range, beginning ~1 s after trial start (~250 ms after the appearance of the fixation target) and throughout the delay period; and *2*) a broad enhancement (~2–3 dB) of higher frequencies in the 30- to 100-Hz range across the same time interval. Visualization of power difference spectrograms of correct and incorrect trial LFPs from different central thalamic populations showed similar but relatively distinct patterns of enhancement and/or suppression of frequencies during the delay period in time and frequency; based on these data visualizations, we collapsed across time periods and used power spectral analyses to assess common findings across the central thalamic recordings.

To focus on the changes in the frequency content of the LFP, we calculated spectra from the precue baseline period (750-ms

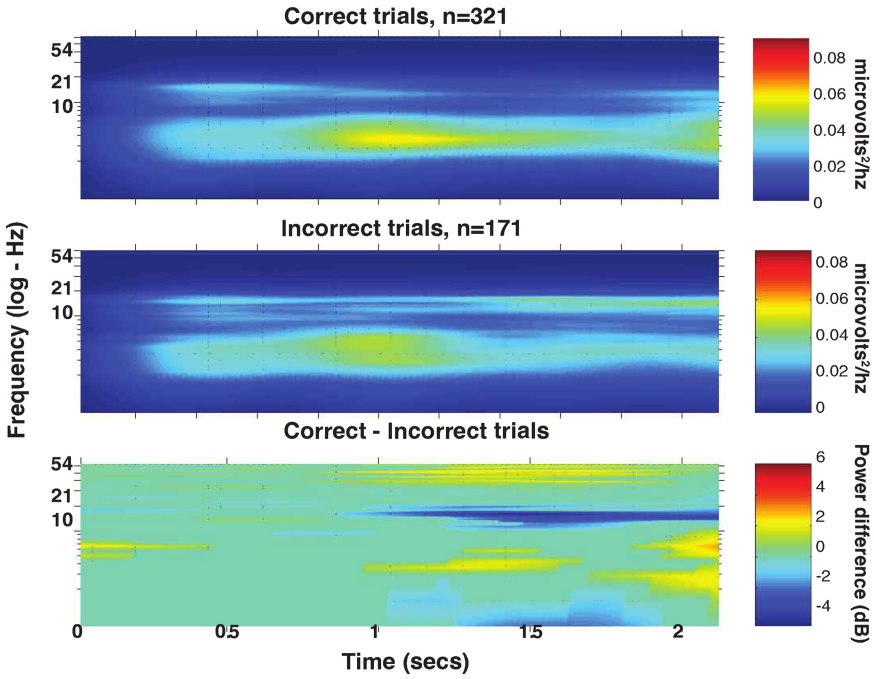

Fig. 6. Analysis of local field potentials (LFPs). Averaged analysis of LFPs obtained across correct and incorrect trials using high-resolution spectrograms (Thomson, 2002, Purpura et al. 2003) are shown. The *top* two panels of the figure show the average spectrograms for the LFPs from correct trials (n = 321; *top*) and incorrect trials (n = 171; *middle*) associated with MUA recordings shown in Fig. 7*A*. The *bottom* panel shows the power difference spectrogram (Purpura et al. 2003), which compares the two populations of spectrograms at a 99% confidence interval for statistical significance and quantifies the significant power differences on a decibel scale.

period prior to the appearance of the red target) and the delay period (250 to 1,000 ms after its appearance), the same periods used to assess RFs for all artifact-free LFP recordings (28 from delay populations, 2 sites M2; 90 nondelay, 10 sites M2). Figure 7 compares analyses of MUA firing rate and LFP power in two different central thalamic populations [M1, central lateral nucleus (*left*) and ventralis anterior (VA; *right*)]. As shown in Fig. 7, several frequency ranges show significant separation across the two time intervals. Compared with baseline, LFP power during the delay period activity is higher in the 3- to 7-Hz and 30- to 100-Hz range, and lower in the 10- to 25-Hz range. These recordings are consistent with MUA and LFP profiles of populations obtained at progressively lower depths along a trajectory moving anterior-posterior and from lateral to medial in M1 spanning 4.5 mm through the central thalamus. The neuronal populations in these regions include neurons from within the paralaminar VA and ventralis lateralis (VL) (plVA/VL) nuclei and central lateral/paracentralis nuclei (Fig. 1). Changes in the background LFP spectral content similar to those seen in Fig. 6 are present with a prominent feature of suppression of 10- to 20-Hz power during the delay period noted in the LFP spectrum for each recording site. A broad elevation of 30- to 100-Hz power is also observed in both the delay compared with predelay periods and correct vs. incorrect trials during the delay period. Figure 8 shows the population summaries for all artifact-free LFP recordings for the comparisons of predelay vs. delay period LFP power and correct vs. incorrect trials during the delay period. Each trace represents the spectral difference for a single data set. Solid black lines represent frequencies within each trace that were significantly different. The thin red lines separate the 1st and 2nd quartiles of the distribution and the 3rd and 4th quartiles. The population summaries demonstrate a strong suppression of 10- to 20-Hz power during delay period in central thalamic populations with increased MUA RF ($n = 28$, 2 M2). A less prominent but similar feature is seen in the summary of populations without increased MUA firing rate ($n = 90$, 10 M2). In both populations, a broad-band increase (30–100 Hz) is present during the delay period of correct trials compared with incorrect trial performance. Of note, the magnitude of the increased 30- to 100-Hz power is greater in the populations without increased MUA during the delay period.

DISCUSSION

The present report examined the neuronal activity within the central thalamus across variations in task performance on a variable foreperiod simple reaction time task. As shown above, both MUA and LFP recordings identify specific neuronal populations distributed throughout the central thalamus whose activity increases during the delay period of the task. We find that elevation of multiunit firing rates during the delay phase of the task in the central thalamus correlates with modulation of the power in the LFP signal. Specifically, in locations at which MUA is increased during the delay period, the LFP signal during this phase shows an increase in spectral power in the gamma range (30–100 Hz) and sharp decreases of spectral power in the beta range (10–20 Hz). Moreover, these changes are substantially more prominent on successful trials than on failures. We find that the animals' initial engagement of the correct and incorrect trials is similar as judged by examination of initial MUA firing rates at the onset of the delay period. Thus it appears that failures of performance are linked to a relatively less robust build-up of neuronal activity within the central thalamus during the delay period. Such failures may reflect transient variations in arousal level, distraction, goal neglect, fatigue, and/or waning motivation. These factors are confounded in the experiment and are recognized to be typically mixed influences altering levels of attentional effort in prolonged performance of simple tasks (Sarter et al. 2006). In the aggregate, the physiological observations reported here indicate that central thalamic neurons participate in short-term gating of attentional effort and behavioral changes associated with variations of task performance.

Our findings can be directly compared with many other studies of variable forewarned simple reaction time tasks. A large literature of experimental studies in humans (reviewed in Langer et al. 2011; Parasuraman et al. 1998; Steinborn and Langer 2012; Vallesi and Shallice 2007) and experimental animals (reviewed in Sarter et al. 2006) have employed similar tasks to study attentional effort. Moment-to-moment effects of the demands induced by continued performance of this task produce variations in arousal regulation and allocation of attentional resources (Steinborn and Langer 2012; Valesi et al. 2007; Vallesi and Shallice 2007). Even in human subjects, performance on such monotonous variable reaction time tasks can only be incompletely rescued by even strong incentives if subjects are sleep deprived (Horne and Pettitt 1985). Continued performance of these tasks, particularly when there is time uncertainty, taxes arousal regulation and attentional effort (Langer et al. 2010) and produces ongoing performance variations (Steinborn and Langer 2012). Sarter and colleagues (2006) propose the term "attentional effort" to define a "cognitive incentive" with a close relationship to motivation as well as arousal regulation to capture these confounded influences into a single conceptual frame. We interpret our findings of differential MUA and LFP profiles in the central thalamus linked to task performance as a physiological correlate of variations of attentional effort that arise on a trial-to-trial basis (cf. Steinborn and Langer 2012). The majority of recordings here are obtained from M1 that showed a lower highest performance rating and typical declines over 1 to 2 h of task performance. These behavioral characteristics are consistent with those of M3 (for further analyses of performance curves of both M1 and M3, see Smith et al. 2009) and also consistent with two additional rhesus monkeys that have performed this task (Baker et al. 2010, 2011). Temporal preparation simple reaction time tasks, as employed here, are known to be more sensitive to arousal effects (Steinborn et al. 2008) and may, in fact, allow a greater role for arousal regulation effects to influence performance (Steinborn and Langer 2012).

The increased overall firing rate for correct vs. incorrect trial performance seen in the majority of MUA populations recorded here can be compared with a similar grading of preparatory activity identified in single-unit recordings in rat anterior cingulate cortex that correlates with correct and incorrect performance of simple reaction time tasks (Totah et al. 2009). Niki and Watanabe (1979) demonstrated similar single-unit firing patterns from neurons within both anterior cingulate and dorsal lateral prefrontal cortex. The central thalamic nuclei sampled in our study (particularly those within the lateral aspect of the central lateral nucleus and the parafasicularis

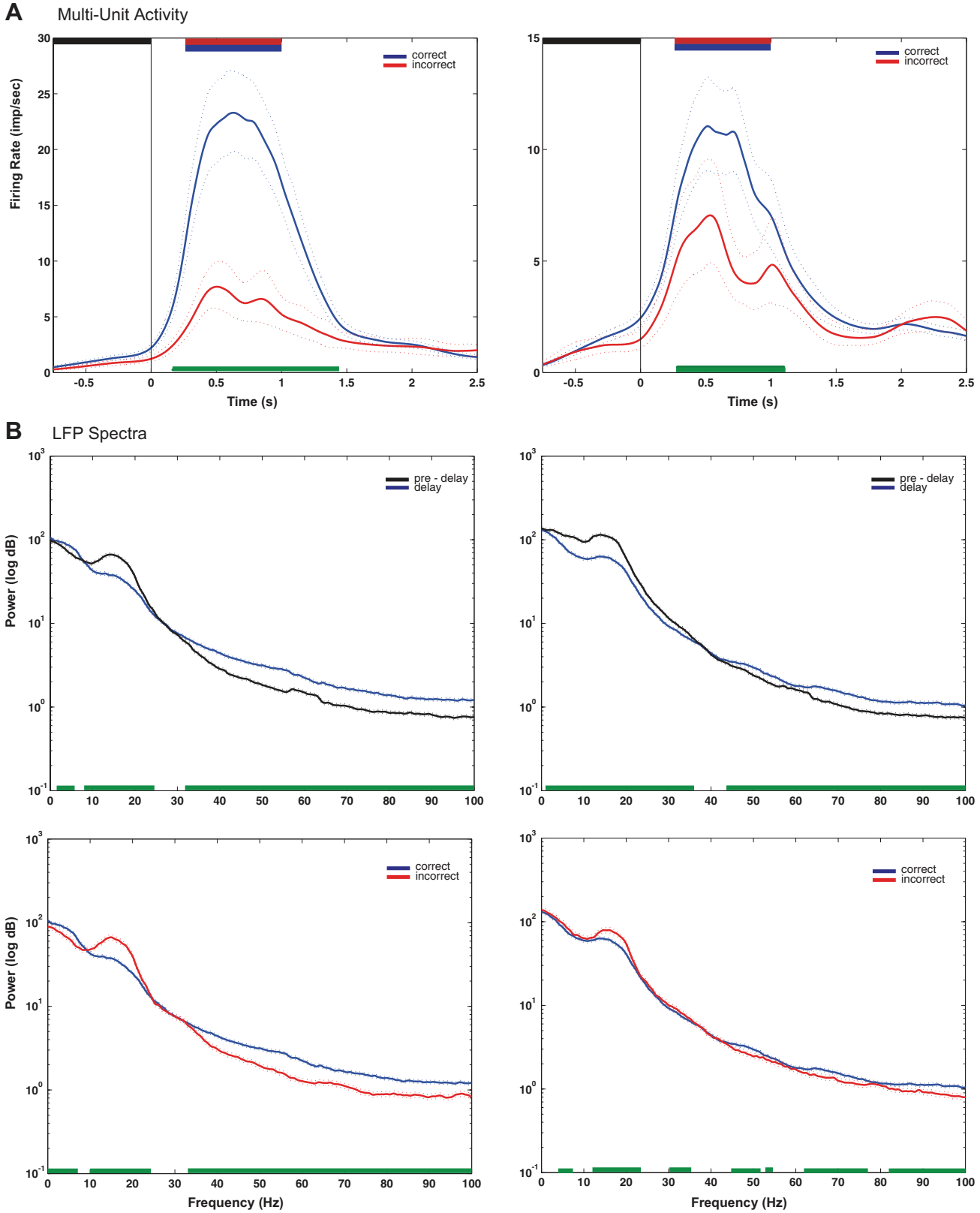

Fig. 7. Comparison of MUA and LFP spectra predelay vs. delay and correct vs. incorrect for two sample recordings (*left* and *right* column). *A*: figure shows correlation of significant differences in MUA RFs in predelay compared with delay period RF correct vs. incorrect trial performance. Significant differences are shown by green line for MUA RFs. *B*: RF changes are correlated with shifts in LFP spectra with prominent suppression of ~10- to 20-Hz power during delay period of correct trials.

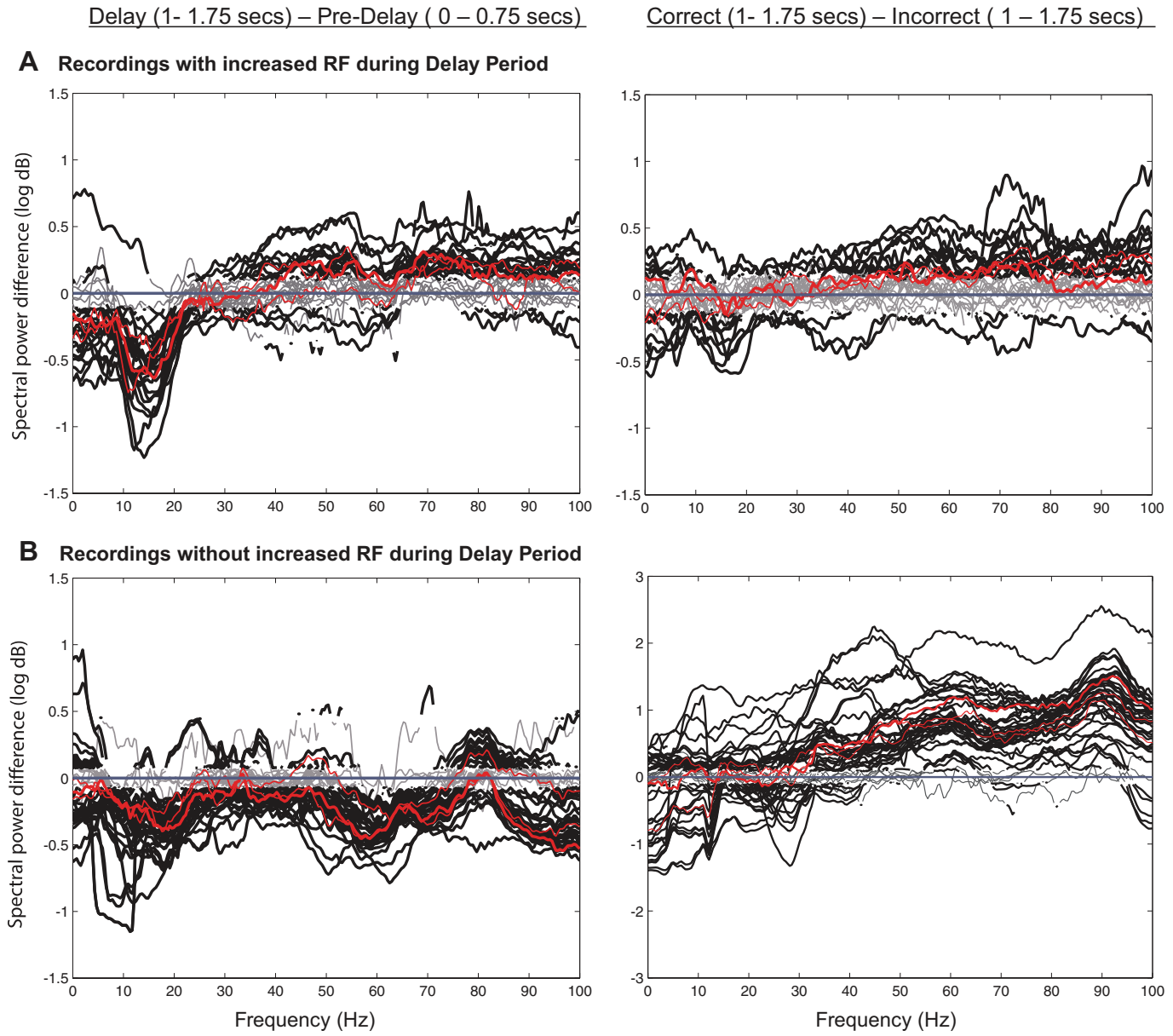

Fig. 8. Population summary. *A*: recordings with increased RF during delay period. *B*: recordings without increased RF during delay period. Each trace represents the spectral difference for a single data set. Solid black lines represent frequencies within each trace that were significantly different (Bokil et al. 2007). Solid and thin red lines represent the median and quantiles, respectively. The population summaries demonstrate a strong suppression of 10- to 20-Hz power during delay period in central thalamic populations with increased MUA RF (n = 28, 2 M2). A less prominent but similar feature is seen in the summary of populations without increased MUA firing rate (n = 90, 10 M2). In both populations, a broad-band increase (30–100 Hz) is present during the delay period of correct trials compared with incorrect trial performance.

complex) strongly project to the anterior cingulate cortex (Morel et al. 2005), and the neuronal populations with increased MUA during the delay period may reflect the populations projecting to the anterior cingulate cortex. Consistent with our findings are studies demonstrating that failures of task performance across delay durations arise in animals lesioned within the central thalamus (central lateral nucleus, Burk and Mair 1998; Mair et al. 1998) and similar dysregulation of arousal and attentional effort seen following discrete central thalamic injuries in humans (van der Werf et al. 1999).

Our findings in MUA and LFP recordings may provide a direct neurophysiological correlate of measured changes in blood flow within the human central thalamus during similar vigilance tasks (Kinomura et al. 1996; Paus et al. 1997). Transient increases of blood flow in the central thalamus (localized to the central lateral/paracentralis and centromedian/parafasicularis thalamic intralaminar nuclei) are identified using variable foreperiod reaction time tasks (Kinomura et al. 1996), whereas slow declines in blood to the central thalamus that statistically covary with declines in the anterior cingulate cortex and pontomesencephalon are correlated with decline in performance in an infrequent target detection task (Paus et al. 1997). Both the weaker elevation of MUA firing rates and the weaker observed reduction of spectral power in the 10- to 20-Hz range of the LFP, in association with incorrect trials, may thus be a physiological correlate of these observed reduc-

tions of blood flow in the central thalamus measured during declines in task performance over long vigils.

A large number of our recording tracks (Fig. 1) overlap closely with the regions sampled near the lower lateral border of the median dorsalis nucleus and the large lateral "wing" of the central lateral nucleus studied by Steriade and Glenn (1982). During the transition to natural wakefulness, these neurons increase their firing rates, consistent with a role in arousal regulation. These neurons receive heavy innervation from glutamatergic afferents from the mesencephalic reticular formation (Glenn and Steriade 1982) and also receive both cholinergic afferents from the pedunculopontine and lateral dorsal tegmental nuclei (Heckers et al. 1993) and noradrenergic afferents from the locus ceruleus (Vogt et al. 2008). In addition, some task delay responsive neurons localize to the plVA/VL nuclei. These plVA/VL neurons have strong afferent projections to both the striatum and frontal cortical regions (Morel et al. 2005). Collectively, the regions sampled in our study are anatomically situated within regions that are under regulation by both frontal cortical and brain stem components of the distributed arousal systems (Schiff 2008).

The consistent observation of a strong suppression of prominent 10- to 20-Hz background activity during the delay period in local populations that significantly increase their multiunit firing rates may be similar to findings in other studies. It is increasingly recognized that 10- to 20-Hz activity within prefrontal and frontal cortical regions with direct anatomical relationships with the central thalamus (Groenewegen and Berendse 1994, Van der Werf 2002, Morel et al. 2005) are important for attentional processing (Buschman and Miller 2010). Suppression of 15- to 20-Hz rhythms in somatosensory cortex are associated with improved detection of stimuli in simple reaction time tasks (Jones et al. 2009), and the findings here may suggest that these central neuronal populations are linked to a general mechanism supporting sensorimotor integration and target detection. Other studies in central lateral nucleus and paralaminar regions of median dorsalis and VA demonstrate responses to visual targets, and recordings in centromedian parafascularis demonstrate neurons linked to a variety of behavioral salient events in alert monkeys (Schlag and Schlag-Rey 1984; Schlag-Rey and Schlag 1984; Wyder et al. 2003, 2004). The modulation of ~10- to 20-Hz rhythm during the delay period seen throughout the central thalamic recording sites (stronger in the local populations with delay period elevations in MUA) here may reflect modulation of both corticothalamic networks, as well as long-loop connections involving the corticostriatopallidal-thalamocortical loop systems (Gronewegen and Berendse 1994).

The presence of strong 10- to 20-Hz rhythms in the majority of our central thalamic recordings also suggests that this rhythm may reflect the strong efference from the central thalamus into the basal ganglia (Courtemanche et al. 2003; Lacey et al. 2007), particularly the striatum where recent experimental and modeling studies indicate that ~10- to 30-Hz activity may reflect normal striatal network dynamics (McCarthy et al. 2011). In support of the possible link to activity within the basal ganglia, we note that, in a small number of recordings from the caudate nucleus, we identified neuronal populations that exhibited suppression of tonic firing during the delay period of the same task (Schiff and Purpura 2002, Schiff et al. 2002). Power difference spectrograms of correct and incorrect trials for these data sets showed selective suppression (−6 dB) in the 15- to 20-Hz band during the delay period as seen in Fig. 6, but without an accompanying elevation of higher frequency rhythms (unpublished data).

The selective enhancement of power in the 30- to 100-Hz frequency range in the central thalamic LFP in the delay period of thalamic populations with MUA increases, and in all thalamic populations in comparisons of correct vs. incorrect trial performance, may also reflect local network activity consistent with increased input from frontal corticothalamic or brain stem afferents at the time of correct trial performance. Similar changes in LFPs are identified during attentional processing in the cortex (Fries et al. 2001). While participation of thalamocortical neurons in synchronizing 30- to 100-Hz oscillatory activity in cortical networks has been previously demonstrated (Llinas et al. 1998, 2002) and linked to arousal state (Steriade et al. 1996), these changes have not been previously correlated in the thalamus with successful task performance. It is also interesting that the nondelay populations show a stronger increase in 30- to 100-Hz power compared with the delay populations, as shown in the *right* column panels of Fig. 8. While both populations show changes in the same direction during correct compared with incorrect trials, the effect of increased 30- to 100-Hz power is stronger for the nondelay populations that show no enhancement of firing rate during the delay period. We speculate that this finding may indicate that the nondelay population is under active suppression during the delay period, and that the elevation in power in Fig. 8*B*, *right*, may reflect this inhibitory activity in the local population.

The present study has only correlated changes in MUA and LFP background in central thalamus with task performance. Importantly, other lines of evidence indicate that central thalamic activity is not just a correlate of attentional effort, but in fact plays a critical, causative role (reviewed in Mair et al. 2011). This evidence takes two forms: clinical observations of patients with direct injury, or loss of input to the central thalamus (Castainge et al. 1981; Van der Werf et al. 1999; reviewed in Schiff and Plum 2000), and studies of the effects of central thalamic stimulation or pharmacological manipulations on arousal regulation in animals and human subjects (Mair et al. 2008; Schiff et al. 2002, 2007; Shah et al. 2009; Shirvalkar et al. 2006; 2011 Smith et al. 2009). These studies indicate that direct activation of the central thalamus can facilitate behavior by counteracting a decrease in arousal resulting from increasing satiety, declining motivation, and boredom (Schiff et al. 2002; Shah et al. 2009; Smith et al. 2009). Electrical stimulation of central thalamic recording sites that demonstrated delay period MUA firing rate elevations in M1 produced increases in correct performance after spontaneous sharp drops in performance (Smith et al. 2009). Studies of central thalamic stimulation in the rat have shown enhancement of working memory performance (Mair and Hembrook 2008), and pharmacological manipulation of the central thalamus in rat can, similarly, be shown to produce inverted U-type effects on arousal regulation (Mair et al. 2011). Importantly, the studies of Mair and Hembrook (2008) provide indirect but specific support for the selectivity of build up of neuronal activity in central thalamus during the delay period, as selective improvements in task performance in rats were statistically linked to electrical stimulation only during the delay or decision periods of the task. In addition to these experimental studies, an extensively

monitored case study in a severely brain-injured human subject with bilateral electrodes within the central thalamus targeting the anterior intralaminar nuclei (Schiff et al. 2007) demonstrated that electrical stimulation facilitated cognitively-mediated behaviors and recovery of a variety of integrative sensorimotor functions (oral feeding, spoken language, limb control). In the context of these prior studies that have identified a causal role for central thalamic neuronal populations in contributions of arousal regulation to attentive behaviors in rodents, monkeys, and humans, the present findings appear to provide a physiological correlate in the monkey of the natural variations in these populations linked to task performance.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

Author contributions: N.D.S. and K.P.P. conception and design of research; N.D.S. and S.F.K. performed experiments; N.D.S., S.A.S., A.E.H., and T.N. analyzed data; N.D.S., S.A.S., and K.P.P. interpreted results of experiments; N.D.S., S.A.S., A.E.H., and T.N. prepared figures; N.D.S. and S.A.S. drafted manuscript; N.D.S., S.A.S., A.E.H., T.N., S.F.K., and K.P.P. edited and revised manuscript; N.D.S. approved final version of manuscript.

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