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Modafinil augments oscillatory power in middle frequencies during rule selection

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Abstract

Control-related cognitive processes are associated with cortical oscillations and modulated by catecholamine neurotransmitters. It remains unclear how catecholamine systems modulate control-related oscillations. We tested modafinil effects on rule-related 4–30 Hz oscillations, with double-blind, placebo-controlled (within-subjects) testing of 22 healthy adults, using EEG during cognitive control task performance. EEG data underwent time-frequency decomposition with Morlet wavelets to determine power of 4–30 Hz oscillations. Modafinil enhanced oscillatory power associated with high-control rule selection in theta, alpha, and beta ranges, with a frontotemporal topography and minimal effects during rule maintenance. Augmentation of catecholamine signaling enhances middle-frequency cortical oscillatory power associated with rule selection, which may subserve diverse subcomponent processes in proactive cognitive control.

Descriptors: Cognitive control, Rule selection, Oscillations, Modafinil, Prefrontal cortex, Theta

Cognitive control is supported by a distributed cortical-subcortical circuitry, with critical elements in the frontal cortex (Miller, 2000). This cognitive function and its neural basis **Q3** are disturbed in a range of neuropsychiatric disorders such as schizophrenia, Parkinson's disease, and attention-deficit/hyperactivity disorder (Banich et al., 2009; Barch, 2005; Durston, de Zeeuw, & Staal, 2009; Melcher, Falkai, & Gruber, 2008; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Rule selection and representation is a critical element of cognitive control, as it guides task- or context-appropriate responses to the environment (Bunge, 2004). Recent investigation has attempted to elucidate the physiological basis for this cognitive process, with increasing emphasis on cortical oscillatory phenomena. Cortical oscillations in the middle frequencies have been implicated in various aspects of complex cognition that relate to control processes in humans, such as theta in working memory and other memory processes (Klimesch, Freunberger, Sauseng, & Gruber, 2008), alpha in active inhibition of task-irrelevant processes (Jensen & Mazaheri, 2010), and beta in top-down control of movement (Engel & Fries, 2010). Studies in animals have further specified the association of rule representation with oscillations, including theta (Benchenane et al., 2010; Womelsdorf, Johnston, Vinck, & Everling, 2010), alpha and beta in both rule acquisition (Benchenane, Tiesinga, & Battaglia, 2011) and rule selection (Buschman, Denovellis, Diogo, Bullock, & Miller, 2012).

An important feature of control processes and cortical oscillations is their modulation by various neurochemical systems, which may have important consequences for the utility of these phenomena as treatment targets. Central catecholamine neurotransmitter systems, arising in the brainstem to innervate virtually the entire brain, have a well-established neuromodulatory role in complex cognitive functions such as working memory and cognitive control (Durstewitz, Seamans, & Sejnowski, 2000; Miller & Cohen, 2001). They exert complex, multiphasic effects on cortical signaling, mediated by a diversity of receptors with heterogeneous distributions on both pyramidal cells and interneurons. The influence on cortical computation appears to be enhancements in the gain in input/output relationships, which may be manifest in both individual neurons and neuronal populations innervated by the locus coeruleus norepinephrine system (LC-NE; Aston-Jones & Cohen, 2005) and the mesocortical dopamine (DA) system (Seamans &

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Yang, 2004). Brain oscillations are an important mechanism of gain control in the brain (Salinas & Sejnowski 2001), and catecholamine systems are well designed to modulate relatively low-frequency brain oscillations. The LC-NE in particular arises from a single (bilaterally paired) source to innervate virtually the entire neuraxis (Berridge & Waterhouse, 2003), permitting simultaneous influence on activity in widely distributed circuits, which support complex cognitive processes and which also reflect the relatively long time frame and spatial extent of oscillations in the lower frequency ranges (von Stein & Sarnthein, 2000). Among the major targets of LC-NE projections, there is dense innervation of the midline frontal cortex (Steketee, 2003), which may be an independent generator of theta oscillations associated with various executive functions (Mitchell, McNaughton, Flanagan, & Kirk, 2008; Raghavachari et al., 2006; Tsujimoto, Shimazu, & Isomura, 2006), and the parietal lobe is also very densely innervated by projections from the LC (Berridge & Waterhouse, 2003). These anatomic features of LC projections suggest that cognitive processes mediated by frontoparietal networks may be particularly strongly modulated by this neurochemical system.

The LC-NE system also exhibits several oscillatory phenomena linked to cortical function. For instance, individual NE cells in the LC show regular discharge rates at frequencies that extend into the theta range during waking and active behavior, in a pattern strongly associated with behavioral state (Aston-Jones, Chiang, & Alexinsky, 1991). In addition, LC-NE cells can resonate with prefrontal cortex (PFC) neurons (Lestienne, Herve-Minvielle, Robinson, Briois, & Sara, 1997), and many LC cells are phase-locked to slow cortical oscillations, preceding cortical "up-states" by about 60 ms (Eschenko, Magri, Panzeri, & Sara, 2012). The absolute or relative power of neocortical and/or hippocampal theta oscillations can be increased with enhanced LC-NE signaling, via pharmacological activation of LC cells (Berridge & Foote, 1991) or norepinephrine transporter (NET) inhibition (Berridge & Morris, 2000; Hajos, Hoffmann, Robinson, Yu, & Hajos-Korcsok, 2003), including theta related to long-term potentiation (Walling, Brown, Milway, Earle, & Harley, 2011) and exploratory behavior (Kocsis, Li, & Hajos, 2007).

The existing literature therefore indicates that catecholamines modulate complex, PFC-dependent cognitive processes and middle-frequency cortical oscillations such as theta. Nevertheless, catecholamine modulation of these oscillations engaged during cognitive control by humans remains largely unstudied. In an earlier fMRI study, we reported that modafinil, a low-potency inhibitor of both NET and the dopamine transporter (DAT; Madras et al., 2006; Volkow et al., 2009), enhances cognitive control-related activity in the LC, the distributed cognitive control network, and functional connectivity between the two (Minzenberg, Watrous, Yoon, Ursu, & Carter, 2008). This was particularly observed for selection of high-control rules. These effects may form the basis of modafinil's enhancement of a range of control-dependent cognitive processes in healthy and clinical populations (reviewed in Minzenberg & Carter, 2008).

Electrophysiology studies demonstrate that modafinil enhances electrotonic coupling between cortical neurons, within interneuron and pyramidal cell classes (Urbano, Leznik, & Llinas, 2007), it augments resting electroencephalogram (EEG) power in the theta range (Gozzi et al., 2012) and alpha range (Chapotot, Pigeau, Canini, Bourdon, & Buguet, 2003), and enhances (normalizes) resting alpha and beta power in healthy sleep-deprived humans (James et al., 2011). It also reverses the hypoexcitability observed in patients with narcolepsy (Joo et al., 2010; Nardone et al., 2010). To date, the effects of modafinil on brain oscillations related to online cognitive processes have not been investigated. In light of these findings, and taken together with the influence of catecholamine systems on middle-frequency oscillations and PFC function, we hypothesized that modafinil administration (in treatment and cognitive task paradigms identical to our fMRI study) would enhance middle-frequency cortical oscillations in support of high-control rule selection in a sample of healthy humans.

Method

Participants

Twenty-two right-handed adults participated in this study, recruited from the local community. The mean age (± *SD*) was 32 ± 7.9 years (range 24–53 years), including 12 males. Each was free of medical/neurological illness (including head injury or sensorimotor disturbances) by report and lifetime psychiatric illness (as determined by the Structured Clinical Interview for DSM-IV Disorders, Non-patient version, administered by trained raters). All subjects were free of psychotropic medication and illicit substances (determined by urine toxicology) at time of study. Informed consent was obtained from all the subjects, using a protocol approved by the local Institutional Review Board at the University of California, Davis. Subjects were compensated for their participation.

Overview of Treatment and Testing Procedure

Randomization of treatment order was performed without stratification, with a computer algorithm by a research pharmacist, who also packaged active medication (modafinil 200 mg for single-oral dose) and placebo in identical-appearing capsules for administration, and was otherwise uninvolved in the study. On a given test day, subjects were administered the drug or placebo in midmorning. Subjects then waited in a quiet room for 1 h before the EEG preparation procedure, and began the cognitive task at approximately 2 h after dosing, within the time span of peak circulating levels of modafinil (Robertson & Hellriegel, 2003). Subjects completed the test session and then returned after at least a 2-day interval to ensure washout of the study drug. Eleven subjects (50%) completed the active drug testing on Day 1, and the other eleven subjects completed the placebo testing on Day 1.

Cognitive Paradigm

The cognitive task was presented using E-Prime (Psychological Software Tools, Pittsburgh, PA). EEG data were acquired during the preparing-to-overcome-prepotency (POP) task (Minzenberg, et al., 2008; Snitz et al., 2005), a variant of a Simon spatial-incompatibility task. The trial structure was as follows: cue (a green or red square), delay period, probe (a centrally presented white arrow pointing left or right, randomized with equal frequency between right and left directions), and a variable intertrial interval (between 1,500 and 2,500 ms after probe-on). Both cue and probe stimuli had durations of 500 ms. The cue-probe delay period (from cue-off to probe-on) was fixed at 1,000 ms, during which subjects were required to maintain fixation on a central fixation cross. Over this delay, subjects were required to maintain the appropriate rule (represented by the cue) to guide stimulus-response (S-R) mappings to the probe. For the low-control condition (green-cued trials), subjects were required to respond with a button press in the

congruent direction of the subsequent arrow (e.g., for a right-pointing arrow, press the right button, and left for left). For the high-control condition (red-cued trials, 45% of total), subjects responded in the incongruent direction (e.g., for a right-pointing arrow, press the left button, and vice versa). Participants received eight blocks of 80 trials each, after one block of practice.

Electroencephalography

Data acquisition and offline processing. EEG data were acquired in a shielded room using a Neuroscan 128-electrode Quik-Cap and Neuroscan SynAmps2 hardware, with a sampling rate of 1000 Hz and a 100 Hz low-pass hardware filter. Data were collected using 32-bit encoding software, eliminating the need for high-pass recording filters. Electrode impedances were kept at < 5 kΩ. All channels were referenced online to Cz. Malfunctioning electrodes were determined and excluded based on visual inspection of the impendence map and recorded waveforms. Data were then imported into EEGLAB (Delorme & Makeig, 2004), rereferenced against the average reference, downsampled to 250 Hz, and high-pass filtered at 0.5 Hz. Epochs were extracted from the continuous EEG data, from −400 to +1,700 ms relative to cue onset. Each epoch was baseline-corrected using the prestimulus interval (−400 to 0 ms) in order to account for possible stimulus-independent ("background") fluctuations. Trials with incorrect responses were removed. Artifact rejection was performed with a probability-based criterion: First, the distribution of voltages averaged across all electrodes for a given trial was compared to the voltage for each individual electrode on that trial. If the individual electrode's voltage within that trial was > 5 standard deviations from the mean of all electrodes, then the electrode was removed from that trial. A problematic case could occur if numerous electrodes exhibited excessive noise on a given trial, thereby making it difficult to discriminate an individual electrode's degree of noise from the full electrode set. However, this special case could be detected and resolved with use of independent components analysis (ICA), which followed this artifact rejection step (Onton & Makeig, 2006). This was performed using the "logistic infomax" ICA algorithm (Bell & Sejnowski, 1995) with the "extended" option of Lee, Girolami, and Sejnowski, 1999; both available within EEGLAB. Seventy-five principal components accounting for the most variance in the signal were derived, and, of those, the top 15 components were identified for visualization and analysis. We used the methods of McMenamin et al., 2010, and Keren, Yuval-Greenberg, and Deouell, 2010, to reject components in a principled manner, as follows. Upon obtaining these independent components, those suggestive of ocular artifacts (primarily eye blinks but also saccade-related components), muscle noise, and other nonneural sources were identified via visual inspection of the equipotential scalp topography maps, the component waveforms, and the component time-frequency distributions, and comparison of each with the data available in McMenamin et al., 2010, and Keren et al., 2010. Eye blink components were determined by their presence and proximity to the ocular area of the topography map and their distinct waveform and time-frequency characteristics. Muscle noise components were determined primarily by their high-frequency character.

Time-frequency transformation of the data. Time-frequency transformation of the data was performed using EEGLAB (Delorme & Makeig, 2004). The transformation was accomplished by convolving the epoched EEG with the complex Morlet wavelet function. These were performed on individual trial segments to identify time-frequency components in the desired ranges. One Hz-wide frequency sub-bands between 4–30 Hz were calculated separately, with each sub-band defined by a logarithmically increasing central frequency and a range subject to a Gaussian kernel defined by the constant c, which is the ratio of the central frequency to the standard deviation. For instance, time-frequency decomposition of the theta band (4.55–8.36 Hz) was performed with c = 4, and the period from −200 to 0 ms relative to cue onset was defined as a baseline; average theta power during the baseline period was subtracted from task-related theta power determined during the trial.

Permutation method to empirically derive statistical thresholds. We sought to derive statistical thresholds appropriate for this data set and, importantly, to support statistical inferences made directly upon visual observation of spectrograms, in order to maximize the utility of time-frequency information available in these spectrograms. We first pooled (for each subject) the trial-averaged time-frequency wavelet coefficients into nine electrode subgroups of approximately equal numbers (12–14 electrodes in each subgroup), identified as frontal, parietal, and occipital subgroups in left, mid, and right locations. We then employed a permutation method implemented in MATLAB (Blair & Karniski, 1993). The procedure involved the following steps, applied to the trial-averaged power values for the red cue minus green cue difference scores, on placebo versus modafinil. First, we randomly switched the grouping of pairs of values from the two treatment conditions (to retain the paired nature of the statistical test), then repeated this for each of the remaining pairs in the conditions, and calculated the t statistics for each pseudocondition. This procedure was then repeated 4,000,000 times (to approximate the number of all possible combinations for this data set), to generate a distribution of t statistics. We then compared the t statistic observed in the comparison of each original time-frequency value between treatment conditions with this generated distribution, and determined the probability of this t value against the distribution. The observed t value is considered statistically significant if it is either less than half of the alpha value (i.e., $p < .025$) or greater than 1 minus half the alpha value (i.e., $p > .975$). Only these values are depicted as color-coded t values in the spectrograms (see Results below).

Results

Cognitive Task Performance

The group means (± *SD*) for each condition were as follows: placebo green cue accuracy, 95.8 ± 5.5%; placebo red cue accuracy, 96.1 ± 4.5%; drug green cue accuracy, 96.8 ± 3.2%; drug red cue accuracy, 96.3 ± 3.7%; placebo green cue reaction time (RT), 466 ± 131 ms; placebo red cue RT, 505 ± 135 ms; drug green cue RT, 464 ± 127 ms; drug red cue RT, 510 ± 142 ms.

In an analysis of variance (ANOVA) of task accuracy, there were no significant effects of treatment, $F(1,21) = 1.25$, $p = .28$; cue, $F(1,21) = 0.06$, $p = .81$; or the Treatment × Cue interaction, $F(1,21) = 2.38$, $p = .14$. In an ANOVA of RT, there was a significant main effect of cue, $F(1,21) = 68.4$, $p < .0005$; but no significant effect of treatment, $F(1,21) = 0.01$, $p = .94$; or the Treatment × Cue interaction, $F(1,21) = 1.15$, $p = .30$.

Post Hoc Analysis of Time Sensitivity of Task Performance and Drug Effects

We analyzed RT cost across blocks to evaluate how RT cost (RT on high-control red cue trials minus RT on low-control green cue trials) varied over time, as a putative measure of practice effects. The group mean decrease in RT cost from the first block to the final block was 11 ms on placebo (from 24 ± 32 ms to 8 ± 35 ms) and 30 ms on drug (from 37 ± 54 ms to 7 ± 52 ms) (the effects of treatment and Treatment × Block on RT cost were not significant in repeated measures ANOVA). The decreases in RT cost on each treatment day were relatively monotonic across blocks, suggesting modest within-session practice effects. In addition, we analyzed RT collapsed across task condition (red cue and green cue trials), again across blocks, separately for placebo and drug test days, to evaluate whether control-independent RT varied across time differently between treatment conditions. This analysis showed that control-independent RT decreased only 2 (± 49) ms on average from the first to the final block on placebo, but decreased 46 (± 68) ms on average on drug (Treatment × Block effect on drug with $p = .017$ in repeated measures ANOVA). This result suggested an effect of general RT speeding over time on drug that was not observed on placebo.

EEG Results

Statistical inferences regarding task and treatment effects on cortical oscillations are made by reference to empirically thresholded spectrograms that depict (in parallel) oscillatory power in electrode subgroups (Figure 1), each throughout the theta to beta range (4–30 Hz) over the course of cue and cue-probe delay periods. As can be observed in Figure 1 top row, oscillatory power was comparable (not significantly different) in response to high-control (red cue) versus low-control (green cue) trials on placebo (top row, "Rule-Selection on Placebo"). In contrast, on modafinil, a relative increase in power for high-control versus low-control rule selection was observed in the theta, alpha, and beta ranges, particularly in frontal and parietal electrode subgroups. Similarly, in direct comparison between modafinil and placebo, drug treatment was associated with a significant relative increase in control-related oscillatory power ("Treatment-by-Rule Interaction") observed in the theta-alpha-beta range, again most apparent in the frontal and parietal electrode subgroups (Figure 1, bottom panel). This drug effect on task-related power was largely absent in occipital electrode subgroups (Figure 1 bottom right). The head maps shown in Figure 2 illustrate the bilateral frontotemporal (extending to parietal scalp) topographic distribution of modafinil effects on control-related theta (6 Hz) power, at 80 ms after cue onset, when robust drug effects were observed in the full-head spectrogram. While there appeared to be transient modafinil-related increases in theta oscillatory power for high-control relative to low-control rule maintenance during the late cue and cue-probe delay periods (e.g., at 300, 840, and 1,300 ms from cue onset; see Figure 2), the topography of these drug effects did not exhibit a pattern comparable to that during the cue-on period.

Because the treatment-by-rule effects were manifest very early with the presentation of the cue, which could suggest drug effects on early perceptual processes, we also evaluated post hoc the drug effects on green cues and red cues separately, as a complementary approach to address the task-specificity of drug effects. The spectrograms shown in Figure 3 indicate a robust drug effect on red cue-related oscillatory power, which was notably absent in the spectrogram depicting drug effects on green cue-related power, and very comparable (in magnitude, temporal distribution, and frequency distribution) to that observed in the treatment-by-rule effects shown in Figure 1. This strongly suggests the specificity of drug treatment effects on oscillatory power associated with the high-control rule condition.

Discussion

In the current study, we tested the role of catecholamine neurotransmitter systems in the modulation of middle-frequency oscillations, in support of rule selection and representation as an aspect of cognitive control. Using the catecholamine transport inhibitor modafinil, we found enhanced cue-period oscillatory power associated with high-control rule selection in the theta, alpha, and beta ranges, particularly in frontal and parietal electrodes. These drug effects were notably more robust than the more transient, weaker, and less topographically coherent drug effects on rule maintenance observed during the delay period. The relative selectivity of modafinil effects on rule selection rather than maintenance, and the topography of these modafinil effects, are highly consistent with the findings from our fMRI study, which used the same treatment and cognitive paradigms as those used here, and found robust drug modulation of the LC, PFC, and LC-PFC functional connectivity, in similar analyses of high-control versus low-control rule selection (Minzenberg et al., 2008).

Interestingly, these drug effects were manifest quite early in the processing of the cue associated with the high-control rule, which might suggest drug effects on early perceptual processes rather than rule selection per se. A supplemental analysis, however, showed that this drug effect arose from a robust effect on oscillatory power with the high-control (red) cue but not the low-control (green) cue. The existing literature on adrenergic effects on mammalian visual perception suggests that this finding is inconsistent with a purely perceptual effect of drug treatment. The dense ascending adrenergic innervation of visual pathways mediates a range of modulatory effects on visual perception, including thresholds for object detection, response properties such as receptive field structure, and detection of features such as orientation and movement (see Edeline, 2012, and Hurley, Devilbiss, & Waterhouse, 2004, for reviews). However, there is no evidence from this literature to suggest that the NE system modulates color perception in a selective manner or differentially modulates any of these other aspects of perception as a function of stimulus color. In addition, there is abundant evidence to suggest that event-related electrical potentials (ERPs) measurable at the scalp in humans are subject to attention modulation as early as 100 ms after stimulus onset (i.e., P1 ERP), probably via top-down modulation of visual pathways by more frontal cortical sites (see Luck, Woodman, & Vogel, 2000, for review). While the present results cannot support a conclusive interpretation on the issue of perceptual effects, this evidence taken together may suggest that the observed modafinil effects are selective for processes associated with high-control rules. This issue may be addressed in future studies where experimental designs include a factorial combination of object perceptual features and object-rule associations.

Sauseng and colleagues (Sauseng, Griesmayr, Freunberger, & Klimesch, 2010) have suggested that an important role of cortical theta is to control the access of information into working memory representations, consistent with the drug effect observed here. Elsewhere, this group has suggested a role for theta and alpha

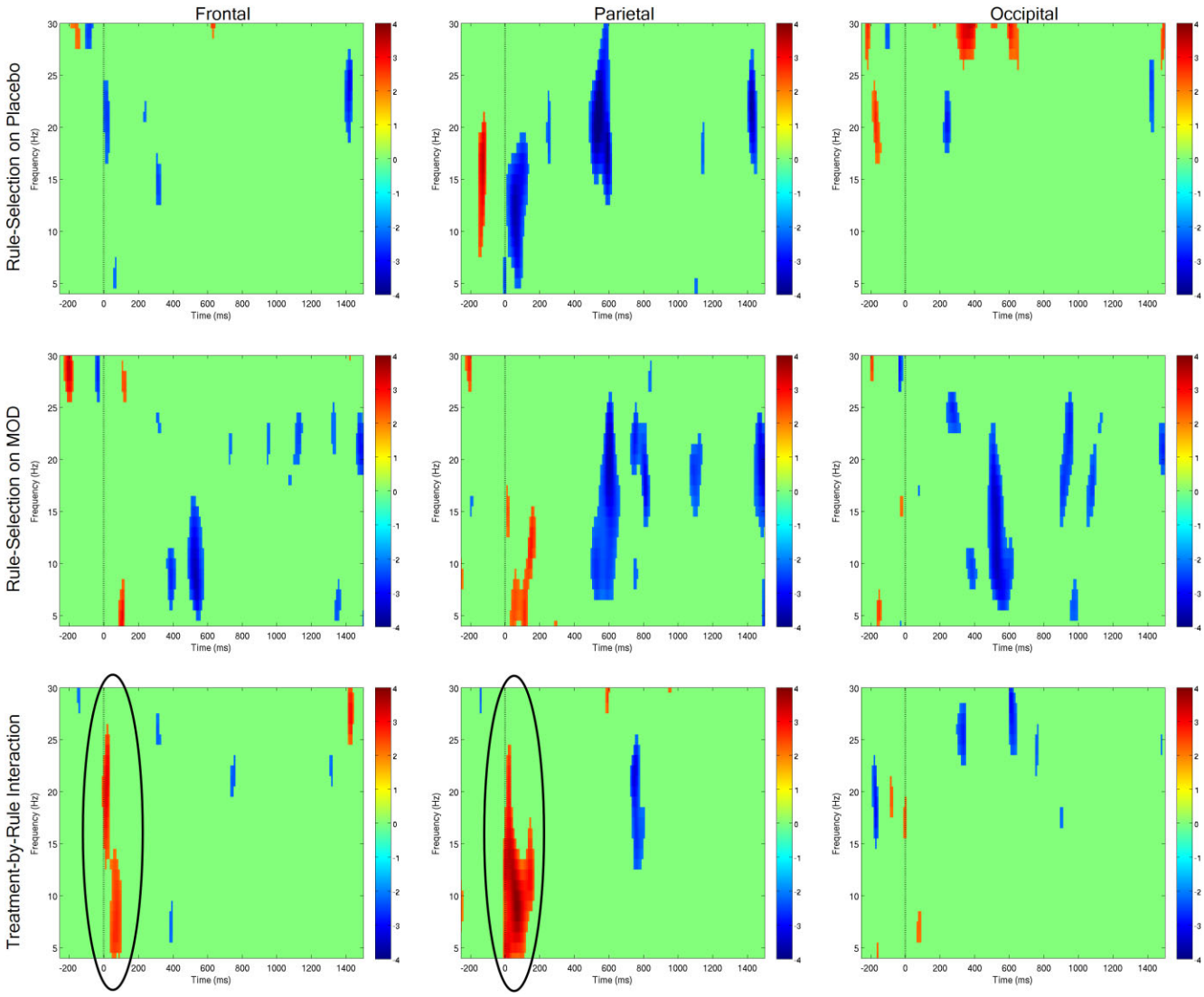

Figure 1. Spectrograms of task and drug effects on control-related middle-frequency power during proactive cognitive control task performance. Trial-averaged spectrograms depicting mean oscillatory power within 4 Hz to 30 Hz range, from baseline period (precue) through cue-on and cue-probe delay period, within electrode subgroups (indicated by headings). Vertical drop lines indicate the onset of the cue, at $t = 0$; cue offset is at $t = 500$ ms. Power is color coded in all spectrograms according to scales at right, and color coded only if exceeding the threshold derived from bootstrapping procedure (see text for details). Top row: oscillatory power in response to high-control (i.e., red cue minus green cue) demands, on placebo. Middle row: oscillatory power in response to high-control (i.e., red cue minus green cue) demands, on modafinil. Bottom row: modafinil effect on oscillatory power in response to high-control demands (i.e., modafinil [red cue minus green cue] minus PLC [red cue minus green cue]), or middle row minus top row. Note the robust relative increase in power in theta, alpha, and beta bands during the cue-on period, particularly in the frontal and parietal electrode subgroups (left and center columns, indicated by ovals).

oscillations in the control of various memory processes (Klimesch et al., 2008). These investigators and others have suggested that top-down control is achieved as a general feature in complex cognition via theta-mediated integration (Sauseng et al., 2010) and maintenance (Palva & Palva, 2007) of information in working memory, and alpha-mediated inhibition of task-irrelevant neuronal ensembles (Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007). These distinctions could explain the co-occurrence of drug effects on these adjacent frequency ranges during high-control rule selection in the present study. Furthermore, a recent study of lateral PFC-mediated control processes in monkeys found beta-range oscillations associated with task-relevant rule selection and alpha oscillations with the unselected rule (Buschman et al., 2012). In humans, beta oscillations have been implicated in the control of both movement and cognition by "endogenous," top-down processes that are usually synonymous with cognitive control (reviewed in Engel & Fries, 2010), and likely mediated via frontostriatal circuitry (Jenkinson & Brown, 2011). Beta coherence is also increased in frontoparietal circuits in monkeys with demands for top-down control of attention (Buschman & Miller, 2007). Jenkinson and Brown (2011) suggest that beta oscillations in frontostriatal circuits may specifically follow cues signaling that a preprepared action must be suppressed, which reasonably describes the high-control task demand with red cues in the present study. These various findings indicate respective roles for theta, alpha, and beta oscillations in PFC-mediated control

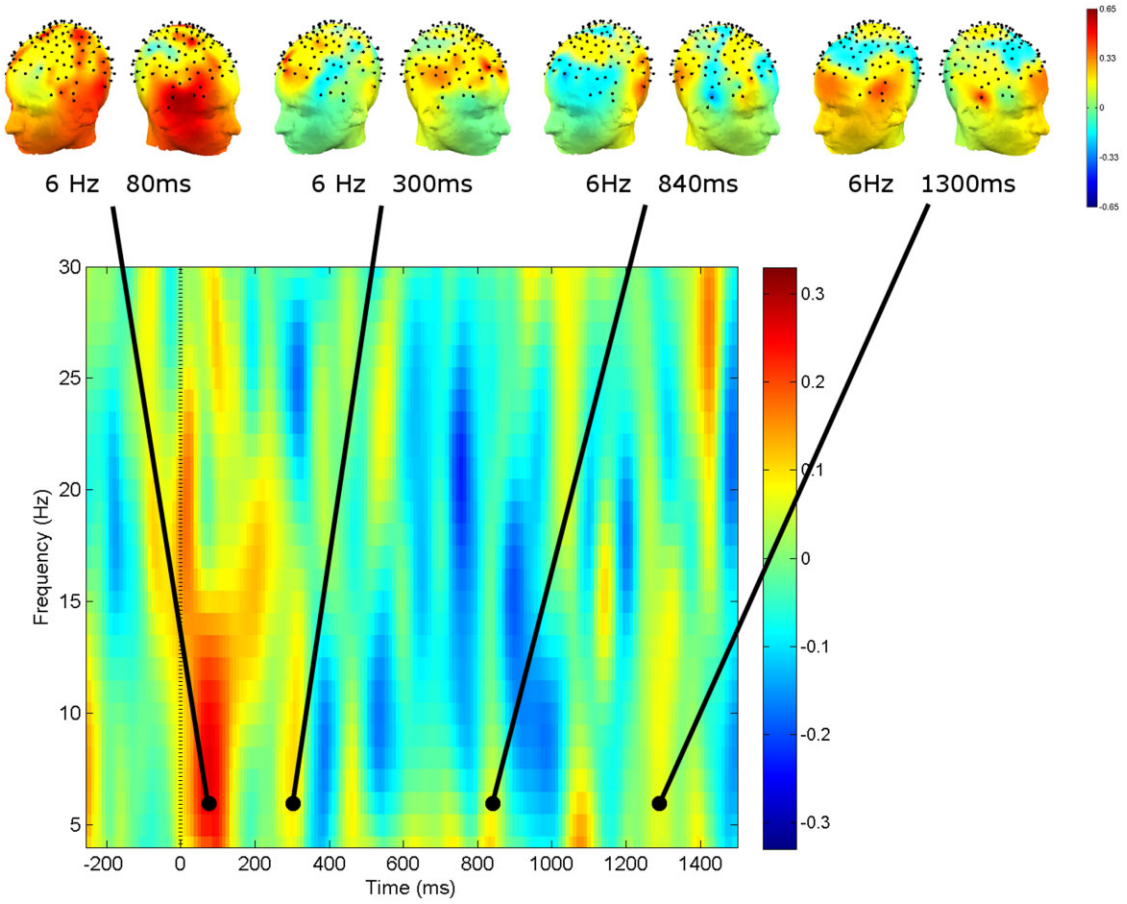

Figure 2. Topography of modafinil effects on control-related theta power. Group-averaged mean power as effect of Drug × Task interaction, across rule-selection and maintenance task phases. Spectrogram depicts the mean power of all electrodes (statistical contrast as for Figure 1, bottom row) and head maps depict scalp topography at time points of elevated 6 Hz power. Note frontoparietal distribution of drug effects during the cue-on period, which is not as clearly evident during delay-period 6 Hz power increases. Drop line at $t = 0$ (cue onset); $t = 500$ ms is cue offset.

processes, and the present sensitivity of these task-related oscillations to modafinil suggests that catecholamine systems may modulate a range of subcomponent processes in cognitive control.

Interestingly, in contrast to cue-period drug effects, we observed minimal effects of modafinil on oscillations associated with the delay-period maintenance of either the high-control or low-control rule (or the difference between them). Catecholamine neurotransmitters have a well-established role in working memory processes such as maintenance of information across delay periods (Aston-Jones & Cohen, 2005; Durstewitz & Seamans, 2002). It is also well established, however, that different working memory phases such as working memory encoding, early maintenance, and late maintenance appear to be mediated by different subpopulations of PFC neurons. While it remains somewhat unclear how these different features of working memory may relate to selective aspects of catecholamine function in the PFC, one influential model proposes that different DA receptor subtypes support stability versus flexibility in representations in working memory (Durstewitz & Seamans, 2002). Therefore, with different PFC neural populations mediating different phases of working memory, and different features of working memory having differential patterns of catecholamine modulation, it may be that modafinil effects (at least in the treatment design used here) are largely selective for oscillations that support the encoding and/or selection of information rather than the maintenance of this information. Because this task paradigm did not involve the experimental manipulation of load, interference, manipulation, or updating of information during the delay period, modafinil effects on delay-period phenomena may be more selectively tested with one of these task features in future studies.

It remains unclear whether these drug effects on cortical oscillations arise primarily from effects on NE or DA systems in the brain. In our fMRI study, we found a complex pattern of modafinil effects on LC activation, which was highly consistent with a sophisticated model of the LC-NE system in the optimization of cognitive processes associated with cortical function (Aston-Jones & Cohen, 2005). However, there is good evidence that DA neurotransmission in the prefrontal cortex is also primarily regulated by the LC-NE system, because there is a paucity of DAT in the PFC, and therefore extracellular DA is primarily removed by NET activity (Carboni, Tanda, Frau, & Di Chiara, 1990; Moron, Brockington, Wise, Rocha, & Hope, 2002). It does remain possible, therefore, that modafinil effects on LC activity are mediated by DA receptor activation in terminal fields in the frontal cortex. Resolution of this issue may require drug-combination studies where the effects of catecholamine transporter inhibition are modified by specific catecholamine receptor ligands, such as beta-blockers or selective DA-receptor antagonists.

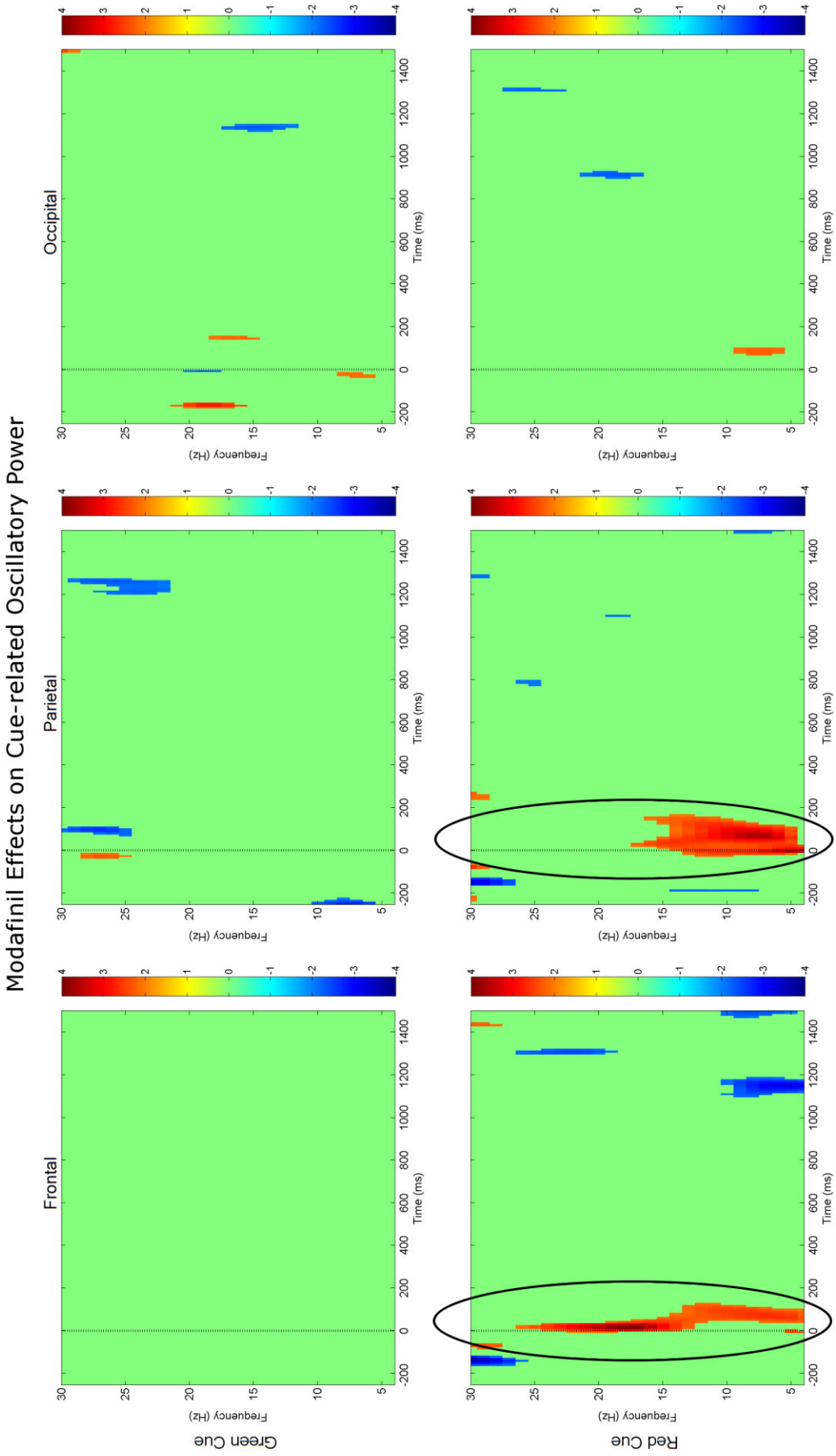

Figure 3. Spectrograms of modafinil effects on control-related middle-frequency power during proactive cognitive control task performance. Trial-averaged spectrograms depicting mean oscillatory power within 4 Hz to 30 Hz range, from baseline period (precue) through cue-on and cue-probe delay period, within electrode subgroups (indicated by headings). Vertical drop lines indicate the onset of the cue, at $t = 0$; cue offset is at $t = 500$ ms. Power is color coded in all spectrograms according to scales at right, and color coded only if exceeding the threshold derived from bootstrapping procedure (see text for details). Top row: oscillatory power in response to low-control (i.e., green cue) demands, on modafinil versus placebo. Bottom row: oscillatory power in response to high-control (i.e., red cue) demands, on modafinil versus placebo. Note the robust relative increase in power in theta, alpha, and beta bands during the cue-on period for red cues only, particularly in the frontal and parietal electrode subgroups (left and center columns, indicated by ovals).

These results are nonetheless consistent with an empirical literature addressing LC-NE effects on cortical oscillatory activity in this frequency range. The input patterns of catecholamine innervation of the cortex suggest an anatomy (both large scale and local) that is well suited to this modulation of middle-frequency cortical oscillations. Both NE and DA have direct influences on cortical pyramidal cells via a diversity of receptors, which include every major subtype among these two neurotransmitter systems, at pre- and postsynaptic sites (Gu, 2002). In addition, catecholamines directly innervate cortical inhibitory interneurons. A significant degree of catecholamine effects on cortical principal cells may be mediated via local inhibitory interneurons (Bacci, Huguenard, & Prince, 2005). Norepinephrine depolarizes fast-spiking interneurons in rat frontal cortex, including chandelier cells (Kawaguchi & Shindou, 1998), has heterogeneous effects on CCK+ interneurons (Kawaguchi & Shindou, 1998), and depolarizes hippocampal interneurons (Bergles, Doze, Madison, & Smith, 1996). Similarly, dopamine increases the excitability of fast-spiking, nonadapting interneurons in primate dorsolateral prefrontal cortex, including basket cells and chandelier cells (Kroner, Krimer, Lewis, & Barrionuevo, 2007). The gating of pyramidal cell inputs and outputs by these interneurons are critical determinants of cortical oscillations, including those in theta, alpha, and beta frequency ranges (Freund, 2003; Gonzalez-Burgos & Lewis, 2008; Jensen & Mazaheri, 2010; Whittington & Traub, 2003).

It is also possible that the drug-induced relative increase in oscillatory power for high-control rules was associated with increased excitability in the cortical ensembles that represent this information. There is good evidence to indicate that oscillatory cycles (e.g., in the theta range) are strong determinants of cyclic modulation of neuronal excitability (Jacobs, Kahana, Ekstrom, & Fried, 2007; Schroeder & Lakatos, 2009), and brain oscillations appear to be a major mechanism to support gain control and spike timing-dependent plasticity (Fell & Axmacher, 2011; Salinas & Sejnowski, 2001). Modafinil remediates the hypoexcitability observed in patients with narcolepsy (Joo et al., 2010; Nardone et al., 2010), an effect that could be mediated by NE (e.g., α_2) or DA receptors, which both have well-established roles in the modulation of cortical excitability (Barth, Vizi, Zelles, & Lendvai, 2008; Carr, Andrews, Glen, & Lavin, 2007).

It is important to note that modafinil administration (at least the 200-mg oral dose used) was not associated with significant effects on task performance. Post hoc exploratory analyses of task and treatment effects revealed within-session practice effects, as the RT cost associated with high-control trials attenuated over time (on both placebo and drug test days). In contrast, trial-independent RT speeding steadily increased over time, but only on drug. The latter finding is consistent with slowly accruing drug absorption and distribution into the brain over the time period of task performance. This combination of time-sensitive effects suggests that practice effects on task performance versus drug effects on task performance worked in opposite directions, potentially attenuating the sensitivity of the task paradigm (including its temporal features) to treatment effects. In this regard, it is interesting that robust drug effects on task-related oscillations were nonetheless observed, which may indicate that these are a more sensitive measure of modafinil effects on cortical activity elicited with this task than are overt behavioral measures such as accuracy and RT. This could also suggest that cortical oscillations in these frequency ranges are necessary but not sufficient to influence overt behavioral performance that is dependent on the targeted cognitive processes. This issue is an important one to clarify, perhaps with future experimental paradigms that systematically vary the elapsed time from drug administration to task performance, and/or task features such as duration, level of difficulty (i.e., control demand), and practice sensitivity. The observed near-ceiling performance on placebo may be considered a study limitation, as this may place sharp constraints on detecting performance enhancement with drug treatment.

Finally, there is consistent evidence that cortical oscillations are impaired in a number of neuropsychiatric illnesses, such as schizophrenia (Uhlhaas & Singer, 2006). While this empirical literature has primarily emphasized disturbances in higher-frequency oscillations, such as those in the gamma range (e.g., Minzenberg et al., 2010), schizophrenia patients also exhibit impairments in task-related power in theta, alpha, and beta ranges (Doege et al., 2009; Gonzalez-Hernandez et al., 2003; Haenschel et al., 2009), and it remains unclear whether gamma oscillatory deficits in schizophrenia, for instance, arise from altered cross-frequency coupling (Canolty & Knight, 2010; Roopun et al., 2008). Catecholamine transport inhibitors such as amphetamine, methylphenidate, and modafinil not only enhance cognition in healthy individuals under certain conditions, but also remediate cognitive deficits in various clinical populations (Minzenberg, 2012; Minzenberg & Carter, 2008). Therefore, it seems warranted to investigate the physiological basis for this cognitive enhancement, using these and related experimental methods, in order to more fully characterize the neural basis for remediation of these deficits, which are not only strong determinants of clinical outcome in these disorders, but remain to be fully realized as treatment targets.

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