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Journal

Neuropsychopharmacology, 41(5)

ISSN

0893-133X

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Publication Date

2016-04-01

DOI

10.1038/npp.2015.271

Peer reviewed

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Neuropsychopharmacology (2016) 41, 1231–1240
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Sustained Modafinil Treatment Effects on Control-Related Gamma Oscillatory Power in Schizophrenia

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Control-related cognitive processes such as rule selection and maintenance are associated with cortical oscillations in the gamma range, and modulated by catecholamine neurotransmission. Control-related gamma power is impaired in schizophrenia, and an understudied treatment target. It remains unknown whether pro-catecholamine pharmacological agents augment control-related gamma oscillations in schizophrenia. We tested the effects of 4-week fixed-dose daily adjunctive modafinil (MOD) 200 mg, in a randomized double-blind, placebo-controlled, parallel-groups design. Twenty-seven stable schizophrenia patients performed a cognitive control task during EEG, at baseline and after 4 weeks of treatment. EEG data underwent time-frequency decomposition with Morlet wavelets to determine power of 4–80 Hz oscillations. The modafinil group ($n=14$), relative to placebo group ($n=13$), exhibited enhanced oscillatory power associated with high-control rule selection in the gamma range after treatment, with additional effects during rule maintenance in gamma and sub-gamma ranges. MOD-treated patients who exhibited improved task performance with treatment also showed greater treatment-related delay period gamma compared with MOD-treated patients without improved performance. This is the first evidence in schizophrenia of augmentation of cognition-related gamma oscillations by an FDA-approved agent with therapeutic potential. Gamma oscillations represent a novel treatment target in this disorder, and modulation of catecholamine signaling may represent a viable strategy at this target.

Neuropsychopharmacology (2016) **41,** 1231–1240; doi:10.1038/npp.2015.271; published online 23 September 2015

INTRODUCTION

Cognitive control arises from the operation of a distributed cortical-subcortical circuitry, with critical elements in the prefrontal cortex (PFC) (Miller, 2000). Rule selection and representation are critical elements of PFC-based control processes, as they guide task- or context-appropriate responses to the environment (Bunge, 2004). These control processes are consistently impaired in schizophrenia, with a basis in impaired dorsolateral PFC function (see meta-analysis in (Minzenberg *et al*, 2009) and review in (Lesh *et al*, 2011)). Control-related gamma oscillations are also impaired in schizophrenia (Cho *et al*, 2006), including in unmedicated recent-onset schizophrenia patients, measurable with EEG (Minzenberg *et al*, 2010). Gamma deficits are also observed in various perceptual processes (Hong *et al*, 2004; Kirihara *et al*, 2012; Light *et al*, 2006; Spencer *et al*, 2008a, b; Wynn *et al*, 2005).

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Received 26 April 2015; revised 7 July 2015; accepted 21 July 2015; accepted article preview online 2 September 2015

Cognitive control is modulated by central catecholamine neurotransmitter systems arising from the locus coeruleus NE system (LC-NE) and the mesocortical dopamine (DA) system (Aston-Jones and Cohen, 2005; Durstewitz *et al*, 2000). This occurs via enhanced gain in input/output relationships of both individual neurons and neuronal populations, which may be manifest in the modulation of brain oscillations (Salinas and Sejnowski, 2001). Catecholamine systems are implicated in modulation of brain oscillations across a range of frequencies, including gamma. For instance, LC activation in anesthetized rats enhances the relative power of low-gamma oscillations, which is partly dependent on beta-adrenergic receptor activation (Berridge and Foote, 1991). LC-NE effects on gamma cortical oscillatory activity in awake, alert and active animals may critically depend on the cognitive and/or behavioral processes engaged by the animal (Berridge and Wifler, 2000). Findings from other experimental paradigms, while conducted *in vitro*, support this notion. The 40-Hz firing of reticular thalamic cells is abolished by local prazosin infusion or bilateral LC lesions (Pinault and Deschenes, 1992); bath-applied NE induces in olfactory bulb slices a long-lasting increase in 30–70 Hz activity of cortical responses to patterned olfactory nerve stimulation that mimics the breathing cycle (Gire and Schoppa, 2008); and NE selectively and

dose-dependently increases stimulation-induced gamma oscillations in hippocampal slices (Wojtowicz *et al*, 2009). It remains unknown whether these LC-mediated effects exist in awake, behaving animals. Nonetheless, these studies support the notion that the spatiotemporal pattern of activity in catecholamine-receptive cortical ensembles is a critical feature of catecholamine modulatory effects, and this in turn relates to the cognitive/behavioral processes engaged by the animal.

Central DA systems also modulate gamma oscillations. Bath-applied DA selectively, dose-dependently increases stimulation-induced gamma oscillations in hippocampal slices (Wojtowicz *et al*, 2009), which is modulated by D4 receptors (Andersson *et al*, 2012b). In addition, haloperidol suppresses the increased gamma oscillations observed in DAT knockout mice (relative to wild-type mice) exposed to a novel environment; haloperidol and clozapine both inhibit hippocampal gamma via a D3 receptor-mediated mechanism (Schulz *et al*, 2012); and awake mice with DA depletion (by α-methyl-p-tyrosine) also show impaired hippocampal gamma (Dzirasa *et al*, 2006). In humans, d-amphetamine increases both 40-Hz auditory steady state responses (Albrecht *et al*, 2013) and gamma power near the peak of the P3 event-related potential (Albrecht *et al*, 2012), haloperidol attenuates the 40-Hz response to selectively attended auditory stimuli (Ahveninen *et al*, 2000), and a gene polymorphism leading to reduced DAT expression is associated with enhanced evoked gamma to targets (Demiralp *et al*, 2007).

Drugs with catecholamine actions might therefore be expected to modulate gamma oscillations in neuropsychiatric patient populations. Modafinil is one such agent, a low-potency inhibitor of the plasma membrane transporters for NE and dopamine (NET and DAT, respectively) (Madras *et al*, 2006; Volkow *et al*, 2009) that increases NE and DA in the cortex (see (Minzenberg and Carter, 2008a) for review). In an earlier fMRI study, we found that modafinil enhances in healthy subjects cognitive control-related activity in the LC, the distributed cognitive control network, and functional connectivity between the two (Minzenberg *et al*, 2008b). These effects may underpin modafinil's enhancement of control-dependent cognitive processes in healthy and clinical populations (Minzenberg and Carter, 2008a). We also recently reported that single-dose modafinil augments oscillatory power in the theta, alpha, and beta ranges with high control rule selection in both healthy subjects (Minzenberg *et al*, 2014a) and schizophrenia patients (Minzenberg *et al*, 2014b). The effects of sustained modafinil treatment on cognition-related gamma oscillations in schizophrenia patients have not been previously investigated. To date, only two reported studies tested pharmacological enhancement of task-related gamma oscillations in schizophrenia, including with a partial agonist at the gamma amino-butyric acid (GABA) A receptor subtype (Lewis *et al*, 2008), and with intravenous ketamine (Hong *et al*, 2010). In light of the foregoing literature linking gamma oscillations to PFC-dependent cognitive processes, and the modulatory role of catecholamine systems, we hypothesized that modafinil administration would enhance gamma cortical oscillations during high control rule representation in a sample of schizophrenia patients.

MATERIALS AND METHODS

Participants

The study was conducted at the University of California—Davis Medical Center from February 2007 to July 2010 (ClinicalTrials.gov identifier is NCT00423943). All procedures were approved by the UCD Institutional Review Board, and all subjects provided informed consent for all procedures and were compensated for participation. Subjects were all outpatients, recruited from the community and our research clinic at UCD, and were included if aged 18–50 years, and lacked the following history: neurological illness, including head injury with loss of consciousness, uncorrectable visual problems or peripheral motor disturbance; full scale IQ <70 (by Wechsler Abbreviated Scale of Intelligence); known intolerance to modafinil; active substance-related disorder within 6 months before study; significant uncontrolled medical illness. All patients were evaluated with the SCID-I with DSM-IV-TR criteria, administered by trained, reliable raters with masters or doctoral-level clinical training, and all subjects were assigned a 295.X diagnosis. The major symptoms of schizophrenia were evaluated using the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms. All subjects were free of illicit substances (determined by urine drug screening) at study. All subjects were in active treatment with antipsychotic medication, including atypical antipsychotics ($n=22$), typical antipsychotics ($n=4$), or both ($n=1$). Haloperidol equivalents were computed as per (Andreasen *et al*, 2010) (see Table 1). Control-related oscillatory power served as the primary outcome measure, and secondary outcome measures included task performance and symptoms.

Overview of Treatment and Testing Procedure

Randomization of treatment group (1 : 1 allocation) was performed without stratification, with a computer algorithm by a research pharmacist, who also packaged active medication (modafinil 200 mg) and placebo in identical-appearing capsules for oral administration, and was otherwise uninvolved in the study. All subjects, providers, and investigators remained blinded throughout data collection for each subject. Subjects maintained their regular outpatient medication treatment regimen throughout the study and ingested the study capsules each morning. Pill counts were conducted with study medications at each weekly clinical evaluation. Baseline testing was conducted within one week before treatment initiation, followed by daily ingestion of modafinil or placebo for four weeks, and then on the final treatment day, subjects withheld their scheduled dose, and instead were administered modafinil or an identically appearing placebo by the blinded research team in mid-morning. On each test day, subjects waited in a quiet room for one hour before the EEG preparation procedure, and initiated the cognitive task at ~2 h after dosing, within the time window of peak circulating levels of modafinil (Robertson and Hellriegel, 2003). Fourteen subjects (52%) were randomized to active modafinil treatment, and 13 (48%) to placebo.

Table 1 Demographic and Clinical Characteristics of Schizophrenia Patients and Healthy Control Subjects

Measure	Placebo group ($n=13$)		Modafinil group ($n=14$)	
Male	11 (85%)		11 (79%)	
Right-handed	13 (100%)		14 (100%)	
	Mean	SD	Mean	SD
Age	25.2	9.1	24.3	5.2
Parental education	16.0	2.4	16.1	1.1
Subject education	13.0	1.7	13.3	1.5
Full-scale IQ (WASI)	106	10	104	15
Clinical measures				
HAL equiv	7.9	4.4	8.0	6.7
GAF baseline	48	10	46	10
GAF 4 week	49	11	51	12
SANS (mean global scores)				
Aff flat baseline	2.1	1.3	1.5	1.0
Aff flat 4 week	2.1	1.1	1.7	1.1
Alogia baseline	1.7	1.2	1.4	1.0
Alogia 4 week	1.6	1.0	1.4	1.1
Avolition baseline	2.3	1.4	2.3	1.1
Avolition 4 week	2.3	1.3	2.2	1.3
Anhedonia baseline	3.0	1.2	2.6	1.6
Anhedonia 4 week	3.4	1.4	2.8	1.8
Attention baseline	1.5	1.2	2.3	1.4
Attention 4 week	1.7	1.2	1.4	1.2
SAPS (mean global scores)				
Hallucinations baseline	1.1	1.6	1.1	1.4
Hallucinations 4 week	1.6	1.7	1.0	1.5
Delusions baseline	1.0	1.1	0.8	0.9
Delusions 4 week	1.2	1.5	0.5	1.1
Bizarre behav baseline	0.2	0.4	0.4	1.0
Bizarre behav 4 week	0.3	0.6	0.0	0.0
Form thought baseline	0.3	0.6	0.7	1.1
Form thought 4 week	0.6	0.9	0.2	0.6

All $p>0.10$ by two-tailed two-sample *t*-test or χ^2 (as appropriate).

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 task (Minzenberg *et al*, 2010), a variant of a Simon spatial-incompatibility task (Supplementary Figure 1). The trial structure was as follows: cue (a green or red square), delay period (with central fixation cross), probe (a centrally-presented white arrow pointing left or right, randomized with equal frequency between right and left directions), and a variable inter-trial interval (continuously varied between 1 500 and 2 500 ms, from probe-onset to cue onset of the subsequent trial). 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. 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 responded with a button-press in the congruent direction of the subsequent arrow (eg, 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 (eg, 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, which all subjects completed with errors on no more than two successive trials, as the criterion for proceeding to the experiment.

Electroencephalography

Data acquisition and offline processing. EEG data were acquired and analyzed as per our prior reports (Minzenberg *et al*, 2014a, b). Data were acquired in a shielded room using a Neuroscan 128-electrode Quik-Cap and Neuroscan SynAmps2 hardware, with a sampling rate of 1 000 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 $<5\,k\Omega$. All channels were referenced on-line to Cz. Malfunctioning electrodes were identified and excluded based on visual inspection of the impendence map and recorded waveforms. Data were then imported into EEGLab (Delorme and Makeig, 2004), re-referenced 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 +1700 ms relative to cue onset. Each epoch was baseline-corrected using the pre-stimulus interval (−400–0 ms) 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 with the voltage for each individual electrode on that trial. If the individual electrode's voltage within that trial was >5 SDs from the mean of all electrodes, then the electrode was removed from that trial. Independent components analysis (ICA) followed this artifact rejection step (Onton and Makeig, 2006), using the 'logistic infomax' ICA algorithm (Bell and Sejnowski, 1995) with the 'extended' option of (Lee *et al*, 1999); both available within EEGLab. Seventy-five independent 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 rejected components in a principled manner, as follows. Those suggestive of ocular artifacts (primarily eyeblinks, but also saccade-related components), muscle noise and other non-neural 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). Eyeblink components were determined by their presence and proximity to the ocular area of the topography map, and their distinct waveform and time-frequency characteristics.

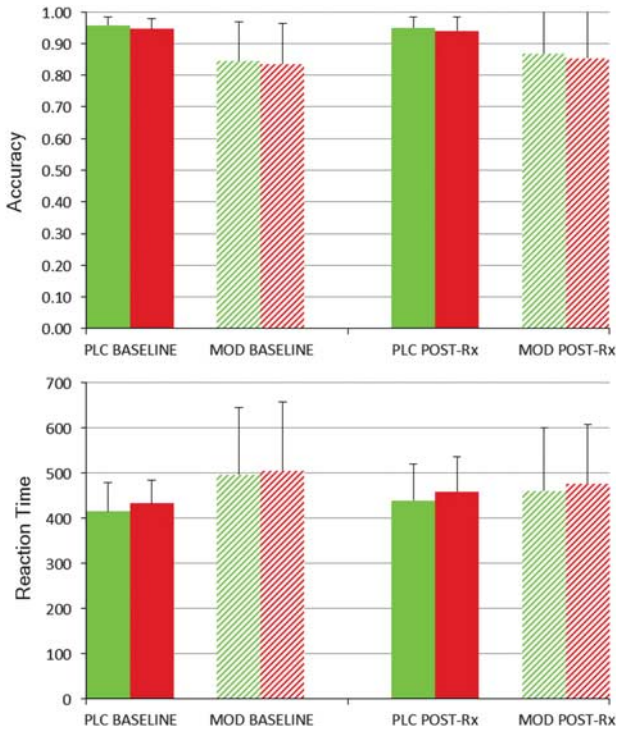

Figure 1 Task performance pre- and post-treatment in placebo and modafinil groups. The color of the bars represents the color of the cue. Accuracy is proportion correct; reaction time is in milliseconds.

Muscle noise components were determined primarily by their high frequency character. These processing steps, and all others before generating statistical contrasts for hypothesis-testing, were conducted by investigators blinded to treatment condition.

Time-Frequency Transformation of the Data

Time-frequency transformation of the data were performed using EEGLab (Delorme and Makeig, 2004), by convolving the epoched EEG with a complex Morlet wavelet function, on individual trial segments to identify time-frequency components in the desired ranges. One Hertz-wide frequency sub-bands between 4 and 80 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 SD. For instance, time-frequency decomposition of the gamma band was performed with $c=6$, and the period from -200 to 0 ms relative to cue onset was defined as a baseline; average power during the baseline period was subtracted from task-related power determined during the trial. Time-frequency spectrograms were then established by pooling oscillatory power across electrodes grouped in topographically organized subgroups (see Supplementary Figure 1).

Permutation Method to Empirically Derive Statistical Thresholds

We derived statistical thresholds appropriate for this data set to support statistical inferences made directly upon visual observation of spectrograms, 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 three electrode subgroups of approximately equal numbers (~40 electrodes in each subgroup), identified as frontal, parietal and occipital subgroups. We then used a permutation method implemented in MatLab (Blair and Karniski, 1993), applied to the trial-averaged power values for the difference scores in the modafinil group minus the placebo group of (4-Week (Red Cue minus Green Cue) minus Baseline (Red Cue minus Green Cue)). First, we randomly switched the grouping of pairs of values from the two treatment groups (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 pseudo-condition. 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 was considered statistically-significant whether it is either less than half of the alpha value (ie, $p<0.025$) or >1 minus half the alpha value (ie, $p>0.975$). Only these values are depicted as supra-threshold color-coded *t*-values in the spectrograms (see Results).

RESULTS

Cognitive Task Performance and Symptoms

The means ($\pm$SD) for each group in each task condition at baseline and post-treatment time points are shown in Figure 1. In ANOVA of task accuracy, there was a significant main effect of Group ($F=7.73$, $p=0.010$) and Task Condition ($F=19.6$, $p<0.0005$), but there were no other significant main effects, nor interaction effects, including factors Time (4-Week *vs* Baseline) or Task Condition (Red Cue *vs* Green Cue) (all $F<0.59$; all $p>0.45$). Similarly, in ANOVA of task reaction time, there was a significant main effect of Group ($F=4.37$, $p=0.047$) and Task Condition ($F=22.4$, $p<0.0005$), but there were no other significant main effects nor interaction effects, including factors Time or Task Condition (all $F<2.30$; all $p>0.14$). In general, red cue trials were associated with slightly lower accuracy and longer RT compared with green cue trials, in both treatment groups. In addition, the MOD group showed relatively lower performance (lower accuracy and longer RT) at baseline than the PLC group, and these differences were stable over time, that is, post-4-week performance was comparable to baseline task performance within each group. There were no significant group differences in symptoms, either at baseline, at 4 weeks, nor with change scores (all $p>0.10$).

EEG Results

Statistical inferences regarding treatment effects on cortical oscillations are made by reference to empirically thresholded

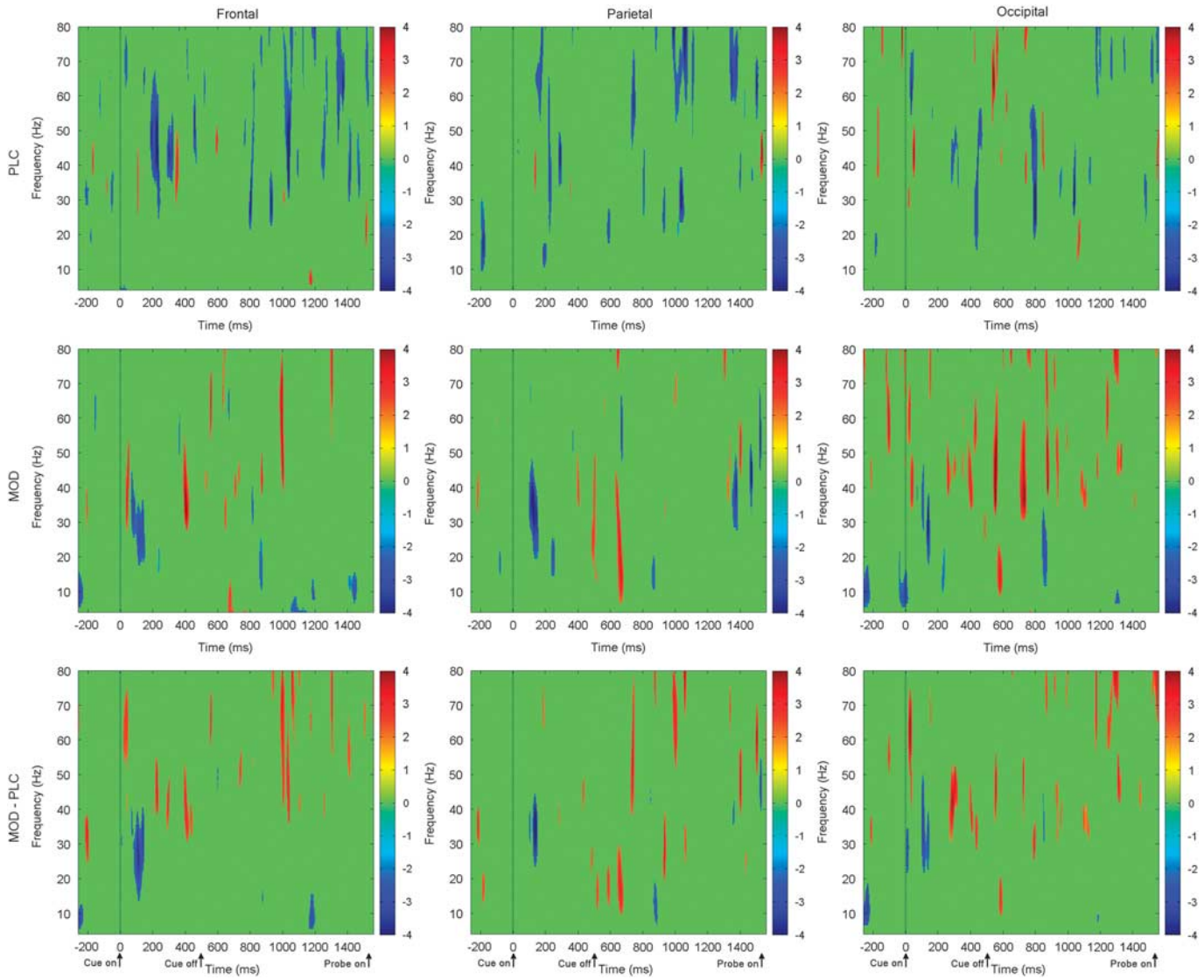

Figure 2 Modafinil effects on control-related gamma power during proactive cognitive control task performance. Trial-averaged spectrograms depicting mean oscillatory power within 4–80 Hz range, from baseline period (pre-cue) through cue-on and cue-probe delay period, within electrode subgroups (indicated 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 (ie, red cue minus green cue) demands, for post-treatment minus baseline, in placebo group (PLC). Middle row: oscillatory power in response to high-control (ie, red cue minus green cue) demands, for post-treatment minus baseline, in modafinil group (MOD). Bottom row: effect on oscillatory power in response to high control demands (ie, red cue minus green cue) for post-treatment minus baseline, for modafinil group (MOD) minus placebo group (MOD). This contrast is equal to the middle row minus top row, and in other words, a directional test of the three-way interaction of treatment, time and task condition. Note the robust relative increase in power in gamma range during the cue-on period.

spectrograms that depict oscillatory power in electrode subgroups throughout 4–80 Hz over cue and cue-probe delay periods, contrasting post-treatment with baseline (Figure 2). The contrasts depicted in the two spectrograms (Figures 2 and 4) depict the control-related (red cue minus green cue) gamma for post-treatment minus pre-treatment, both within and between treatment groups. As observed in Figure 2 top row, in the placebo group oscillatory power was roughly comparable (not significantly different) in response to high-control (red cue) *vs* low control (green cue) trials (top row, 'PLC'). There were in fact transient, paradoxical decreases in gamma power in the high-control *vs* low-control conditions, distributed throughout the cue and delay periods, which we have previously observed in a different sample of schizophrenia patients (Minzenberg *et al*, 2010). In contrast, in the modafinil group (Figure 2 middle row, 'MOD') a relative increase in power for high-control *vs* low-control rule selection was observed in the low-gamma ranges in frontal electrodes, with power increases during rule maintenance (in the delay period) in relatively higher gamma ranges in frontal electrodes. In addition there were increases in power in alpha, beta, and low-gamma ranges in the early delay period in parietal electrodes, and power increases that were more widely distributed over time and frequency in occipital electrodes.

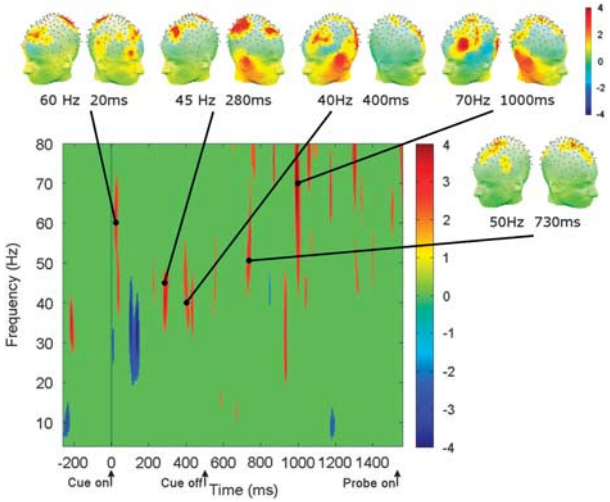

Figure 3 Topography of modafinil effects on control-related gamma power. Group-averaged mean power as effect of Treatment × Time × Task Condition interaction, across rule selection and maintenance task phases. Spectrogram depicts the unthresholded mean power of all electrodes (statistical contrast as for Figure 2 bottom row) and head-maps depict scalp topography at time points of supra-threshold power within gamma range as a function of modafinil treatment. Note frontotemporal and frontotemporal-parietal distributions of drug effects on gamma power evident during cue and delay-periods. Drop line at $t=0$ (cue onset); $t=500$ ms is cue offset.

In direct comparison between modafinil and placebo groups (Figure 2 bottom row, 'MOD–PLC'), the MOD-treated groups exhibited a significant relative increase in oscillatory power during rule selection observed in the gamma range, compared with the PLC-treated group. In the frontal electrode subgroup, modafinil effects were primarily manifest at 60–70 Hz within 100 ms after cue onset, and lower-gamma (30–50 Hz) later in the cue-on period, between 200–450 ms after cue onset. Delay period drug effects on gamma were observed in both overlapping and superjacent ranges within the gamma range, especially in the mid to late delay period. In the more posterior electrode subgroups, significant modafinil effects were evident in a relatively more widely distributed spatial and temporal manner, including in 30–50 Hz and higher ranges during rule selection, and throughout the delay period, accompanied by increases in power in sub-gamma ranges such as beta and alpha. Interestingly, there was also a relative decrease in oscillatory power centered in the beta range (20–30 Hz) ~100 ms after cue onset and distributed across all major electrode groups in the MOD group, which was not observed in the PLC group. In each electrode subgroup, the MOD group had more clusters of increased power, and fewer clusters of decreased power, compared with the PLC group; these between-group differences were significant χ^2 (positive clusters: $\chi^2=11.96$, $p<0.001$; negative clusters: $\chi^2=9.63$, $p<0.01$). The head-maps shown in Figure 3 illustrate the general frontotemporal and frontoparietal topographic distributions of control-related gamma power in MOD group compared with the PLC group, with peak power increases both in the cue-on and delay periods, when robust MOD treatment effects were observed in the full-head spectrogram also depicted in Figure 3.

We also sought to test whether those MOD-treated patients who exhibited improved task performance with MOD treatment also showed relatively greater treatment-related gamma power, compared with MOD-treated patients without performance improvements. MOD subjects were subgrouped according to whether they showed an improved accuracy cost after 4 weeks of MOD compared with pre-treatment baseline (ie, a relatively smaller decrement in accuracy in the high-control condition relative to the low-control condition; task performance in Supplementary Figure 2). Fifty percent ($n=7$ treatment 'Responders') showed the former pattern of MOD effects, and the other 50% ($n=7$) showed a worsened accuracy cost after MOD treatment ('non-responders'). In direct comparison of control-related gamma power between these two subgroups (with statistical analyses identical to those for full sample), the responders showed significantly increased gamma particularly during the delay period, with rule maintenance (Figure 4). This effect was most evident in the frontal electrodes (Figures 4 and 5). This finding indicates that performance improvements with MOD treatment corresponded to relatively greater frontal gamma with rule maintenance. In contrast, there were a few relative attenuations of control-related gamma during the cue-on period among the Responders, relative to the non-responders. These were evident in frontal electrodes between 200 and 300 ms after cue onset in the 30–50 Hz range, and in occipital electrodes later in the cue-on period (200–400 ms after cue onset) in the upper gamma range, between 40 and 80 Hz (Figure 4).

We conducted a few other Supplementary analyses to evaluate the specificity of the observed MOD treatment-related effects on oscillatory power. To evaluate whether oscillatory power changed over time in association with task performance in a manner that was unrelated to modafinil treatment (eg as a practice effect), we examined control-related oscillatory power within the placebo group, sub-grouping PLC subjects by whether or not they exhibited improved performance (accuracy cost) after 4 weeks (fully analogous to the MOD-group responder analysis). This analysis showed that among both the PLC subgroup showing improved performance (improver subgroup) and the PLC subgroup showing no performance improvement (non-Improver subgroup), neither group exhibited increases in control-related oscillations in the gamma or other frequency ranges at 4 weeks (Supplementary Figure 3). This suggests that there were no gamma-performance associations in the PLC group that could represent a non–treatment–related effect, which would in turn confound the interpretation of the effects in the MOD group.

Finally, to evaluate whether the non-responder subgroup of MOD-treated patients exhibited a specific treatment-related (*vs* more general time-related) effect on gamma oscillations, which did not happen to translate into performance enhancement, we directly contrasted the (post-treatment minus pre-treatment) difference in control-related gamma power between the MOD Non-Responder (MOD-NR) subgroup and the full PLC group. Here (Supplementary Figure 4), the MOD-NR subgroup exhibited increased control-related oscillatory power during cue-on and delay periods across the electrode subgroups, and particularly prominent in occipital electrodes, whereas the

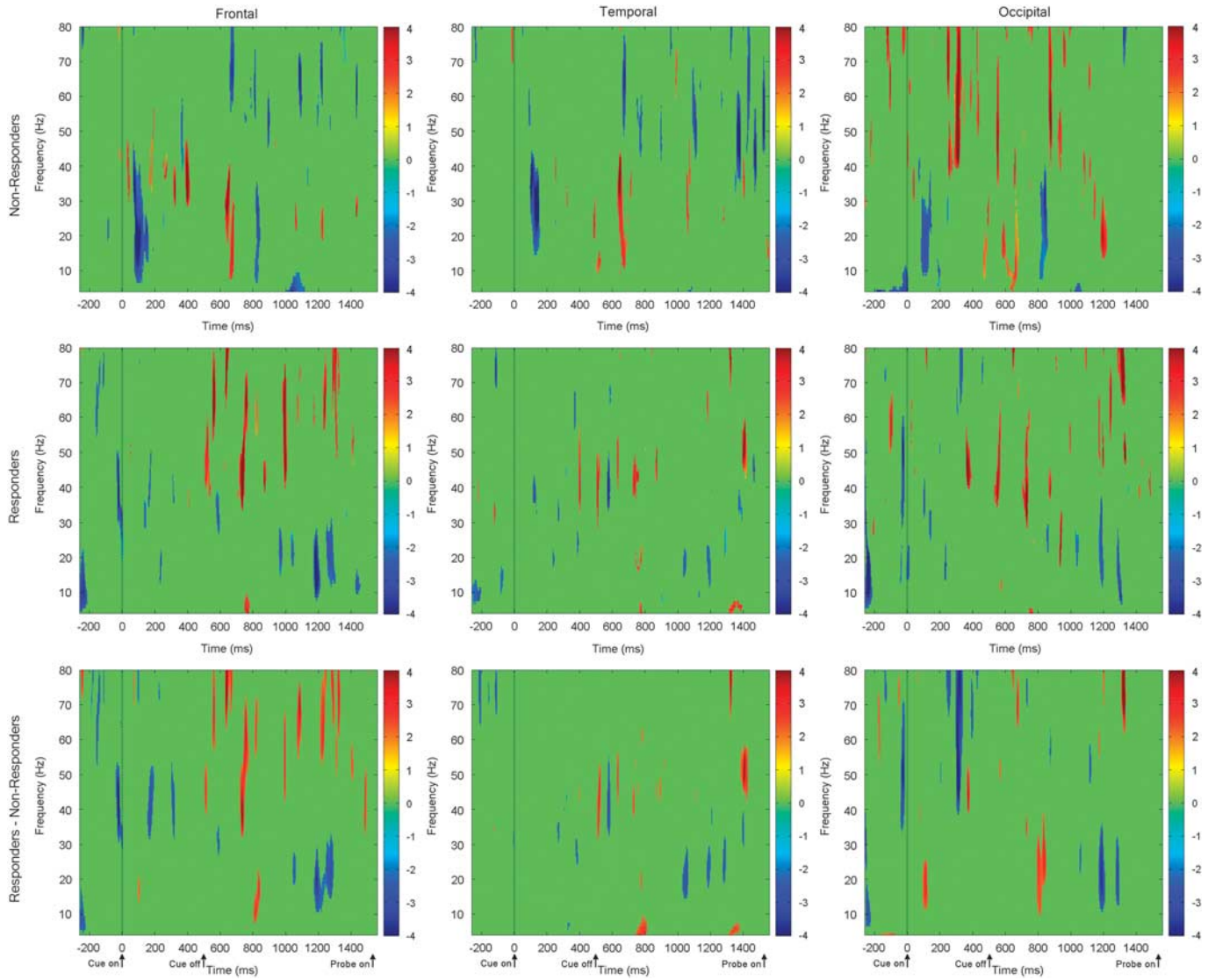

Figure 4 Modafinil effects on control-related gamma power as a function of treatment-related performance improvement. Trial-averaged spectrograms depicting mean oscillatory power within 4–80 Hz range, from baseline period (pre-cue) through cue-on and cue-probe delay period, within electrode subgroups (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 (ie, red cue minus green cue) demands, for post-treatment minus baseline, in MOD subgroup lacking treatment-related performance improvement (Non-Responders). Middle row: oscillatory power in response to high-control (ie, red cue minus green cue) demands, for post-treatment minus baseline, in MOD subgroup exhibiting treatment-related performance improvement (Responders). Bottom row: effect on oscillatory power in response to high-control demands (ie, red cue minus green cue) for post-treatment minus baseline, for MOD-responders minus MOD-non-responders. This contrast is equal to the middle row minus top row. Note the robust relative increase in treatment-related gamma power during the delay period in the Responder subgroup, particularly in frontal electrodes.

PLC group did not generally show increased control-related gamma at 4 weeks. Taken together with the MOD Responder analysis presented in Figure 4, these results suggest a decreasing order of time-sensitive effects on oscillatory power in this order: MOD Responder > MOD Non-Responder > Placebo.

DISCUSSION

In the current study, we tested the effects of sustained modafinil treatment on task-related gamma oscillations in schizophrenia, in support of rule selection and maintenance. We found that modafinil enhanced cue- and delay-period oscillatory power associated with high-control rule selection, in the gamma range over frontal electrodes, and to a lesser extent in sub-gamma frequency ranges in other electrode groups. Among MOD-treated patients, those with improved performance also showed stronger treatment-related gamma power during rule maintenance compared with MOD-treated patients without improved performance. In contrast, among PLC patients, there were no associations of gamma with performance over time that would suggest non-treatment-related effects on gamma. To our knowledge, this is the first evidence of augmentation of cognition-related

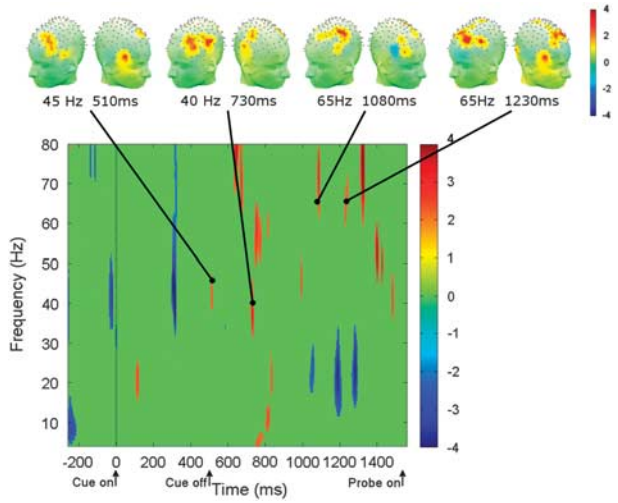

Figure 5 Topography of modafinil effects on control-related gamma power among treatment responders *vs* treatment non-responders. Statistical contrast of MOD subgroup who exhibited improved performance (responders) *vs* MOD subgroup who did not exhibit improved performance (non-responders). Between-group contrast of group-averaged mean power as effect of Subgroup × Time × Task Condition interaction, across rule selection and maintenance task phases. Spectrogram depicts the unthresholded mean power of all electrodes (statistical contrast as for Figure 4 bottom row) and head-maps depict scalp topography at time points of supra-threshold power within gamma range. Note frontotemporal and frontotemporal-parietal distributions of stronger drug effects on gamma power among subgroup showing improved performance, evident particularly during the delay period. Drop line at $t = 0$ (cue onset); $t = 500$ ms is cue offset.

gamma oscillations in schizophrenia by an FDA-approved agent with therapeutic potential.

It remains unclear whether modafinil effects on cortical oscillations arise primarily from NE and/or DA systems in the brain. In an fMRI study, we found modafinil effects on LC activation, together with enhancement of control-related cortical activation and LC-PFC functional connectivity (Minzenberg *et al*, 2008b). In addition, DA neurotransmission in the PFC may be primarily regulated by the LC-NE, because there is a paucity of DAT in the PFC, and extracellular DA action is primarily terminated by the NET (Carboni *et al*, 1990; Moron *et al*, 2002). It remains possible, therefore, that modafinil effects on LC activity are mediated by DA receptor activation in terminal fields in the PFC.

The present findings may in fact arise via effects on both NE and DA, which have direct influences on cortical pyramidal cells via a diversity of receptors, including every major subtype among these two neurotransmitter systems, at both pre- and post-synaptic sites (Gu, 2002). Catecholamines also directly innervate cortical inhibitory interneurons, which mediate some catecholamine effects on cortical principal cells (Bacci *et al*, 2005). Norepinephrine depolarizes fast-spiking interneurons in rat frontal cortex, including chandelier cells (Kawaguchi and Shindou, 1998), with heterogeneous effects on CCK+ interneurons (Kawaguchi and Shindou, 1998), and also depolarizes hippocampal interneurons (Bergles *et al*, 1996). Similarly, DA increases the excitability of fast-spiking, non-adapting interneurons in primate DLPFC, including basket cells and chandelier cells (Kroner *et al*, 2007), and D4 receptor activation increases hippocampal gamma via enhanced synchronization of fast-spiking interneurons (Andersson *et al*, 2012a). These interneurons gate pyramidal cell inputs and outputs as critical determinants of gamma and other cortical oscillations. These cortical interneuron cell types, cellular and population-level physiological phenomena are implicated in schizophrenia (Gonzalez-Burgos and Lewis, 2008). These observations suggest that catecholamine systems modulate cortical oscillations that are highly relevant for the pathophysiology of schizophrenia, and therefore serve as candidate treatment targets (Minzenberg and Carter, 2012).

It remains unclear what type of treatment regimen might optimize modafinil effects on cortical gamma in schizophrenia. Modafinil shares many cellular and clinical effects with classic stimulants, which remediate cognition on a dose-by-dose basis in attention-deficit disorder (see reviews in (Minzenberg, 2012) and (Minzenberg and Carter, 2008a)). Yet modafinil also shares effects on NET with many classic antidepressants, which have a well-established latency to therapeutic action, likely based on downstream, intracellular effects on second messengers, gene transcription and possibly neurogenesis (Tanis and Duman, 2007). Interestingly, we found previously that single-dose modafinil effects on cortical oscillations in both healthy subjects (Minzenberg *et al*, 2014a) and schizophrenia patients (31) are primarily manifest in lower, sub-gamma frequencies, and moreso with rule selection than rule maintenance. Although some control-related oscillations were augmented with sustained modafinil treatment in these same lower frequencies (beta in particular), the predominant effects of sustained treatment were manifest in higher frequencies and relatively more strongly during rule maintenance. This suggests that with sustained treatment, changes evolve in catecholamine signaling and/or catecholamine-receptive neurons such that the temporal dynamics of cognition-related cortical oscillations shifts from lower to higher frequencies, and perhaps also to support maintenance of information over encoding or selection. One intriguing possibility is that adaptive changes occur over time in GABAergic cortical interneurons to mediate this shift in cortical oscillations into the gamma range. For instance, there is evidence that in schizophrenia patients, gamma power and peak frequency during working memory processes are related to GABA levels in left DLPFC measured by magnetic resonance spectroscopy (Chen *et al*, 2014). Further elaboration of the time-course of modafinil effects on gamma oscillations may therefore point toward cellular and molecular mechanisms that underpin these effects, and how to optimize cognition-related oscillations.

In schizophrenia, some clinical considerations exist with the use of modafinil as an adjunctive treatment. First, modafinil induces the CYP3A4 isozyme (Robertson and Hellriegel, 2003), which could lead to reduced bioavailability of concurrent antipsychotics. Second, modafinil is a weak psychostimulant that could in principle directly provoke psychosis. Fortunately, the available empirical evidence suggests at most a small risk of provoking psychosis in non-psychotic (Davies *et al*, 2013) or schizophrenia (Saavedra-Velez *et al*, 2009) patients. In addition, antipsychotics have variable but significant DA receptor antagonism, and many have significant anti-adrenergic effects as well (Minzenberg and Yoon, 2011). These effects could mitigate the benefit of pro-catecholaminergic agents that might otherwise effectively modulate these neurotransmitter

systems. The converse may also hold, that is, that modafinil effects on cognition-related brain oscillations observed here may represent to some extent the reversal of antipsychotic-related impairment of these oscillations. It is also presently unknown how aging or chronicity of illness might alter the brain's response to a drug like modafinil. These issues could be addressed in future studies that compare patients based on these demographic or clinical measures.

Study Limitations

In this study, the sample sizes were modest. In addition, in the full-sample analysis, there were no significant effects of MOD treatment *vs* placebo. This appears likely due to ceiling effects on performance pre-treatment, limiting the sensitivity to treatment-related improvement. Effects of treatment on task performance and symptoms may have been more readily detected with a larger sample size, or alternatively a more difficult task of cognitive control. Nonetheless, our primary outcome measure, control-related gamma oscillatory power, showed robust effects of the intervention. These findings should therefore support further investigation of catecholamine modulation of cognition-related brain oscillations in schizophrenia.

CONCLUSION

Gamma oscillations are associated with important component processes of cognitive control, and these oscillations and their cognitive correlates are impaired in schizophrenia. The present results indicate that modafinil enhances control-related gamma oscillations in medicated schizophrenia patients. Future work should further elaborate on mechanisms of action in catecholamine modulation of these physiological phenomena, and address the optimal conditions for remediation of these deficits in schizophrenia, including treatment considerations such as optimal dose and duration of treatment, potential interactions with other existing and potential treatments, and the clinical and functional consequences of these effects for schizophrenia patients.

FUNDING AND DISCLOSURE

This work was supported by Clinical Scientist Development Award from the Doris Duke Charitable Foundation, and a Young Investigator award from NARSAD (Brain and Behavior Foundation), to MJM. The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The authors would like to acknowledge the assistance of Glenn Gomes, Janeth Nunez del Prado, Jenny Yen and Dennis Thompson in the conduct and analysis of the study.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)