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ORIGINAL INVESTIGATION

Effects of modafinil on electroencephalographic microstates in healthy adults

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Abstract

Rationale Modafinil has been proposed as a potentially effective clinical treatment for neuropsychiatric disorders characterized by cognitive control deficits. However, the precise effects of modafinil, particularly on brain network functions, are not completely understood.

Objectives To address this gap, we examined the effects of modafinil on resting-state brain activity in 30 healthy adults using microstate analysis. Electroencephalographic (EEG) microstates are discrete voltage topographies generated from resting-state network activity.

Methods Using a placebo-controlled, within-subjects design, we examined changes to microstate parameters following placebo (0 mg), low (100 mg), and high (200 mg) modafinil doses. We also examined the functional significance of these microstates via associations between microstate parameters and event-related potential indexes of conflict monitoring and automatic error processing (N2 and error-related negativity) and behavioral responses (accuracy and RT) from a subsequent flanker interference task.

Results Five microstates emerged following each treatment condition, including four canonical microstates (A–D). Modafinil increased microstate C proportion and occurrence regardless of dose, relative to placebo. Modafinil also decreased microstate A proportion and microstate B proportion and occurrence relative to placebo. These modafinil-related changes in microstate parameters were not associated with similar changes in flanker ERPs or behavior. Finally, modafinil made transitions between microstates A and B less likely and transitions from A and B to C more likely.

Conclusions Previous fMRI work has correlated microstates A and B with auditory and visual networks and microstate C with a salience network. Thus, our results suggest modafinil may deactivate large-scale sensory networks in favor of a higher order functional network during resting-state in healthy adults.

Keywords EEG · Microstates · Modafinil · Flanker · Event-related potential · Dopamine

Introduction

Modafinil is a medication used to promote wakefulness in sleep disorders such as narcolepsy (Golicki et al. 2010) and has been investigated as an off-label treatment for neuropsychiatric disorders, including depression (Ballon and Feifel 2006; Goss et al. 2013). Modafinil acts in part by inhibiting striatal dopamine (DA) transporter (Kim et al. 2014; Madras et al. 2006; Volkow et al. 2009) and norepinephrine (NE) transporter (Madras et al. 2006), leading to an increase in both DA and NE in the brain. Given that DA modulates cognitive control (e.g., Cools & D'Esposito 2011), modafinil may act as a cognitive enhancer in healthy adults (see review

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by Minzenberg & Carter 2008). Indeed, several studies have observed better cognitive performance following a single dose of modafinil (100–200 mg) across several tasks relative to placebo (Müller et al. 2013; Pringle et al. 2013; Turner et al. 2003). However, more recent work has shown little or no effect of modafinil on cognitive performance in healthy adults (Repantis et al. 2021; Roberts et al. 2020). Additionally, our recent EEG study reported no effect of modafinil on several cognitive control indexes (the anterior N2, error-related negativity, and frontal theta power) in healthy adults and rats (Robble et al. 2021). Thus, the extent of modafinil's cognitive enhancing benefits remains unclear. A better understanding of how modafinil may act to improve cognition is therefore necessary for the continued development of novel drug treatments for neuropsychiatric disorders and/or to identify individuals who might preferentially benefit from these agents.

Recent fMRI work has demonstrated effects of modafinil on large-scale resting-state brain networks in healthy adults, which may help explain the cognition-enhancing benefits of this drug. Resting-state networks (RSNs) are large-scale distributed brain regions that exhibit functional connectivity when an individual is awake but not actively engaged in a task. Current understanding of these RSNs is largely based on examining correlations between fMRI BOLD fluctuations among different brain regions during periods of rest. Several RSNs have been consistently identified across studies, including the frontoparietal, cingulo-opercular, default mode, dorsal attention, visual, and somatomotor networks (Ji et al. 2019; Power et al. 2011; Yeo et al. 2011). Using a between-subjects design, Esposito et al. (2013) examined the effects of a single 100 mg dose of modafinil on resting-state functional connectivity (rsFC) relative to placebo. The modafinil group exhibited significantly greater rsFC in the anterior cingulate cortex (ACC) node of the left frontoparietal network, involved in cognitive control, and in the bilateral occipitoparietal junction of the dorsal attention network, involved in regulating externally oriented attention. Using a within-subjects design, Minzenberg et al. (2011) examined the effects of a single 200-mg dose of modafinil on task-induced deactivation of the default mode network (DMN) during a simple sensorimotor task, relative to placebo. After taking modafinil, healthy participants exhibited greater task-induced DMN deactivation in response to the sensorimotor processing demand. This suggests that greater DMN suppression during a cognitively demanding task may be part of modafinil's cognitive enhancing benefits. Together, these studies suggest modafinil can induce changes in large-scale resting-state networks involved in higher-order cognitive and attentional control processes, which may help to explain the cognitive enhancing benefits of modafinil reported in other studies in healthy adults (Müller et al. 2013; Pringle et al. 2013; Turner et al. 2003). Crucially, however, the slow speed of the hemodynamic response measured with fMRI contrasts with the precise temporal dynamics of these RSNs, which are dynamically organized at the sub-second level (Custo et al. 2017). Consequently, such fMRI techniques preclude a closer examination of the underlying neural processes involved in the effects of modafinil. This is an important gap, since understanding potential aberrations in the dynamic temporal reorganization of large-scale RSNs can elucidate the neurochemical mechanisms of action of modafinil and how it can produce cognitive enhancement.

One powerful and data-driven approach to fill this gap and probe the temporal signatures of these RSNs following modafinil is EEG microstate analysis. Decades of work have shown that resting-state EEG signals can be parsed into a small number of discrete semi-stable voltage topographies, known as microstates (Lehmann et al. 1987). Each microstate topography remains stable for tens of ms before transitioning to another microstate (Michel & Koenig 2018). Microstate analysis simultaneously considers the signal from all electrode sites to create a global representation of a functional brain state, with each microstate believed to be generated from the coordinated activity of large neural assembles across the cortex (Khanna et al. 2015). Many studies have described the existence of four canonical microstates (labelled A–D). Some studies have argued that the RSNs observed using fMRI are the same RSNs that give rise to EEG microstates (Britz et al. 2010; Musso et al. 2010; Yuan et al. 2012). For example, Britz et al. (2010) collected simultaneous resting-state EEG-fMRI data to examine relationships between EEG microstates and fMRI RSNs. The convolution of each microstate map's time course with the hemodynamic response function suggested that microstates A through D corresponded to established RSNs. Specifically, microstate A was associated with negative BOLD activation in the bilateral superior and middle temporal lobe (auditory network); microstate B was associated with negative BOLD activation in bilateral occipital cortex (visual network); microstate C was associated with positive BOLD activation in the dorsal ACC, bilateral inferior frontal cortices, and right insular area (salience network); and microstate D was associated with negative BOLD activation in the dorsal/ventral areas of the frontal and parietal cortices (attention network). Despite this, more recent work has performed source localization directly on the EEG data to measure the neural processes that underlie each microstate map (Custo et al. 2017). While this work revealed similar results to Britz et al. (2010), regarding microstates A, B, and D, microstate C was associated with more parietal neural sources including the posterior cingulate cortex and the precuneus (i.e., DMN regions). Thus, there remains some question as to whether microstates are precise maps of established fMRI RSNs or whether they provide additional, unique information about resting-state brain activity (Murphy et al. 2020b).

The current study aimed to examine whether modafinil would dose-dependently induce changes to resting-state temporal dynamics using microstate analysis in healthy participants. Based on previous studies that observed greater rsFC in cognitive and attention networks following modafinil (Esposito et al. 2013; Minzenberg et al. 2011), we predicted modafinil would dose-dependently increase activation of microstates C (salience network) and D (attention network) but not A (auditory network) and B (visual network). In addition to resting-state, our study participants completed a newly developed flanker task (data published in Robble et al. 2021) which measured behavioral interference effects (accuracy and RT), as well as N2 and error-related negativity (ERN) event-related potential (ERP) components as neural indexes of cognitive control. The N2 is a negative fronto-central deflection that is larger in response to incongruent versus congruent flanker trials, while the ERN is a negative deflection that is larger following error versus correct responses. These N2 and ERN ERP signals are believed to originate in the ACC and are related to conflict monitoring and error detection mechanisms, respectively (van Veen and Carter 2002; Yeung et al. 2004). Therefore, to probe the functional significance of the resting EEG microstates, we also examined associations between drug-induced changes to resting microstate parameters and behavioral, N2, and ERN responses during the flanker task.

Methods

Participants

In total, 30 healthy adults were recruited from the greater Boston area (15 female, *M age* = 24.47 years, *SD* age = 6.10 years, range = 18–45 years). Participants identified as White ($N = 16$, two participants identified as Hispanic or Latino) or Asian ($N = 14$). Participants were right-handed and nonsmoking, had normal or corrected-to-normal vision and hearing, and were free from any acute or chronic medical or neurological illness. Participants were also free from any lifetime psychiatric illness (including alcohol or substance abuse) as assessed by the Structured Clinical Interview for DSM-V (SCID-5; First et al. 2015), which was administered by a PhD- or MA-level clinician.

Participants had no history of DA-related drug use (e.g., cocaine or other stimulants like amphetamine or methylphenidate) in the last 6 months or five or fewer lifetime uses and no current drug use (e.g., cocaine, cannabinoids, opiates, amphetamines, benzodiazepines, barbiturates), as confirmed by a urine drug test before each testing session. Participants had not taken psychotropic medication in at least the past 6 months, had not taken certain medications 24 h before the EEG sessions (e.g., antibiotics, pain relievers, nonsteroidal anti-inflammatory drugs, warfarin, anticoagulants, antihistamines, or over-the-counter medications), and had not taken melatonin in the 5 days prior to an EEG session. Written informed consent was obtained from all participants while in the presence of a medical doctor, who outlined the potential risks of modafinil. All study procedures were approved by the Mass General Brigham Institutional Review Board.

EEG data acquisition and task procedure

Continuous EEG data were recorded using a customized 96-channel actiCAP system and an actiCHamp amplifier (Brain Products GmbH, Golching, Germany). The ground channel was embedded in the cap and corresponded roughly to channel AFz. The data were referenced online to channel Cz, digitized at 500 Hz using BrainVision Recorder Software, and impedances were kept below 25 KΩ as recommended by the manufacturer.

Participants completed a total of three EEG sessions, recorded at least 1 week apart, as part of a structured double-blind, within-subject, placebo-controlled design. Each EEG session included 8 min of resting EEG data recorded in 1-min segments (4 min eyes open, 4 min eyes closed), the order of which was counterbalanced. Participants then completed a newly developed version of the Eriksen flanker task (see Robble et al. 2021) and a probabilistic reversal learning task (not examined here). Two hours before each EEG session, participants received either a placebo (0 mg), low (100 mg), or high (200 mg) dose of modafinil. The 2-h timeframe was selected to achieve peak plasma concentration during the EEG sessions (Robertson & Hellriegel 2003). The current study focused on conducting a microstate analysis of the resting-state EEG data (eyes closed only) and examining whether modafinil modulated resting microstate parameters (occurrence, proportion, duration). Additionally, we examined associations between resting microstate parameters and flanker task behavior (accuracy and RT) and ERP indexes of conflict monitoring (the N2) and automatic error monitoring (the ERN).

Resting-state EEG data processing

Continuous resting-state EEG data were processed in BrainVision Analyzer (Version 2.2). Only eyes closed data were analyzed, with roughly 240 s of total data available per participant, per treatment condition. EEG data were first visually inspected to identify gross muscle artifacts and artifactual channels. Data were then band-pass filtered (0.1–100 Hz, 60-Hz notch). An independent components analysis (ICA) was computed to identify and remove any components which were characteristic of eyeblinks, saccadic eye movements, or electrocardiogram. Artifactual channels were interpolated using a spherical spline interpolation

(Perrin et al. 1989). There were no significant differences in the amount of EEG data rejected for artifact, the number of ICA components removed, and the number of artifactual channels interpolated across the treatment conditions (Supplementary Table 1). Following this, data were bandpass filtered using a 0.5–40 Hz cut-off and re-referenced to the average of all channels. We then extracted each participant's processed EEG data as a series of nonoverlapping segments (2.048 s each), skipping over any segments that had been identified as artifactual during visual inspection. The minimum number of artifact-free segments available for analysis was 98 for each participant per treatment condition (approximately 200 s of data). To ensure proper interpretations of the microstate analysis, we selected each participant's first 98 segments per treatment condition, so all participants' EEG data were of equal length. These processed EEG datasets were submitted to microstate analysis.

The microstate analysis was conducted in Cartool software designed by Denis Brunet (cartoolcommunity.unige.ch). We ran two stages of segmentation, the first at the individual participant level and the second at the group level (placebo, low-dose, high-dose modafinil). During the first segmentation stage, we computed the global field power (GFP) across all electrodes for each participant. We retained EEG voltage topographies at the GFP peaks and spatially filtered the data to further increase the signal-to-noise ratio (Michel & Brunet 2019). We then submitted these GFP data to an adapted k-means clustering analysis (Brunet et al. 2011; Pascual-Marqui et al. 1995) with a k ranging from 1 to 10. The polarity of the data was ignored by the clustering algorithm. This analysis identified the most dominant microstate topographies for each participant's dataset, and a meta-criterion was used to determine their optimal number of microstates (Bréchet et al. 2019). During the second segmentation stage, we computed a k-means cluster analysis on the concatenated microstates from the first round of clustering for each treatment condition (placebo, low-dose, high-dose modafinil) with a k ranging from 1 to 10. For each treatment condition independently, the meta-criterion suggested that five microstates provided the best fit to the data. However, given the high spatial correlation between the resulting microstate maps across the different treatment conditions (Pearson's r ranging from 0.97 to 0.99), which suggested the maps were virtually identical across doses (as shown in Supplementary Fig. 1), we opted to recompute the k-means cluster analysis on the concatenated microstates collapsed across treatment conditions. This generated one set of microstate maps for all three treatment conditions and eliminated potential spurious drug effects caused by subtle differences between maps. The resulting maps (Fig. 1) consisted of the four canonical microstates A–D (see reviews by Khanna et al. 2015; Michel & Koenig 2018) along with a fifth microstate E also reported in previous work (Murphy et al. 2020b; Tomescu et al. 2022).

Following this, we fitted these five microstates back to the original EEG data. Short microstate segments were rejected if they were 10 ms or less. We obtained a series of microstate labels for each original EEG dataset and used these labels to extract three parameters: *occurrence* (i.e., the number of times a microstate occurred per second), *proportion* (i.e., the amount of the participant's total EEG session that was dominated by each microstate), and *duration* (i.e., the average length of time a microstate lasted in ms). Moreover, to examine the transition probabilities between microstates (e.g., how likely it is for participants to transition from one microstate to another), we computed a Markov matrix on the observed transitions between microstates, as well as an expected Markov matrix containing the transition probabilities that would be expected based on the distribution of microstate labels. Comparisons between *observed* and *expected* transition probabilities determined whether observed microstate transitions occurred with a higher probability than would be expected by random chance.

Flanker task EEG data processing

To examine associations between resting microstate parameters and cognitive control indexes from the flanker task, behavioral data (accuracy and RT, summarized in Supplementary Table 2) and ERP data (N2 and ERN mean amplitudes) were extracted from our recent paper (Robble et al. 2021). In brief, ERP processing of the flanker data was consistent with the resting-state EEG processing described above (band-pass filtered, ICA, interpolation of bad channels, average reference). The primary difference was our use of a 0.1–30 Hz bandpass filter on these ERP data, rather than the 0.5–40 Hz bandpass filter used for the resting-state data in the microstate analysis. This filter was selected based on

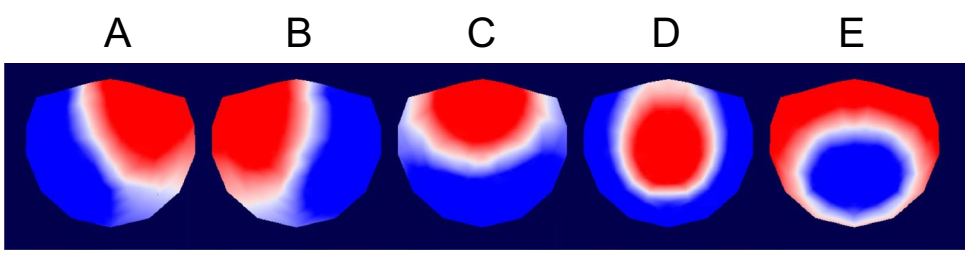

Fig. 1 Five microstates produced the best fit to the data. Virtually identical microstates were produced for the placebo, low-dose, and high-dose modafinil conditions (see Supplementary Fig. 1)

expert recommendations for the analysis of healthy adult ERPs (Luck 2014). From these processed data, we extracted epochs for ERP averaging. Epochs were rejected if they met any of the following criteria: (1) a voltage step exceeded 50 μV in 200-ms time intervals, (2) a voltage difference was greater than 150 μV within a trial, or (3) a maximum voltage difference was less than 0.5 μV within a trial. Four participants were removed from ERP analyses because they had fewer than six artifact-free ERP trials. This left a final sample of 26 participants for our correlational analysis. For ERN analyses, we extracted mean amplitudes from 0–100 ms following an error response on incongruent trials from an electrode that roughly corresponded to Fz. For N2 analyses, we extracted mean amplitudes from 230 to 290 ms following the presentation of an incongruent flanker trial (for correct responses only) from an electrode that roughly corresponded to FCz.

Statistical analysis

To examine the effects of modafinil (placebo, low-dose, high-dose) on resting microstate parameters (occurrence, proportion, duration), we computed one-way within-subjects analyses of variance (ANOVA) models for each of the five microstates and followed up significant models using pairwise *t* tests. For each ANOVA model, we specified treatment condition as the independent variable (placebo, low-dose modafinil, high-dose modafinil) and either microstate occurrence, proportion, or duration as the dependent variable. We adjusted the significance threshold for each set of five ANOVA models and any subsequent set of three pairwise *t* tests, using a Benjamini–Hochberg correction.

Next, to examine the effects of modafinil on microstate transitions, we computed paired *t* tests to compare the observed and expected transitions for each set of microstate transitions (e.g., from microstate A to B and so on) for each treatment condition separately. We also examined whether there were differences in these observed minus expected transition probabilities across each treatment condition. To achieve this, we computed within-subjects ANOVAs for each possible transition. Finally, we computed Pearson's correlations to measure the association between microstate parameters (occurrence, proportion, duration) and the flanker behavioral responses (accuracy and RT) and N2/ERN mean amplitudes for each treatment condition separately. However, to reduce the number of possible correlations, we only computed drug difference scores (e.g., microstate C occurrence [high-dose] minus microstate C occurrence [placebo]) for microstate parameters where a significant effect of modafinil was observed. These difference scores were then correlated with their corresponding behavioral/ERP drug difference scores (e.g., ERN [high-dose] minus ERN [placebo]). This allowed us to test whether drug-induced changes in microstate parameters were associated with a similar change in flanker behavior/ERPs. Paired *t* tests, ANOVAs (and subsequent pairwise comparisons), and correlations were corrected using Benjamini–Hochberg correction procedures.

Results

Microstate parameters

Table 1 and Fig. 2 display the average occurrences (i.e., the number of times a microstate occurred per second), the average proportions (i.e., the amount of the total EEG session), and the average durations (ms) for each of the five microstates (A–E) for each treatment condition (placebo, low-dose modafinil, high-dose modafinil). Table 2 provides

Table 1 Summary of microstate parameters (A–E)

	Occurrence per second (M) SD)			Proportion (M) SD)			Duration in ms (M) SD)		
	Placebo	Modafinil (Low)	Modafinil (High)	Placebo	Modafinil (Low)	Modafinil (High)	Placebo	Modafinil (Low)	Modafinil (High)
A	5.06, 1.14	4.90, 1.02	4.83, 1.00	0.179, 0.064	0.168, 0.058	0.162, 0.055	28.56, 3.83	28.12, 3.48	27.75, 3.35
B	4.95, 1.24	4.81, 1.22	4.60, 1.16	0.182, 0.080	0.172, 0.075	0.158, 0.067	28.96, 4.74	28.36, 4.20	27.79, 4.05
C	6.64, 1.50	6.95, 1.39	7.15, 1.35	0.262, 0.072	0.285, 0.079	0.294, 0.074	32.15, 2.57	33.03, 3.21	33.22, 2.94
D	5.39, 1.08	5.47, 0.97	5.65, 0.94	0.174, 0.046	0.174, 0.040	0.182, 0.038	27.49, 2.93	27.16, 2.67	27.53, 2.63
E	5.84, 1.77	5.97, 1.67	6.02, 1.72	0.202, 0.085	0.201, 0.074	0.204, 0.079	28.55, 2.65	28.08, 2.19	28.15, 2.63

The number occurrences per second spent in each microstate, the proportion of the total EEG recording spent in each microstate, and the average duration of each microstate in ms, arranged by treatment condition. Abbreviations: M, mean; SD, standard deviation; ms, milliseconds

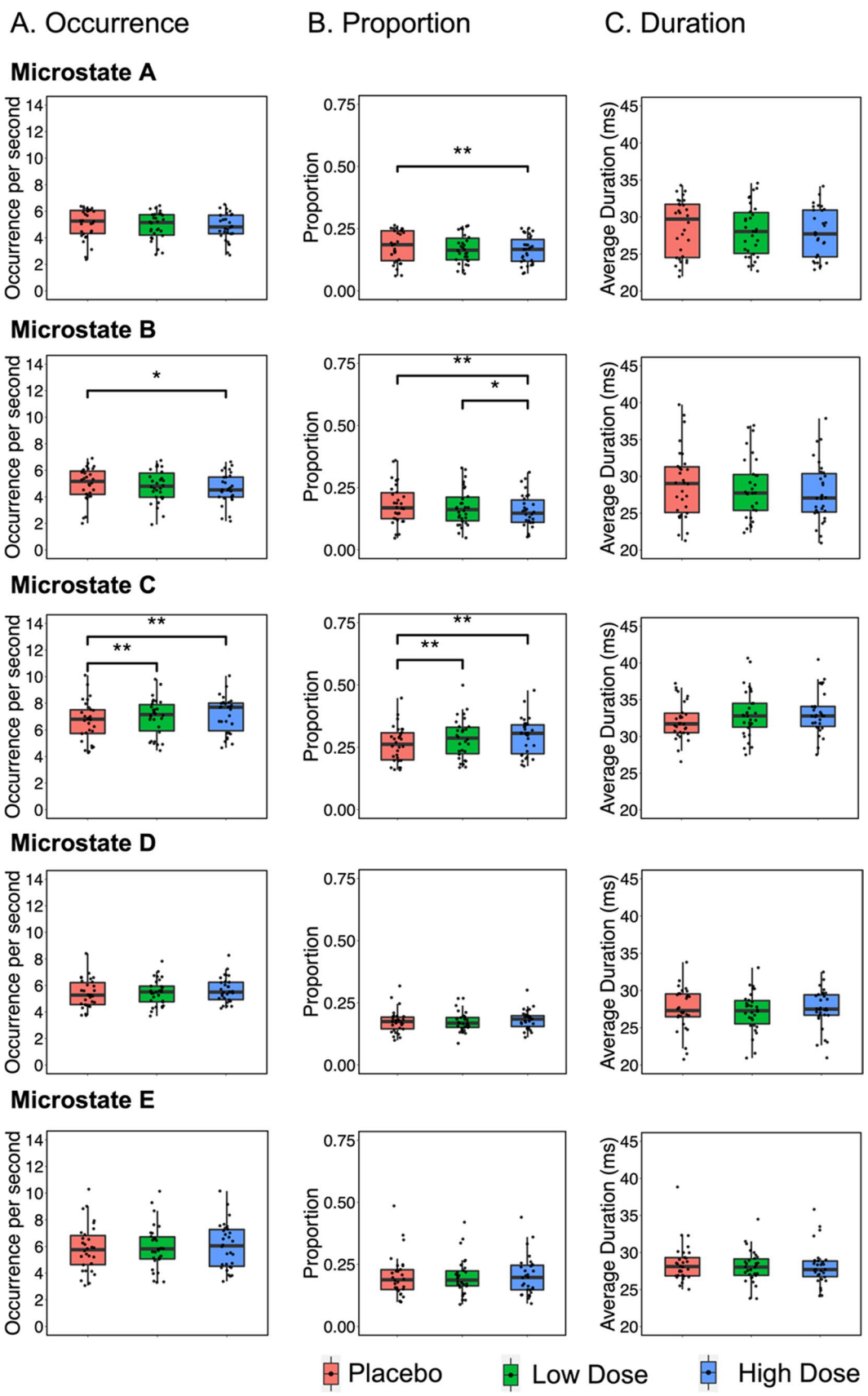

Fig. 2 Microstate occurrence (**A**), proportion (**B**), and duration (**C**). ***$p < .001$, **$p < .01$, *$p < .05$

Table 2 Summary of our results in the context of past work that has identified likely neural sources of EEG microstates. 1. Britz et al. (2010), 2. Custo et al. (2017)

Microstate	Topography	Hypothesized RSN/regions	Results from the current study
A	Left-right	Auditory network[1, 2]	High-dose modafinil decreased microstate A proportion compared to placebo
B	Right-left	Visual network[1,2]	High-dose modafinil decreased microstate B occurrence compared to placebo High-dose modafinil decreased microstate B proportion compared to low-dose and placebo
C	Anterior-posterior	Salience network (involving posterior ACC, frontoinsular cortex, left claustrum)[1], or default mode network (involving posterior cingulate cortex and precuneus)[2]	High and low-doses of modafinil increased microstate C occurrence and proportion compared to placebo
D	Frontocentral	Dorsal attention network[1]	No drug effects observed
E	Occipital	Dorsal ACC, middle and superior frontal gyri, and insula)[2] Similar topography to microstate F in other work[2], authors demonstrated this microstate becomes merged with microstate C when analysis was restricted to the four canonical maps (A–D)	No drug effects observed

a summary of our main findings in the context of past research that has identified the likely neural generators of EEG microstates.

Occurrence

There was a significant drug difference for microstate B occurrence, $F(2, 58) = 4.80$, $p = 0.012$, $\eta_p^2 = 0.14$. Pairwise comparisons demonstrated that modafinil decreased microstate B occurrence at the high-dose ($M = 4.60$, $SEM = 0.21$) relative to placebo ($M = 4.95$, $SEM = 0.23$, $p = 0.010$). Additionally, as hypothesized, there was a significant drug difference for microstate C occurrence, $F(2, 58) = 6.55$, $p = 0.003$, $\eta_p^2 = 0.18$. Pairwise comparisons demonstrated that microstate C occurrence was significantly increased by both the low-dose ($M = 6.95$, $SEM = 0.25$) and the high-dose of modafinil ($M = 7.16$, $SEM = 0.25$) relative to placebo ($M = 6.64$, $SEM = 0.27$, $ps = 0.008$ and 0.003, respectively). There were no drug-related differences in the occurrences of microstates A, D, or E.

Proportion

There was a significant drug difference in microstate A proportion, $F(2, 58) = 5.49$, $p = 0.007$, $\eta_p^2 = 0.16$. Pairwise comparisons demonstrated that microstate A proportion was decreased by the high-dose of modafinil ($M = 0.16$, $SEM = 0.010$) relative to placebo ($M = 0.18$, $SEM = 0.012$, $p = 0.006$). Although microstate A proportion was also numerically lower following the low-dose of modafinil ($M = 0.17$, $SEM = 0.011$) compared to placebo, this difference did not survive our multiple comparisons correction ($p = 0.034$). There was also a significant drug difference in microstate B proportion, $F(2, 58) = 7.41$, $p = 0.001$, $\eta_p^2 = 0.20$. Pairwise comparisons demonstrated that microstate B proportion was reduced by the high-dose of modafinil ($M = 0.16$, $SEM = 0.012$) relative to both the low-dose ($M = 0.17$, $SEM = 0.014$, $p = 0.029$) and placebo ($M = 0.18$, $SEM = 0.015$, $p = 0.002$). Lastly, there was a significant difference in microstate C proportion, $F(1.66, 48.04) = 6.33$, $p = 0.006$, $\eta_p^2 = 0.18$. Pairwise comparisons demonstrated that microstate C proportions were increased by both the high-dose ($M = 0.29$, $SEM = 0.014$) and the low-dose ($M = 0.28$, $SEM = 0.014$) of modafinil compared to placebo ($M = 0.26$, $SEM = 0.013$, p's $= 0.004$ and 0.002, respectively). There were no drug effects on microstate D or E proportions.

Duration

After correcting for multiple comparisons, there were no significant drug differences in the duration of any microstate.

Transition probabilities

For all treatment conditions, most of the observed transition probabilities were significantly different from the expected transition probabilities (Fig. 3). This suggests the observed transitions occurred with a higher probability than expected by random chance. Following the placebo, transitions preferentially occurred between microstates A and B and between C, D, and E. These findings are generally consistent with prior results from healthy participants (Murphy et al. 2020a, b).

A. Placebo

From \ To	A	B	C	D	E
A		0.019	-0.005	-0.007	-0.007
B	0.017		-0.005	-0.007	-0.006
C	-0.006	-0.008		0.007	0.007
D	-0.007	-0.007	0.006		0.008
E	-0.009	-0.007	0.014	0.002	

B. Low Dose

From \ To	A	B	C	D	E
A		0.016	-0.002	-0.007	-0.006
B	0.016		-0.003	-0.007	-0.006
C	-0.006	-0.008		0.008	0.006
D	-0.008	-0.007	0.006		0.009
E	-0.009	-0.007	0.015	0.001	

C. High Dose

From \ To	A	B	C	D	E
A		0.012	0.000	-0.006	-0.006
B	0.012		-0.002	-0.005	-0.005
C	-0.005	-0.007		0.008	0.004
D	-0.007	-0.007	0.005		0.009
E	-0.008	-0.006	0.015	0.000	

Fig. 3 The observed transition probabilities given the known distribution of microstate labels minus the expected transition probabilities. Positive (green highlighted) values indicate significantly more transitions were made from one microstate to another than would be expected by random chance. Negative (red highlighted) values indicate significantly fewer transitions were made from one microstate to another than would be expected by random chance. Values which have not been highlighted represent observed probabilities that did not significantly differ from expected probabilities

A. Placebo vs Low Dose

From \ To	A	B	C	D	E
A		0.003	-0.003	0.000	0.000
B	0.002		-0.002	0.000	0.000
C	0.000	-0.001		-0.001	0.001
D	0.001	0.000	0.000		-0.001
E	0.000	0.000	-0.001	0.000	

B. Placebo vs High Dose

From \ To	A	B	C	D	E
A		0.007	-0.005	-0.001	-0.001
B	0.005		-0.003	-0.001	-0.001
C	-0.001	-0.002		-0.001	0.003
D	0.000	0.000	0.001		-0.001
E	-0.001	-0.001	0.000	0.002	

C. Low Dose vs High Dose

From \ To	A	B	C	D	E
A		0.004	-0.002	-0.001	-0.001
B	0.003		-0.001	-0.001	-0.001
C	-0.001	-0.001		0.000	0.002
D	0.000	0.000	0.001		0.000
E	-0.001	0.000	0.000	0.001	

Fig. 4 Statistical comparisons of the observed minus expected microstate transitions between placebo, low-dose, and high-doses of modafinil. Positive (green highlighted) values indicate significantly more transitions were made in the first listed treatment condition compared to the second. For example, significantly more A to B transitions were made during the placebo condition compared to the low-dose condition. Negative (red highlighted) values indicate significantly more transitions were made in the second listed treatment condition compared to the first. Values which have not been highlighted represent nonsignificant differences between treatment conditions

We also examined whether there were drug-related differences in the observed minus expected transition probabilities. We found four of these transition probabilities differed by treatment condition (Fig. 4). First, there was a significant difference in A to B transitions, $F(2, 58) = 7.78$, $p = 0.001$, $\eta_p^2 = 0.21$, with pairwise comparisons showing that significantly fewer A to B transitions were made during the high-dose condition ($M = 0.012$, $SEM = 0.002$) compared to both the low-dose ($M = 0.016$, $SEM = 0.002$, $p = 0.031$) and placebo conditions ($M = 0.019$, $SEM = 0.003$, $p = 0.002$). There were also fewer A to B transitions during the low-dose compared to the placebo condition ($p = 0.050$). These results suggest that modafinil dose-dependently reduced microstate A to B transitions. Second, there was a significant difference in B to A transitions, $F(2, 58) = 5.64$, $p = 0.006$, $\eta_p^2 = 0.16$, with pairwise comparisons showing significantly fewer B to A transitions were made during the high-dose condition ($M = 0.012$, $SEM = 0.002$) compared to both the low-dose ($M = 0.016$, $SEM = 0.003$, $p = 0.031$) and placebo conditions ($M = 0.017$, SEM = 0.003, $p = 0.003$). However, B to A transitions did not differ between low-dose and placebo conditions ($p = 0.284$). Third, there was a significant difference in A to C transitions, $F(1.57, 45.64) = 6.74$, $p = 0.005$, $\eta_p^2 = 0.19$, with pairwise comparisons showing significantly fewer A to C transitions were made during the placebo condition ($M = -0.005$, $SEM = 0.001$) compared to both the low-dose ($M = -0.002$, $SEM = 0.001$, $p = 0.013$) and high-dose conditions ($M = 0.000$, $SEM = 0.002$, $p = 0.005$). Lastly, there was a significant difference in B to C transitions, $F(2, 58) = 5.37$, $p = 0.007$, $\eta_p^2 = 0.16$, with pairwise comparisons showing significantly fewer B to C transitions were made during the placebo condition ($M = -0.005$, $SEM = 0.001$) compared to both the low-dose ($M = -0.003$, $SEM = 0.001$, $p = 0.022$) and high-dose conditions ($M = -0.002$, $SEM = 0.001$, $p = 0.005$). Together, these results suggest that modafinil reduced the likelihood of transitions being made between microstates A and B and increased the likelihood of transitions being made from microstates A and B to microstate C.

Correlations between microstate parameters and flanker behavior (accuracy and RT) and ERPs (ERN, N2)

The full results of our correlational analyses with flanker behavior are displayed in Supplementary Tables 3–6, while correlational analyses with flanker ERPs are displayed in Supplementary Tables 7–8. Importantly, after applying a correction for multiple comparisons, all correlations were nonsignificant. This suggests that drug-related effects on resting microstate parameters were not associated with similar changes in flanker behavior or ERPs.

Discussion

This study aimed to examine whether resting EEG microstate parameters (occurrence, proportion, duration) and transitions would be modulated by modafinil, a drug that inhibits striatal DA transporter (Kim et al. 2014; Madras et al. 2006; Volkow et al. 2009), in healthy adults. A secondary aim was to examine whether modafinil-induced changes in microstate parameters were associated with a similar change in conflict monitoring/error detection indexes from a subsequent flanker task. This was achieved by examining associations between resting microstate parameters and flanker behavior (accuracy and RT) and ERPs (N2/ERN). For all three treatment conditions (placebo, low-dose, high-dose modafinil), five microstates provided the best fit to the data. Of these five microstates, we observed the four canonical microstates (A–D) reported throughout the literature (Khanna et al. 2015; Michel & Koenig 2018) along with a fifth microstate (E) reported in recent work (Murphy et al. 2020b; Tomescu et al. 2022). We observed no effect of modafinil on microstate durations, which suggests that modafinil does not modulate the stability of any microstates underlying neural assemblies (Khanna et al. 2015). Instead, modafinil altered the activation patterns of certain microstates and their relative time coverage. As predicted, microstate C proportion and occurrence were increased by both low and high-doses of modafinil relative to placebo. These changes in resting microstate parameters were not associated with similar drug-related changes in flanker behavior or ERPs. Unexpectedly, microstate D was not affected by modafinil. Instead, modafinil decreased microstate A proportion and microstate B proportion and occurrence relative to placebo. Additionally, several microstate transitions were nonrandom. Thus, transitions between microstates A and B were less likely to occur and transitions from microstates A and B to microstate C were more likely to occur following modafinil relative to placebo.

Past research has suggested that microstate C may represent areas belonging to the salience network. Notably, using combined EEG-fMRI measures, Britz et al. (2010) reported that microstate C was most strongly associated with positive BOLD activation in the bilateral inferior frontal gyri and right anterior insula (i.e., frontoinsular cortex), posterior ACC, and left claustrum. Several of these areas have been identified as part of the salience network (Fox et al. 2006; Seeley et al. 2007; Sridharan et al. 2008). This network is primarily involved in the detection of homeostatically relevant stimuli and achieves this by coordinating multiple key brain regions that respond to subjective salience to guide behavior (Seeley et al. 2007). Greater DA levels have been shown to be associated with greater salience network connectivity in healthy adults (Cole et al. 2013; McCutcheon et al. 2019). Together, we suggest modafinil modulates microstate C, which reflects output activity from regions associated with the salience network, and this may occur through the release of extracellular striatal DA.

Notwithstanding the above suggestion, the true neural sources of microstate C have been debated within the microstate literature. For example, instead of using fMRI BOLD signals to identify the neural sources of microstates, Custo et al. (2017) performed source localization on their EEG data to directly measure the neural processes that produced the microstate maps. They found seven microstate maps, including the four canonical microstates (A–D), best fit their data. Their results were similar to Britz et al. (2010) regarding the neural sources of microstate A (auditory network), microstate B (visual network), and microstate D (attention network). However, Custo and colleagues reported that microstate C was not associated with the salience network but, instead, was associated with more parietal regions including the posterior cingulate cortex and the precuneus. These brain regions are major components of the default mode network (Fransson & Marrelec 2008; Raichle et al. 2001) and are involved in internally directed thought and in the retrieval of autobiographical memories (Buckner et al. 2008; Leech et al. 2011; Maddock et al. 2001). As with the salience network, evidence suggests DA modulates the DMN during resting-state. For example, higher DA synthesis capacity has been associated with greater coupling between the frontoparietal control network (FPCN) and the DMN and with reduced coupling between the FPCN and the dorsal attention network (Dang et al. 2012). Thus, previous work provides support that changes in DA levels can modulate activation of several resting-state networks. However, we cannot be certain from the current study whether modafinil-induced changes to microstate C reflect changes to the salience network or the DMN.

Unexpectedly, microstate A and B parameters and transitions between these two microstates were reduced by the highest dose of modafinil, relative to placebo. Previous studies have localized the neural sources of microstates A and B to the auditory and visual networks, respectively (Britz et al.

2010; Custo et al. 2017). Our results suggest that modafinil may contribute to the deactivation of large-scale sensory networks in favor of a higher-order functional network, like that underlying microstate C, during resting-state in healthy adults. This may occur via modafinil's primary neurochemical effects that involve catecholamine systems, specifically through the inhibition of striatal DA transporter and thalamic NE transporter (Kim et al. 2014; Madras et al. 2006; Volkow et al. 2009). Despite this, microstate D parameters were not increased after participants received modafinil. Although previous studies have suggested microstate D reflects activation of a dorsal attention network (Britz et al. 2010; Custo et al. 2017), additional work has found microstate D parameters were only increased during a serial subtraction task relative to a resting-state condition, suggesting this microstate may reflect a task-positive network (Seitzman et al. 2017). Thus, modafinil might have increased microstate D parameters if participants were engaged in a task that required attentional resources at that time.

Notably, drug-related changes in resting microstate A, B, and C parameters were not significantly associated with similar changes in flanker behavioral performance or ERP indexes of conflict monitoring/error detection. Similarly, in our recent paper, where the full results of the flanker task are reported (Robble et al. 2021), we also saw no overall effect of modafinil on behavior, ERPs, or frontal theta power in healthy adults and rats. This suggests that, while modafinil increases both DA and NE in the brain and can promote wakefulness in sleep-related disorders, this may not translate to a cognitive-enhancing benefit in the flanker task in healthy adults and with a single-dose administration.

Several lines of evidence suggest our microstates are highly reliable. Specifically, we initially computed microstate maps for the three treatment conditions separately, producing three sets of microstate maps for the high-dose, low-dose, and placebo conditions. These maps were highly spatially correlated across the treatment conditions, suggesting that a virtually identical set of 5 microstates emerged from EEG data collected at three different timepoints from the same individuals. Furthermore, the microstate parameters (occurrence, proportion, duration) extracted from each microstate were strongly positively correlated with one another in spite of the different treatment conditions (Supplementary Table 9). Together, this additional evidence provides support for the reproducibility of the microstate maps and reliability of the microstate parameters extracted. Lastly, recent studies have systematically examined the reliability of microstates like those reported in the current study. For example, Liu et al. (2020) reported good test retest reliability of microstate parameters (occurrence, proportion, duration) and transition probabilities when at least 2 min of data were used to compute the microstates. Moreover, Zhang et al. (2021) reported consistent microstate parameter results when microstates were computed using 91-, 64-, and 32-channel arrays, relative to 8- and 19-channel arrays. Given that the microstates in the current study were computed using 96 channels with over 3 min of data, we argue that these studies provide further support for the reliability of the microstate findings reported in this paper.

Despite strengths, there are several key limitations of the current study, which should be addressed in future research. First, we recruited a healthy adult population. These individuals had no previous history of neuropsychiatric illness or history of DA drug use, so were likely not experiencing altered DA levels. Furthermore, we did not include sleep deprivation as a pre-condition for the study, nor did we assess sleep quality the night before a testing session. Modafinil is primarily a medication used to promote wakefulness in sleep disorders like narcolepsy, obstructive sleep apnea, and shift work disorder (Czeisler et al. 2005; Golicki et al. 2010; Pack et al. 2001). Thus, the microstates of healthy adults in the current study may differ from individuals who would be more likely to be prescribed modafinil (e.g., individuals with sleep-related disorders). It would be beneficial to replicate and extend the current study by either recruiting individuals with a sleep-related disorder or including sleep deprivation as a precondition for the study of healthy adults. This would enable a better understanding of the effects of modafinil on those most likely to use it. Second, roughly 50% of our sample self-identified as Asian and 50% self-identified as White (two participants identified as Hispanic or Latino). Past research suggests Black adults are more likely to develop sleep apnea and experience a higher prevalence and greater severity of sleep-disordered breathing compared to White adults (Chen et al. 2015; Ruiter et al. 2010). Furthermore, past research has suggested narcolepsy is more prevalent in black adults compared to White or Asian adults (Longstreth Jr et al. 2009). This suggests that Black adults may be more likely to be prescribed modafinil. Thus, the current study would have benefitted from recruiting a larger number of Black adults to increase the validity of the reported findings. This should be a focus of future work in this area and of EEG studies in general (Choy et al. 2021). Lastly, we recruited right-handed participants to this EEG study, which limits the generalizability of our findings.

In summary, the current study assessed the effect of modafinil on resting EEG microstate parameters in healthy adults. Modafinil reduced the activation of microstates A and B and increased the activation of microstate C. In addition, modafinil decreased the likelihood of transitions occurring between microstates A and B and increased the likelihood of transitions occurring from microstates A and B to microstate C. Taken together, we suggest modafinil may act to deactivate large-scale sensory networks in favor of a higher-order functional network in healthy adults. Future work focused on examining the effects of modafinil on individuals who

are DA-depleted (e.g., individuals with MDD), or those with sleep-related disorders, would further elucidate the neurochemical effects and potentially therapeutic impact of this drug.

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Declarations

Conflict of interest Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Neumora Therapeutics (former BlackThorn Therapeutics), Boehringer Ingelheim, Compass Pathways, Concert Pharmaceuticals, Engrail Therapeutics, Neurocrine Biosciences, Neuroscience Software, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; honoraria from the Psychonomic Society (for editorial work) and Alkermes; and research funding from NIMH, Dana Foundation, Brain and Behavior Research Foundation, Millennium Pharmaceuticals. In addition, he has received stock options from Neumora Therapeutics (former BlackThorn Therapeutics), Compass Pathways, Engrail Therapeutics, and Neuroscience Software. Over the past 3 years, Dr. Carlezon has received consulting fees from Psy Therapeutics. Dr. Der-Avakian holds equity ownership in PAASP US. Dr. Risbrough has received consulting fees from Engrail and Farallon Capital. Except for NIMH, no funding from these entities was used to support the work presented in this manuscript. All views expressed are solely those of the authors. All other authors confirm they have no disclosures to make in association with the work presented in this manuscript.

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