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The Effects of Methylphenidate on the Neural Signatures of Sustained Attention

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ABSTRACT

BACKGROUND: Although it is well established that methylphenidate (MPH) enhances sustained attention, the neural mechanisms underpinning this improvement remain unclear. We examined how MPH influenced known electrophysiological precursors of lapsing attention over different time scales.

METHODS: We measured the impact of MPH, compared with placebo, on behavioral and electrocortical markers while healthy adults (n = 40) performed a continuous monitoring paradigm designed to elicit attentional lapses.

RESULTS: MPH led to increased rates of target detection, and electrophysiological analyses were conducted to identify the mechanisms underlying these improvements. Lapses of attention were reliably preceded by progressive increases in alpha activity that emerged over periods of several seconds. MPH led to an overall suppression of alpha activity across the entire task but also diminished the frequency of these maladaptive pretarget increases through a reduction of alpha variability. A drug-related linear increase in the amplitude of the frontal P3 event-related component was also observed in the pretarget timeframe (3 or 4 seconds). Furthermore, during immediate target processing, there was a significant increase in the parietal P3 amplitude with MPH, indicative of enhanced perceptual evidence accumulation underpinning target detection. MPH-related enhancements occurred without significant changes to early visual processing (visual P1 and 25-Hz steady-state visual evoked potential).

CONCLUSIONS: MPH serves to reduce maladaptive electrophysiological precursors of lapsing attention by acting selectively on top-down endogenous mechanisms that support sustained attention and target detection with no significant effect on bottom-up sensory excitability. These findings offer candidate markers to monitor the therapeutic efficacy of psychostimulants or to predict therapeutic responses.

Keywords: EEG oscillations, Inattention, Perceptual decision making, Psychostimulants, Ritalin, Time-on-task decrement

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Although methylphenidate (MPH) is the most universally prescribed psychostimulant for the treatment of attention-deficit/hyperactivity disorder (ADHD) (1), we lack a clear understanding of the neurophysiological bases of its ability to enhance attention. Such insights are critical for the identification of robust biomarkers of drug response that may ultimately facilitate personalized approaches to treatment in disorders such as ADHD.

It is well established that MPH leads to reductions in behavioral symptoms of inattention, in particular the capacity to sustain attention via modulations of catecholamine transmission (2). Although functional imaging studies have demonstrated that MPH strengthens the connectivity of fronto-striato-thalamic networks that are integral to sustained attention (3,4), it is less clear how the temporal dynamics of electrocortical activity, associated with attentional control in humans, are augmented by MPH. Some electrophysiological studies have reported correlations of electroencephalography (EEG) power (averaged at rest or across task-active conditions) with MPH-related improvements in sustained attention (5–8). However, it is not apparent whether these changes arise from direct augmentation of sustained attention mechanisms or indirectly through facilitation of task-relevant cortical regions. For example, behavioral improvements on sustained attention tasks could potentially be achieved through pharmacological regulation of sensory encoding, selective attention, or working memory capacity.

The high temporal resolution of EEG offers the potential to pinpoint MPH's influence on the electrophysiology of sustained attention as it unfolds in time. O'Connell *et al.* (9) devised a continuous monitoring paradigm, the Continuous Temporal Expectancy Task (CTET), to facilitate the identification of maladaptive patterns of EEG activity that predict forthcoming lapses of attention. Neural activity in the alpha frequency (8–14 Hz) was predictive of lapses and was observable up to 20 seconds in advance. Interestingly, the quality of basic sensory encoding, indexed by the steady-state visual evoked potential (SSVEP), was not predictive of attentional performance, suggesting that lapses arose primarily from a failure to sustain goal-directed attention as opposed to

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fluctuations in visual baseline activity. Finally, the parietal P3 was reduced in amplitude during lapses of attention, indicative of momentary disruption of decision-formation processes.

The CTET is thus well suited to identify the neural mechanisms through which monoaminergic manipulations affect sustained attention. Here, MPH was administered within a placebo (PLA)-controlled, double-blinded, crossover design while participants undertook the CTET EEG paradigm. We first examined the efficacy of MPH to influence neural signals at different time scales: 1) across the entire task, 2) in the pretarget interval, and 3) in the immediate period of target processing. Next, we established whether MPH affected all stages of stimulus processing through general effects of increased arousal and bottom-up visual excitability or, alternatively, whether it acted more selectively on higher-order endogenous mechanisms that support sustained attention.

METHODS AND MATERIALS

Participants

A total of 40 individuals (mean age = 24.3 years, SD = 5.6) participated in the study. All participants provided informed consent, in accordance with the ethics committee of The University of Queensland. Inclusion criteria were male, aged 18 to 45 years, right-handed, nonsmoking, no history of drug abuse, no current use of recreational drugs, no history of neuropsychiatric disorder, and not currently taking psychoactive medication. A consultant psychiatrist screened all participants using the Mini-International Neuropsychiatric Interview to confirm absence of psychiatric illness (10). Participants were excluded due to contraindications to the medication employed in the study (n = 4) or a technical fault on day of testing affecting one condition (n = 3). Exclusions from the EEG analyses were due to excessive EEG channel artifacts (n = 4) or because participants had $<$ 10 target hits/misses per condition (n = 3). We note the sample size for each analysis conducted in the Results. Further details regarding participant recruitment, screening, and testing can be found in Barnes *et al.* (11).

Study Design and Drug Administration

A randomized, double-blinded, PLA-controlled, four-arm crossover design was employed (11). Each participant attended four sessions at the same time of day, spaced at least 1 week apart. At each session, a single blue gelatin capsule containing MPH (30 mg, mixed dopaminergic and noradrenergic action), atomoxetine (ATM, 60 mg, primarily noradrenergic action), citalopram (CIT, 30 mg, primarily serotonergic action), or PLA (dextrose) was administered. Cognitive testing began 90 minutes following drug administration, coinciding with the peak plasma levels for each of the study drugs (12–14), and doses were selected based on clinical relevance (15–17) and demonstrated cognitive effects (18–20).

Continuous Temporal Expectancy Task

Full details of the task are provided in the Supplement and in O'Connell *et al.* (9) (see also Figure 1). Briefly, the CTET (9) involves the central presentation of a patterned stimulus that changes orientation at regular intervals. Participants monitored the orientation transitions and made a speeded button press when they detected infrequent targets defined by their duration being longer (1120 ms) than the standard transitions (800 ms). The discrimination of target from nontarget frames thus required continuous monitoring, placing significant demands on sustained attention and engendering frequent attentional lapses. To avoid eye movements, participants were instructed to fixate on a centrally presented white cross throughout the task. The stimulus also flickered at a rate of 25 Hz to generate an SSVEP that served as a measure of basic visual stimulus processing.

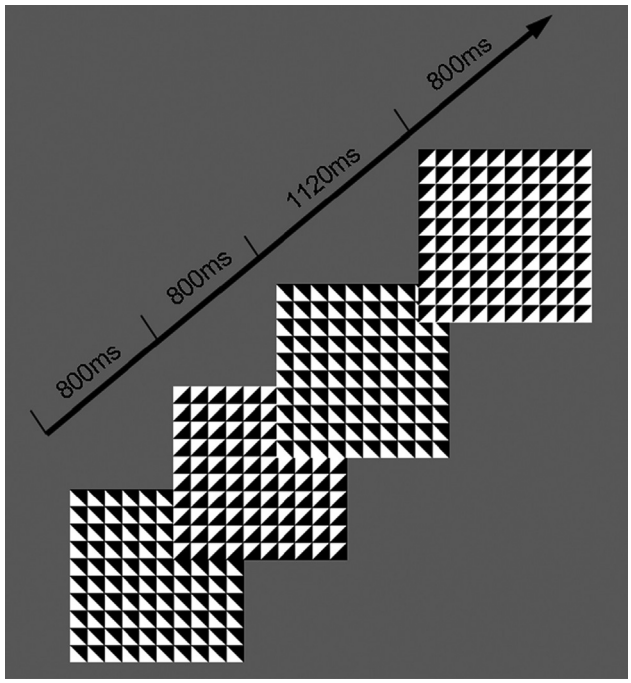

Figure 1. Task schematic for Continuous Temporal Expectancy Task. Participants monitored a continuous stream of patterned stimuli centrally presented and flickering at a rate of 25 Hz. Standard stimuli were presented for 800 ms, and participants were required to monitor for the occurrence of target stimuli defined by their longer duration (1120 ms) relative to other stimuli. Target detection was indicated by a speeded button press. All participants were practiced to a criterion level of performance and completed 10 blocks of the task.

Behavioral Analysis

Performance was assessed by determining the proportion of targets that were correctly identified. Reaction time (RT) was measured relative to the point at which target frames became distinguishable from nontarget frames (800-ms poststimulus onset). Button presses were considered to represent target detections only if they occurred within two nontarget frames following the target frame (1600 ms). The proportion of targets detected was analyzed across all four conditions (MPH, ATM, CIT, and PLA). As reported in the Results, only MPH improved sustained attention. Therefore, all subsequent analyses focused on the direct comparison between the MPH and PLA conditions to isolate behavioral and electrocortical changes associated with MPH. In subsequent analyses, mean detection latency was calculated, and the coefficient of variation