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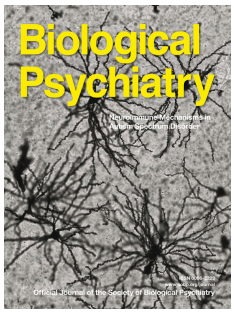

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The Effects of Methylphenidate on the Neural Signatures of Sustained Attention

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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 (EEG) precursors of lapsing attention over different time-scales.

Methods: We measured the impact of MPH, compared with placebo, on behavioural 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 α-activity that emerged over periods of several seconds. MPH led to an overall suppression of α-activity across the entire task but also diminished the frequency of these maladaptive pre-target increases through a reduction of α-variability. A drug-related linear increase in the amplitude of the frontal P3 event-related component was also observed in the pre-target timeframe (3 – 4 s). Further, 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 25Hz 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.

Trial Registration:

The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN)

(Trial ID: ACTRN12609000625279,

Url: http://www.anzctr.org.au/ACTRN12609000625279.aspx).

Scientific title: The effect of methylphenidate, atomoxetine and citalopram versus placebo on behavioural and physiological indices of executive control in healthy individuals.

Introduction

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 which may ultimately facilitate personalised approaches to treatment in disorders such as ADHD.

It is well established that MPH leads to reductions in behavioural 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 electro-cortical activity, associated with attentional control in humans, are augmented by MPH. Some electrophysiological studies have reported correlations of EEG power (averaged at rest or across task-active conditions) with MPH-related improvements in sustained attention (5-8). However, it is not apparent if these changes arise from direct augmentation of sustained attention mechanisms or indirectly through facilitation of task-relevant cortical regions. For example, behavioural 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 and colleagues (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 α-frequency

(8-14 Hz) was predictive of lapses and was observable up to 20s 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 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 impact sustained attention. Here, MPH was administered within a placebo-controlled, double-blinded, cross-over design while participants undertook the CTET EEG paradigm. We first examined the efficacy of MPH to influence neural signals at different timescales: 1) across the entire task; 2) in the pre-target interval; and 3) in the immediate period of target processing. Next, we established whether MPH impacted 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.

Materials and methods

Participants

Forty 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 18-45, right-handed, non-smoking, 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 M.I.N.I. Screen 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 (2014) (11).

Study design and drug administration

A randomised, double-blinded, placebo-controlled, four-arm cross-over design was employed (11). Each participant attended four sessions at the same time of day, spaced at least one week apart. At each session, a single blue gelatine capsule containing methylphenidate (MPH, 30 mg, mixed dopaminergic and noradrenergic action), atomoxetine (ATM, 60 mg, primarily noradrenergic action), citalopram (CIT, 30 mg, primarily serotonergic action) or placebo (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 upon clinical relevance (15-17) and demonstrated cognitive effects (18-20).

Continuous temporal expectancy task (CTET)

Full details of the task are provided in Supplementary Materials and in O'Connell et al (2009) (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 non-target 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 in order to generate a steady-state visually evoked potential (SSVEP) that served as a measure of basic visual stimulus processing.

Behavioural analysis

Performance was assessed by determining the proportion of targets that were correctly identified. Reaction time was measured relative to the point at which target frames became distinguishable from non-target frames (800 ms post stimulus onset). Button presses were only considered to represent target detections if they occurred within 2 non-target frames following the target frame (1600ms). The proportion of targets detected was analysed across all four conditions (MPH, ATM, CIT, 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 behavioural and electrocortical changes associated with MPH. In subsequent analyses,

mean detection latency was calculated, and the coefficient of variation (standard deviation/mean detection latency) was derived as a measure of response variability for target detection. Each measure was analysed using repeated measures statistics with Bonferroni correction. Subjective ratings of alertness were measured using a visual analogue scale (21); see supplementary material.

EEG recording

EEG was recorded using an ActiveTwo BioSemi system of 64 scalp electrodes with an equiradial montage (https://www.biosemi.com/headcap.htm), sampled at 1024 Hz. Vertical eye movements were recorded with two vertical electrooculogram (EOG) electrodes placed above and below the left eye, while horizontal eye movements were recorded with two horizontal EOG electrodes placed at the outer canthus of each eye.

Electrophysiological Analysis

Data were pre-processed using MATLAB (The Mathworks, Inc.) and the EEGlab plug-in (22). Pre-processing involved resampling the data to 512 Hz, applying a 40 Hz low-pass filter and re-referencing data offline to the average of all scalp electrodes. All electrode channels were subjected to an artifact criterion of 100 mV to reject trials with excessive EOG or other noise transients. To remove errors that may have arisen from blinking rather than true failures of attention, a 4 s interval prior to each target trial was scanned, and any trial that included an artifact (100 mV) that was evident across eight or more channels was excluded from all analyses.

Long-term analysis of the EEG amplitude spectrum: A fast-Fourier transform (FFT) was carried out for all standard frames across all 10 blocks of the CTET. Amplitude spectra, comprising the time period -80 to 800 ms relative to standard frame onset, were extracted. Grand average spectra were obtained for activity in the α-band (8-14 Hz) and the SSVEP (25 Hz) for each Drug condition (MPH, PLA). α-amplitude was measured from a cluster of parietal and occipital electrodes (CPz, Pz, POz) and SSVEP amplitude was measured from a midline occipital electrode (Oz) guided by field pattern distribution on the scalp topographies, centred where amplitude was maximal. Paired t-tests were conducted to examine differences in α-band and SSVEP amplitude and α-amplitude variability (stdev/mean) as a function of drug condition.

Short-term analysis of the pre-target interval: ERP and oscillatory measures of EEG activity were examined in a time period of 4 seconds that encompassed four standard frames and the subsequent target frame. This time period was chosen to allow investigation of pre-target activity without including activity related to previous target frames, as the minimum interval between targets was 5.6 seconds. An FFT was applied to derive α-band (8-14 Hz) and SSVEP (25 Hz) amplitude spectra across the epoch -3200 to 800 ms relative to target frame onset. Amplitude measurements were taken from the same scalp sites as described above for the analysis of the whole task period.

ERP components of interest were guided by O'Connell et al (2009) (9). Time intervals for the measurement of ERPs and the definition of baseline periods were in multiples of 40 ms, incorporating an integer number of SSVEP cycles, which prevented contamination of activity by residual SSVEP power following notch filtering. The 5 frames that comprised an epoch were baseline corrected separately to the time period -80 to 0 relative to each frame onset. Peak amplitude measurements, relative to pre-stimulus baseline activity for each component of interest were extracted. First, the visual P1 was extracted from a cluster of occipital scalp electrode sites (O1, Oz, O2) between 95-135 ms. Second, a

frontal positive potential labeled standard-P3 was measured from a cluster of frontal scalp electrode sites (FC1, FCz, FC2) between 225-285 ms. Data for each component were analysed using a repeated measures ANOVA with factors, Drug (MPH, PLA), Accuracy (hit, miss) and Frame (standard -4, standard -3, standard -2, standard -1, target frame). The number of trials was equated for Hit and Miss conditions for each participant. The mean (min, max) number of trials for the MPH condition was 46.38 (12, 99), and the Placebo condition was 50.34 (13, 92). There was no statistical difference in number of trials across the two Drug conditions, $t<1$.

Analysis of immediate target period: Stimulus-locked data were segmented into epochs of 100 ms before to 2000 ms after target frame onset and averaged according to Drug (MPH, PLA) and accuracy (Hits, Misses). Target epochs were baseline corrected to the pre-stimulus interval and any epochs with absolute amplitude values exceeding 100mV were excluded from analysis. The parietal P3 was confirmed by visual inspection of grand-average waveforms and scalp topographies and measured from scalp electrode site Pz. The width of the latency window used to measure component peak amplitudes was 1250ms to 1800ms relative to the onset of the target frame. The P3 onset latency was calculated as the time point at which the P3 signal reaches half of its peak voltage (23). P3 peak latency variability was calculated using the coefficient of variation (peak amplitude variability/mean amplitude).

Results

Behavioural analysis

There was a significant effect of drug across all conditions (n=33) on the proportion of targets detected (see Table 1), $F(3,96)=14.42$, $p<.0001$, $\eta^2p = .31$. Pairwise comparisons showed that MPH increased the proportion of targets detected relative to placebo ($p=.001$), ATM ($p=.0001$) and CIT ($p=.0001$). ATM was not significantly different from PLA ($p = .671$). There was a marginal reduction of performance in the CIT condition compared to PLA ($p = .033$) but this did not survive Bonferroni correction ($p < .01$).

Subsequent analysis was restricted to MPH vs. PLA (n=36). MPH had no significant impact on Reaction Time (RT), $t(35) = 1.54$, $p = .13$, $d = 0.26$. However, we found that participants' RT variability, as measured by the coefficient of variation, was reduced in the MPH condition compared to the PLA condition, $t(35) = 3.42$, $p = .002$, $d = 0.56$[1] (see Table 2). Individual subject data are summarised in supplementary Fig. S2.

A 2 × 10 ANOVA with the factors, Drug (MPH, PLA) and Block (1 to 10) was conducted to examine time-on-task effects on the target detection accuracy. There was a Drug × Block interaction, $F(9, 279) = 2.38$, $p = .013$, $\eta^2p = .07$, driven by a marked linear decrease in performance in the PLA condition with time ($p = .0001$, $\eta^2p = .36$), which was offset by MPH ($p = .84$) (see supplementary Fig. S1a).

[1] N.b. The behavioural effects for target detection ($p = 0.0001$) and RT variability ($p = 0.003$) remained when conducted on the smallest subset of the sample (n=29) used for EEG analysis.

Electrophysiological Analysis[2]

Long-term drug effects on the EEG amplitude spectrum

We first examined EEG spectral amplitude changes induced by MPH across the entire task (*n*=32), averaged across all non-target frames (See Figure 2).

Parietal Alpha (8-14 Hz): Participants exhibited a reduction in mean α-amplitude in the MPH compared with PLA condition, $t(31) = 2.63$, $p = .013$, $d = 0.46$. We also observed a decrease in mean α-amplitude variability in the MPH compared with the PLA condition, $t(31) = 2.58$, $p = .015$, $d = 0.46$.

A subsequent Drug x Block analysis of mean α-amplitude revealed a main effect of Block, $F(9, 279) = 2.19$, $p = .023$, $\eta^2 p = .07$, indicative of a time-on-task increase in α-amplitude from its lowest amplitude in block 2 to its highest in the last block (p = .01, $\eta^2 p = .2$). See supplementary Fig. S1b. There was no Drug x Block interaction, $F<1$.

SSVEP (25Hz): SSVEP amplitudes over occipital scalp were not significantly influenced by Drug condition, $t < 1$, indicating that basic visual processing was not significantly enhanced by MPH. However, Bayesian analysis did not provide evidence in favour of the null hypothesis of no difference between conditions, $B_{H(0,10)} = 0.98$[3].

Short-term drug effects in the pre-target interval

[2] Tables of means and standard deviations are presesented for all EEG analyses in the supplementary materials.

[3] Criteria for calcuating Bayes Factors are described in the supplementary materials.

Divergences in spectral and ERP amplitude changes were analysed within a 4 s time-frame before target onset as a function of Drug condition (*n*=29) (See Figure 3).

Parietal Alpha (8-14 Hz): A 2 × 2 ANOVA, with the factors Drug (MPH, PLA) and Accuracy (Hit, Miss), revealed a main effect of Accuracy, $F(1,28) = 6.91$, $p = .014$, $\eta^2p = .20$, indicating reduced α-amplitude prior to target hits compared to target misses. There was also a main effect of Drug, $F(1,28) = 4.63$, $p=0.04$, $\eta^2p = .14$, driven by reduced α-amplitude in the pre-target period for the MPH compared with PLA condition. There was no Drug × Accuracy interaction, $F < 1$.

SSVEP (25 Hz): A further 2 × 2 ANOVA found no main effect of Drug, $F < 1$, Accuracy, $F < 1$, or Drug × Accuracy interaction, $F(1, 28) = 1.82$, $p = .19$, $\eta^2p = .06$

P3 to standards:. P3 peak amplitude measures were entered into a 2 × 2 × 5 ANOVA with factors of Drug (MPH, PLA), Accuracy (Hit, Miss) and Frame, representing each frame in the 4 s interval up to the target frame (i.e. standard -4, standard -3, standard -2, standard -1, target frame). There was a significant main effect of Accuracy, $F(1,28) = 49.07$, $p < .0001$, $\eta^2p = .64$, indicating larger P3 peak amplitudes prior to hits than misses. However, there was no main effect of Drug, $F(1,28) = 2.61$, $p = .117$, $\eta^2p = .09$, or Frame, $F(4, 112) = 2.28$, $p = .07$, $\eta^2p = .08$, and no significant interactions for Drug × Accuracy, $F(1,28) = 2.60$, $p = .12$, $\eta^2p = .08$, nor Drug × Accuracy × Frame, $F < 1$. There was however a significant Drug × Frame interaction, $F(4, 112) = 2.59$, $p = .04$, $\eta^2p = .09$. Polynominal contrasts revealed a linear trend in the MPH condition with increasing P3 amplitude across non-target frames until the target frame ($p = .017$, $\eta^2p = .19$), which was absent in the placebo condition ($p = .62$). The numerical increase in the P3 amplitude across frames in the MPH condition was significantly different from the placebo condition on the target frame ($p = .003$, $d = 0.6$).

Occipital P1: A further 2 × 2 × 5 ANOVA was conducted for the peak P1 amplitude measures. There was no signficant effect of Drug, $F < 1$. Further, Bayesian analysis did not find evidence in support of the null hypothesis predicting no difference between conditions, $B_{H(0,27)} = 0.63$. There were no effects of Accuracy, $F < 1$, Frame, $F(4, 112) = 3.08$, $p = .067$, $\eta^2p = .10$, Drug x Accuracy, $F(1, 28) = 2.05$, $p = .16$, $\eta^2p = .07$, or Drug x Accuracy x Frame interaction, $F < 1$.

Drug effects on target processing

To examine the effects of Drug and Accuracy on immediate target processing (n=33), three features of the parietal P3 component – peak amplitude, peak latency variability and onset latency – were analysed with 2 × 2 factorial ANOVAs. Figure 5 illustrates the amplitude and onset latency effects for the parietal P3.

Parietal P3 peak amplitude: We observed a main effect of Accuracy, $F(1,32) = 57.35$, $p < .0001$, $\eta^2p = .64$, driven by greater peak amplitudes on target hits compared with misses. There was also a main effect of Drug, $F(1,32) = 25.99$, $p < .0001$, $\eta^2p = .45$, indicating greater peak amplitudes under MPH compared with PLA, and there was no Drug × Accuracy interaction, $F(1,32) = 1.92$, $p = .18$. $\eta^2p = .06$

Parietal P3 onset latency: Onset latency was significantly earlier for target hits compared with misses, $F(1,32) = 45.62$, $p < .0001$, $\eta^2p = .59$ but there was no effect of Drug $F(1,32) = 1.26$, $p = .27$, $\eta^2p = .04$ and no Drug × Accuracy interaction, $F < 1$.

Parietal P3 peak latency variability: There was a main effect of Accuracy, $F(1,32) = 7.04$, $p = .01$, $\eta^2p = .18$, indicating that peak latency variability was reduced on target hits

307 compared with misses. There was no effect of Drug, $F < 1$, or Drug × Accuracy
308 interaction, $F < 1$.
309

Discussion

This study examined the modulation of electrophysiological precursors of lapsing attention by MPH. Our findings demonstrate that MPH affects both the oscillatory dynamics in the α-band during sustained attention and shorter-term ERP signals in the period before and during target processing. MPH acts to avert lapses of attention and time-on-task performance decrements by reducing maladaptive neural synchronisation in the α-band over a broader time-scale, indicative of a change in attentional state or tonic alertness. Further, MPH led to a reduction in α-variability indicating that such fluctuations were less frequent. MPH affected the frontal P3 signal, which showed a linear increase in amplitude in the pre-target period, indicative of improved task monitoring. The parietal P3 peak amplitude during the target frame was also modulated by MPH suggesting that the drug refines endogenous mechanisms that support the temporal integration of perceptual evidence required for target detection. By contrast, there was no significant effect of MPH on early sensory processing, measured by SSVEP (25 Hz) and visual P1 amplitude.

These data demonstrate that attentional enhancement by MPH is supported by augmentation of electro-cortical signals across multiple times-scales, from shorter-term, phasic increases in target-related activity (P3) to longer-term tonic suppression of neural synchronisation and variability in the α-band. In so doing, this study identifies novel markers to further understand the physiology of disorders of attention, such as ADHD, or to be leveraged as surrogate endpoints for pharmacological interventions.

Greater α-band activity has previously been shown to be a strong predictor of attentional lapses during the CTET (9) and we replicate this effect here. Importantly, we also found that MPH suppressed α-amplitude and rendered oscillatory α-activity less variable across the entire task. Furthermore, α-amplitude increased with time-on-task in

both conditions but remained at a lower amplitude throughout in the MPH condition, suggesting that the threshold at which mental fatigue compromises sustained attention may be increased with MPH. Increased α-amplitude has traditionally been thought to reflect cortical idling (24) and is associated with the emergence of a resting state (25, 26) in which goal-directed processes are diminished in the absence of task engagement. An alternative view, based on the α-inhibition hypothesis (27), proposes that α-synchronisation reflects re-allocation of attention from an outward to an inward focus (28, 29), thus inhibition of task processing may occur during periods of task-unrelated thought that culminate in error.

Simultaneous EEG-fMRI has demonstrated that α-oscillations correlate with a cingulo-insular-thalamic network, which have been implicated in the maintenance of tonic alertness (30). It is noteworthy that MPH not only suppressed α-activity but also minimised the frequency of α-signal fluctuations (after controlling for differences in amplitude), facilitating the maintenance of more stable α-levels associated with improved behavioural performance. This effect is of significance given greater trial-by-trial performance variability (31, 32) and neural variability (33) are prominent features in clinical disorders of attention such as ADHD. A potential mechanism by which MPH could modulate EEG alpha is through an agonistic effect on D2 receptors located in the thalamus (34) and stimulation of dopaminergic transmission via thalamocortical and mesocortical pathways.

There was no significant neuromodulatory effect of MPH on early visual activity, measured by SSVEP amplitude across the entire task and neither the drug nor attention performance affected SSVEP or P1 amplitude during the pre-target 4 s period. However, Bayes Factors calculated for these non-significant effects of drug revealed no substantive evidence in support of the null hypothesis. Nevertheless, it appears reasonable to conclude that, if MPH does impact on early visual processing, its effects

366 are weak in comparison to the much stronger changes observed in posterior α-band
367 activity.
368
369 In addition to changes in α-activity over longer timescales, we also observed short-term
370 changes in P3 signals. We found that a frontal P3 component was diminished in
371 amplitude prior to misses in the pre-target interval, reproducing the same effect
372 observed by O'Connell and colleagues (9) Furthermore, we found that MPH induced a
373 linear increase in P3 amplitude in the pre-target period. These short-term changes
374 suggest that MPH may help offset transient disengagement of monitoring processes
375 that foreshadow lapses of attention. Previous work has shown that P3 amplitude is
376 enhanced by improved regularity of perceived rhythm (35) and enhanced attention to
377 the regularity of the temporal pattern of the CTET may, in part, underlie the increase in
378 P3 amplitude with MPH.
379
380 MPH also increased the amplitude of the parietal P3 during target detection. Recent
381 research suggests that a centro-parietal positive (CPP) waveform bears a strong
382 functional similarity to the parietal P3 and has a specific role in the formation of target
383 decisions (36). The dynamics of this signal traces cummulative evidence of perceptual
384 information as it evolves over time and can be clearly dissociated from signals that
385 represent the sensory evidence (e.g., SSVEP) or motor preparation (e.g., left hemisphere
386 beta band activity) (37). In the current study, the target frame could only be
387 discriminated from a standard frame on the basis of a temporal judgment - in all other
388 respects, the target and standard frames were perceptually the same. We interpret the
389 parietal P3, as functionally equivalent to the CCP, and reflecting an endogenous process
390 of accumulating perceptual information to support a target decision. MPH therefore
391 engenders greater accumulation of perceptual evidence, and we note that under MPH,
392 even the attenuated P3 signal for missed targets was greater in amplitude than in the
393 placebo condition and, hence, nearer a threshold level for detection. In addition to its

effect on the dopaminergic system, animal studies have reported that MPH exerts modest changes in locus coeruleus-noradrenergic (LC-NA) discharge (38). It is therefore possible that the MPH-related enhancement of the P3 may, in part, reflect noradrenergic modulation because of the strong similarities between the P3 and the phasic LC-NA responses (39, 40).

In conclusion, the indirect agonistic effect of MPH on dopamine and noradrenaline affected the electrophysiological signatures of sustained attention over different time-scales. We observed suppression of α-amplitude and variability supporting maintenance of tonic alertness over longer time-scales and the enhancement of P3 event-related components supporting task-related endogenous processes over shorter time-scales. At both time-scales there was an absence of change to bottom-up sensory excitability with MPH. These findings show specificity in the electrophysiological basis by which MPH improves sustained attention and decision-making offering candidate markers for remediation of clinical disorders of attention

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Table/Figure Legends

Table 1. Proportion of targets detected for the Methylphenidate (MPH), Atomoxetine (ATM) Citalopram (CIT) and Placebo (PLA) conditions (n=33).

Table 2. Behavioural Results (n=36) for Methylphenidate (MPH) vs. Placebo (PLA). Mean (standard deviation) for the proportion of targets detected, reaction time (RT) and the coefficient of variation (RT standard deviation/RT mean).

Figure 1. Task Schematic for Continuous Temporal Expectancy Task (CTET). 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.

Figure 2. (A) Fast Fourier Transform (FFT) showing suppression of α band amplitude (8-14Hz) in MPH vs. PLA condition, shown for posterior scalp site (Pz). Inset figure: α band amplitude variability (stdev/mean) for each subject, showing that MPH reduces alpha signal variability in the vast majority of subjects. (B) FFT showing parity of SSVEP (25 Hz) amplitude in MPH vs. PLA condition.

Figure 3. (A) FFT showing greater suppression of α band amplitude (8-14 Hz) in 4 s period prior to a 'hit' vs. a 'miss' Greater suppression is also observed in this period for MPH vs. PLA (shown for parietal scalp site Pz). (B) FFT showing no changes in SSVEP (25 Hz) amplitude in the pre-target 4 s interval as a function of accuracy or drug condition (shown for occipital scalp site Oz).

Figure 4. (A) Grand-average frontal P3 waveform for five frames in the 4 s interval preceding the target. The P3 was predictive of accuracy exhibiting greater peak amplitudes prior to a hit than a miss. There was a systematic linear increase in P3 amplitude across frames in the MPH condition but not in the PLA condition. Differences between MPH and PLA were apparent on the final target frame. (B) Grand-average Occipital P1 waveform. No changes in the P1 component were observed in the pre-target 4 s interval as a function of accuracy or drug condition.

Figure 5 . Grand-average parietal P3 component stimulus locked to the onset of the target (shown for parietal scalp site Pz). In the MPH condition, compared to placebo, there was an increased peak P3 amplitude. There was also a greater peak amplitude on target hits compared to target misses. Furthermore, onset latency was earlier for target hits compared to misses. There was no effect of drug on onset latency of the P3. Note that a target frame can only be identified by participants when the frame duration passes that of a standard frame (800 –1120 ms). We describe this period as the target interval and it is marked by dashed vertical lines

TABLE 1

	Methylphenidate (MPH)	**Atomoxetine (ATM)**	**Citalopram (CIT)**	**Placebo (PLA)**	***p* value & effect size**
Mean proportion of targets detected (n=33)	**0.75 (0.22)**	**0.63 (0.20)**	**0.60 (0.23)**	**0.64 (0.24)**	**p<.0001,** η_p^2 **= .31**

TABLE 2

	Methylphenidate (MPH)	Placebo (PLA)	***p* value & effect size**
Mean proportion of targets detected **(n=36)**	0.74 (0.21)	0.63 (0.23)	***p* = 0.0001, *d* = 0.78**
Mean reaction time (RT); **ms**	581 (109)	602 (96)	***p* = .13, *d* = 0.26**
Mean coefficient of variation; **std/mean RT**	0.22 (0.04)	0.24 (0.06)	***p* = .002, *d* = 0.56**

FIGURE 1

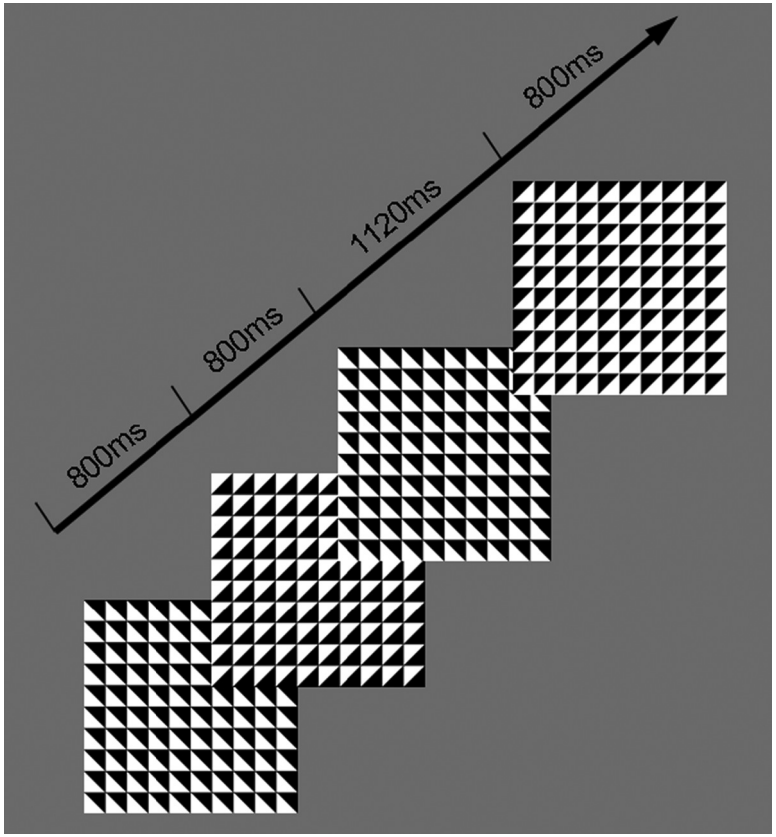


FIGURE 2

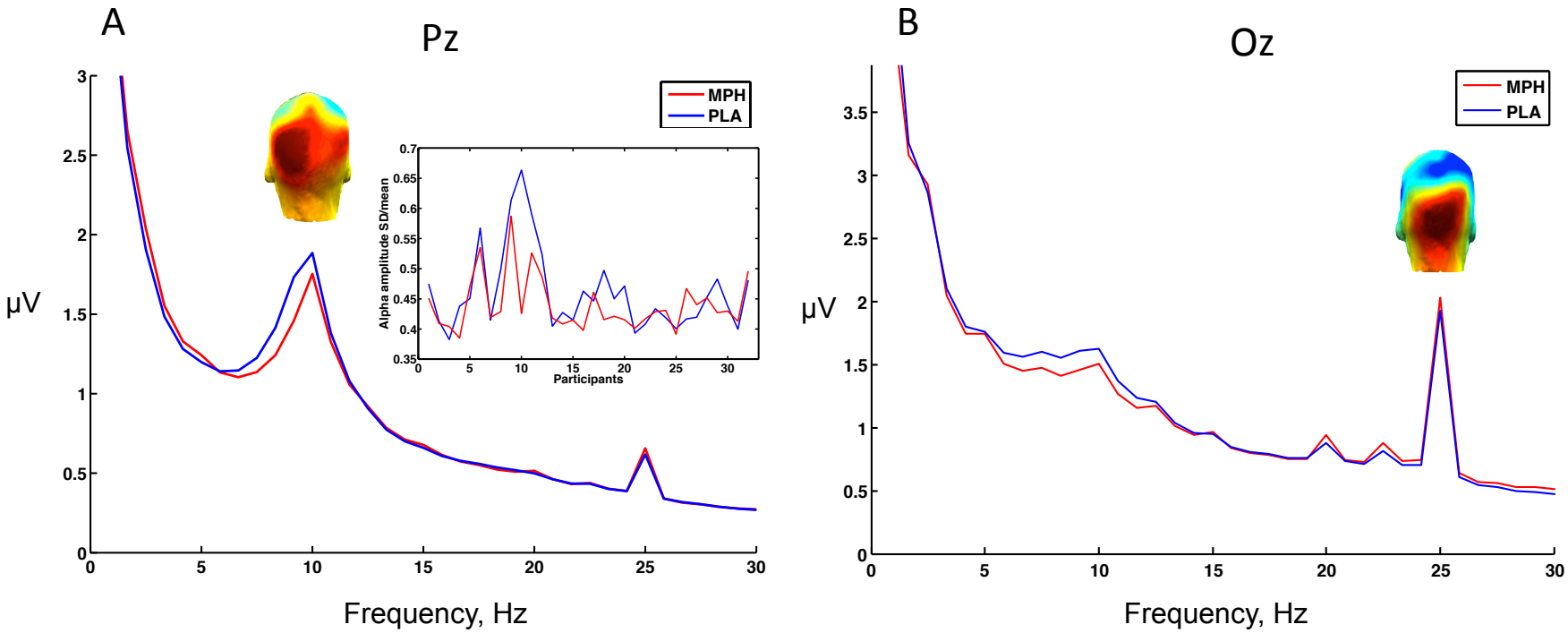

A
Pz
MPH
PLA
μV
Frequency, Hz
Alpha amplitude SD/mean
Participants
B
Oz
MPH
PLA
μV
Frequency, Hz

FIGURE 3

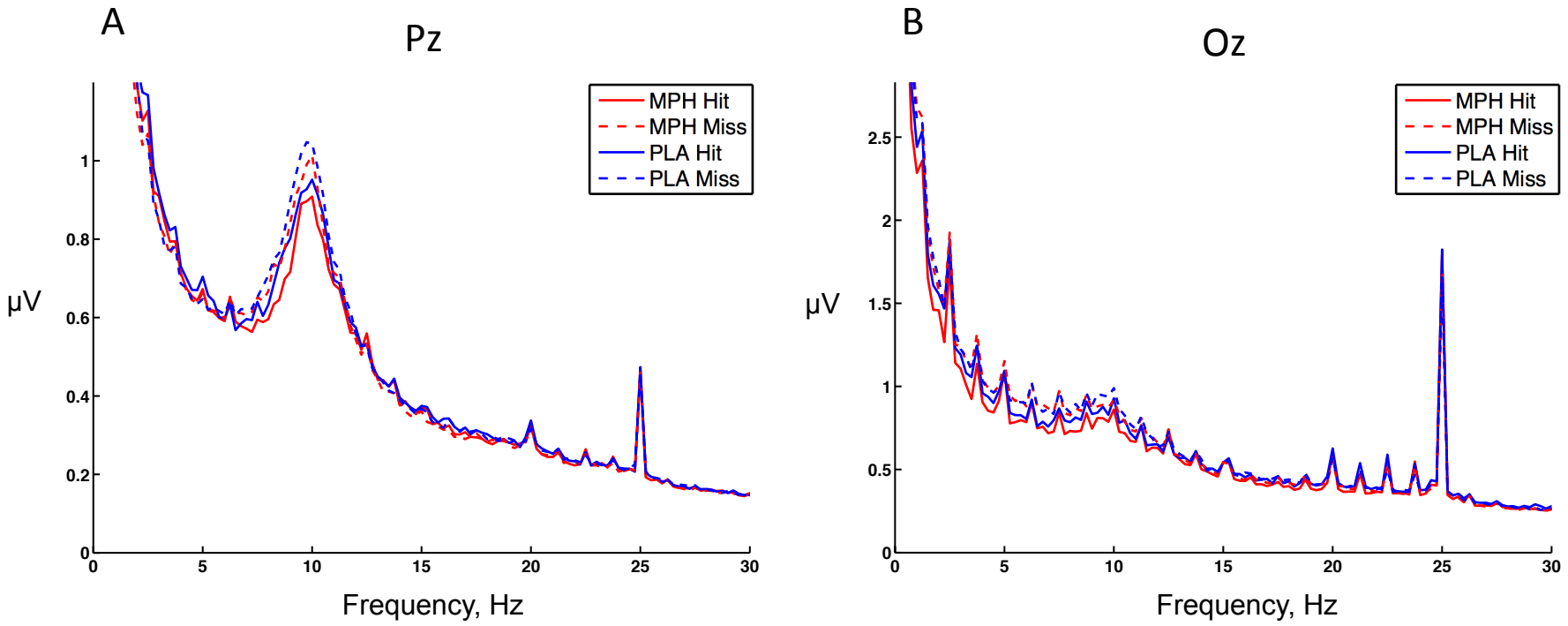

A
Pz
MPH Hit
MPH Miss
PLA Hit
PLA Miss
μV
0
0.2
0.4
0.6
0.8
1
0
5
10
15
20
25
30
Frequency, Hz
B
Oz
MPH Hit
MPH Miss
PLA Hit
PLA Miss
μV
0
0.5
1
1.5
2
2.5
0
5
10
15
20
25
30
Frequency, Hz

FIGURE 4

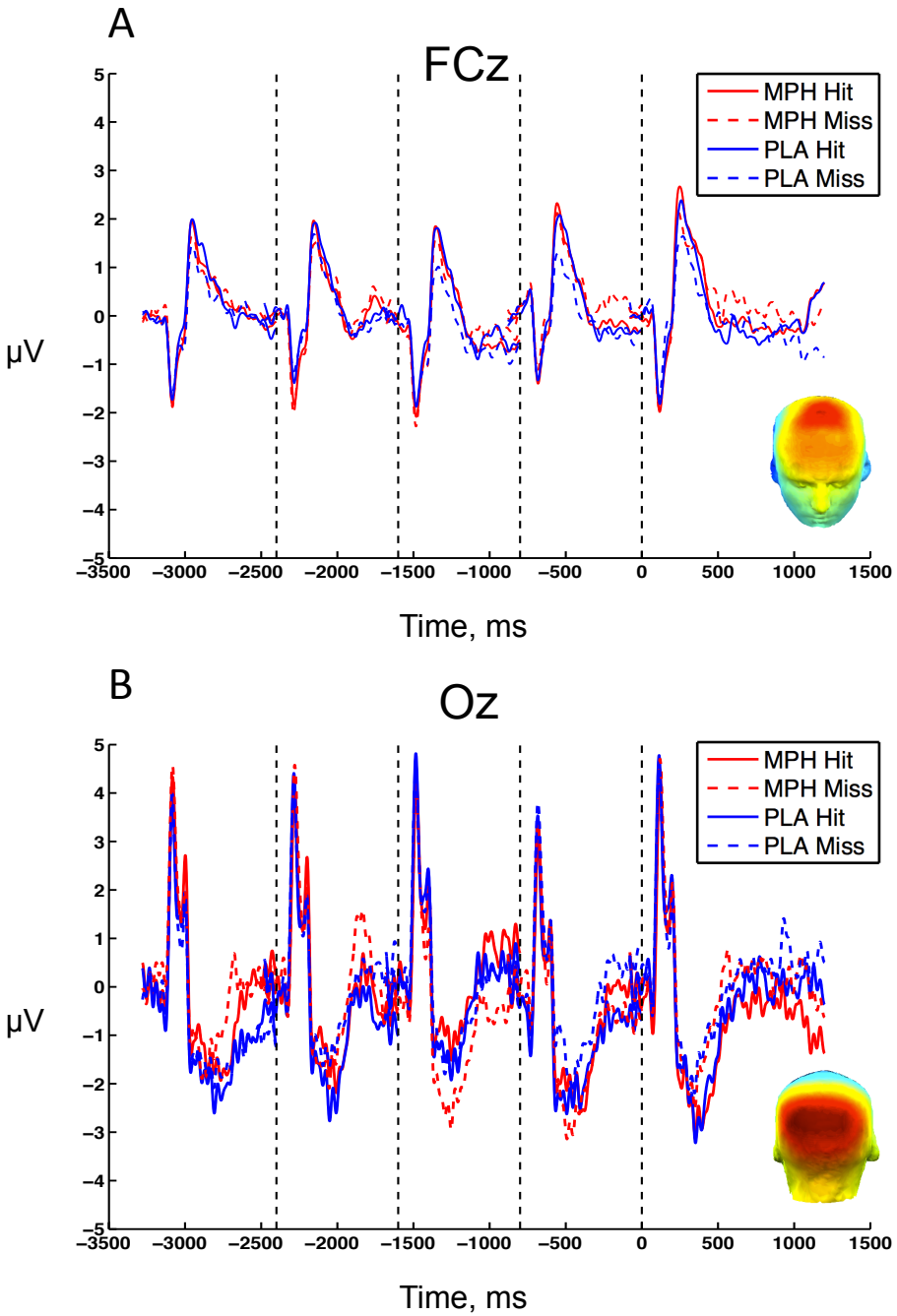
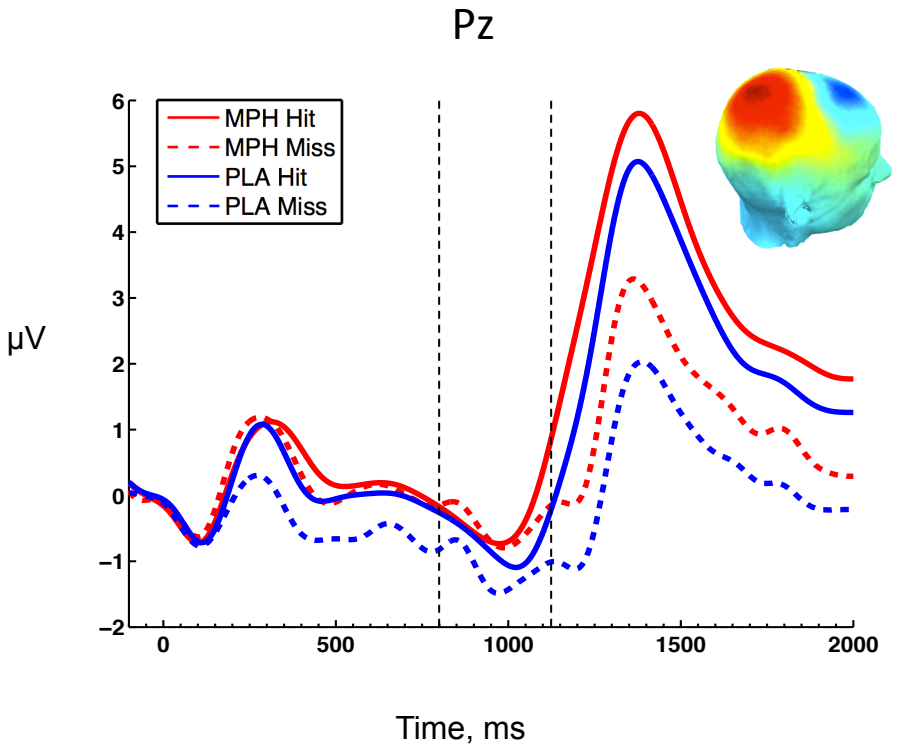

A
FCz
MPH Hit
MPH Miss
PLA Hit
PLA Miss
μV
5
4
3
2
1
0
−1
−2
−3
−4
−5
−3500
−3000
−2500
−2000
−1500
−1000
−500
0
500
1000
1500
Time, ms
B
Oz
MPH Hit
MPH Miss
PLA Hit
PLA Miss
μV
Time, ms

FIGURE 5


Pz
MPH Hit
MPH Miss
PLA Hit
PLA Miss
μV
6
5
4
3
2
1
0
−1
−2
0
500
1000
1500
2000
Time, ms