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Behavioral and neurophysiological signatures of cognitive control in humans and rats

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Abstract

Background: Deficits in cognitive control are implicated in numerous neuropsychiatric disorders. However, relevant pharmacological treatments are limited, likely due to weak translational validity of applicable preclinical models used. Neural indices derived from electroencephalography may prove useful in comparing and translating the effects of cognition-enhancing drugs between species. In the current study, we aimed to extend our previous cross-species results by examining if methylphenidate (MPH) modulates behavioral and neural indices of cognitive control in independent cohorts of humans and rats.

Methods: We measured continuous electroencephalography data from healthy adults (n = 25; 14 female) and Long Evans rats (n = 22; 8 female) and compared both stimulus- and response-locked event-related potentials and spectral power measures across species, and their MPH-related moderation following treatment with vehicle (placebo) or 1 of 2 doses of MPH.

Results: Across both species, linear mixed effects modeling confirmed the expected Flanker interference effect on behavior (eg, accuracy) and response-related event-related potentials. Unexpectedly, in contrast to past work, we did not observe any task-related effects on the spectral power of rodents. Moreover, MPH generally did not modulate cognitive control of either species, although some species-specific patterns offer insight for future research.

Conclusions: Collectively, these findings in independent human and rodent subjects replicate some of our previously reported behavioral and neurophysiological patterns partly consistent with the notion that similar neural mechanisms may regulate cognitive control in both species. Nonetheless, these results showcase an approach to accelerate translation using a coordinated between-species platform to evaluate pro-cognitive treatments.

Keywords: cross-species, electrophysiology, dopamine, cognitive control, cingulate

Significance Statement

EEG-based neurophysiological indices may enable the comparison and translation of the effects of pro-cognitive drug treatments across species. Using a modified Flanker task, we replicated and extended previously reported effects in humans and rats, observing the expected behavioral and neurophysiological indices and responses. Moreover, in both species, these indices were generally not modulated by methylphenidate, a cognition-enhancing drug. These results are partly consistent with the notion that similar neural mechanisms may regulate cognitive control in both species. Furthermore, our results highlight that EEG indices can be used to establish a coordinated between-species platform for evaluating cognition-enhancing drugs, and such a platform may enhance across-species translation.

INTRODUCTION

Cognitive control refers to the ability to regulate one's thoughts and actions in accordance with internally directed goals (Braver, 2012; Friedman and Miyake, 2017). While deficits in cognitive control are observed across neuropsychiatric disorders (Millan et al., 2012), the development of effective drugs to treat these deficits has been limited. This is due, in part, to weak translational

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validity of preclinical models relevant to the cognitive effects of drugs (Blokland et al., 2015) and psychiatric disorders (Barroca et al., 2022). EEG may be useful in evaluating cognition-enhancing drugs (Blokland et al., 2015), and recent efforts have focused on identifying translationally valid EEG markers of cognitive control (Cavanagh et al., 2021; Robble et al., 2021).

Cognitive control can be evaluated using the Eriksen Flanker task, which probes attention and response inhibition (Eriksen and Eriksen, 1974). In addition, when combined with EEG, the Flanker task offers the ability to evaluate the neural activation associated with cognitive control processes including discrimination (eg, incongruent/congruent trials) and error monitoring (eg, error/correct trials). For example, midfrontal theta activity may index the need for cognitive control, while event-related potentials (ERPs) including the negative frontocentral N2 and the error-related negativity (ERN) components (Cavanagh and Frank, 2014) index conflict and error monitoring, respectively. More specifically, the N2 is elicited by incongruency effects and tracks the need to inhibit incorrect responses (Folstein and Van Petten, 2008), while the ERN indexes the preconscious detection of committed errors (Nieuwenhuis et al., 2001). Both components have been localized to the anterior cingulate cortex (ACC) (Bekker et al., 2005; Yeung and Cohen, 2006), a region critically implicated in cognitive control (Cole and Schneider, 2007).

We recently developed a modified Flanker task for use with EEG in rats and humans (Kangas et al., 2021; Robble et al., 2021) and evaluated several neurophysiological metrics, including theta activity, the N2, the ERN, and the error positivity (Pe; an ERP indexing conscious awareness of error commission in humans (Wessel et al., 2011)). In both species, the task elicited an interference effect on accuracy (ie, greater accuracy for congruent vs incongruent trials), increased target-locked theta power for incongruent trials, and increased ERN and Pe following errors, suggesting that similar neural mechanisms may regulate cognitive control across species. However, while humans exhibited greater error-related theta power, rats displayed a suppression of ACC delta power. We postulated that this discrepancy may point to species-specific metrics and represent a functional and neural divergence. Both instrumental responding for reward and free access to food increases delta power in the rodent brain (Fu et al., 2008; Fujisawa and Buzsáki, 2011), suggesting that rats are driven by reward, whereas humans are driven by error avoidance and exhibit associated theta activation. Moreover, contrary to prediction, modafinil, a drug shown to improve human cognitive performance (Turner et al., 2003; Müller et al., 2013) and rodent inhibitory control (Morgan et al., 2007), did not modulate any neurophysiological measure. These findings provide a basis for further investigations to determine whether other cognition-enhancing drugs modulate these processes across species.

Here, we aimed to replicate our previous work (Robble et al., 2021) by using the same Flanker task to examine cognitive control in new cohorts of rats and humans. We predicted that we would observe greater midfrontal theta power and N2 amplitude in incongruent vs congruent trials, and greater theta power (humans), reduced delta power (rats), and greater ERN amplitude (both species) following erroneous versus correct responses. We then sought to extend this work by examining if methylphenidate (MPH) modulates these metrics. MPH blocks dopamine transporter and increases synaptic dopamine (DA) (Volkow et al., 2001, 2002). Previous research has found that MPH significantly increases Flanker accuracy and ERN amplitude (Barnes et al., 2014), as well as dorsal ACC activation in healthy adults (Hester et al., 2012). Thus, we expected that MPH would promote cognitive control across species and hypothesized that MPH would dose-dependently reduce Flanker effects, increase midfrontal theta power and N2 amplitude for incongruent trials, and increase error-related theta power and ERN amplitude.

MATERIALS AND METHODS

Humans

Twenty-five right-handed nonsmoking adults were recruited from the Greater Boston area. Data from 1 participant with less than 6 artifact-free ERP trials were excluded (Olvet and Hajcak, 2009), leaving a final sample of 24 adults (14 female) aged 27.66 ± 5.69 years (range: 18-40 years). Participants were psychologically healthy as assessed by the Structured Clinical Interview for DSM-V (First et al., 2016), had normal or corrected-to-normal vision, and no history of use of methylphenidate or other drugs with DA effects in the last 6 months or ≤5 lifetime uses. Participants abstained from caffeine for 12 hours before testing and were confirmed to have no current drug use (eg, cannabinoids, opiates, benzodiazepines, barbiturates, etc.) via urine screening before each session. Written informed consent was obtained in the presence of a physician who described the potential risks of taking MPH. The Mass General Brigham Institutional Review Board approved all human-related study procedures. Participants were compensated $50 USD for the diagnostic interview session, $75 USD per EEG session, and an additional $75 USD for completing all 3 EEG sessions for a possible total of $350 USD.

Human EEG Data Acquisition and Task Procedure

Continuous EEG data were recorded using a 96-channel equidistant spherical actiCAP and actiChamp amplifier (Brain Products GmbH, Gilching, Germany) digitized at 500 Hz using BrainVision Recorder Software. Data were referenced online to a vertex channel with a ground electrode located approximately at AFz, and impedances were maintained below the manufacturer recommended 25 KΩ.

Participants completed 3 EEG sessions, separated by at least 3 non-test days as part of a double-blind, placebo-controlled cross-over design. Two hours before each session, participants received either a placebo (0 mg), low (15 mg), or high (30 mg) dose of MPH. These doses were selected because they produce approximately 50% and 65% occupancy of striatal dopamine transporter, respectively, 2 hours after oral administration (Volkow et al., 1998). Moreover, in a prior human ERP Flanker study, a 30-mg dose improved accuracy and increased ERN amplitude (Barnes et al., 2014).

Each session began with recording 8 minutes of resting EEG data in 1-minute segments (4 minutes with eyes open, 4 minutes with eyes closed, with counterbalanced randomized order), followed by the modified Flanker task (Figure 1B; see Supplement for more detail) (Schroder et al., 2020, 2022) and a Probabilistic Reversal Learning task in an order counterbalanced across participants; the present study reports only the data from the Flanker task.

To encourage task engagement participants were told that they would receive additional compensation of 5 cents for each correct response. However, regardless of their performance, all participants were paid the full amount ($27 USD per session for a possible additional $81 USD).

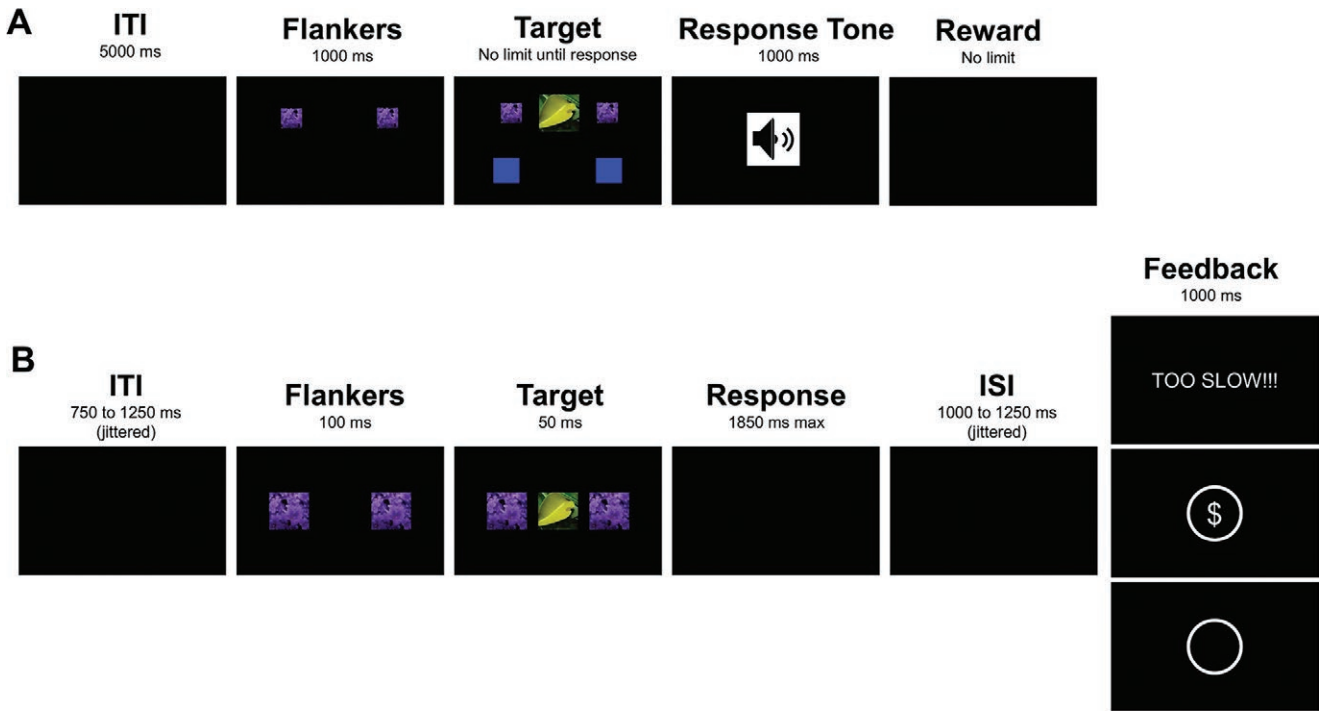

Figure 1. Task design. (A) Trial design for the rodent version of the modified Flanker task. In each trial, flankers were presented first for 1000 milliseconds, after which the target stimulus and 2 response boxes (shown in blue) were presented, and the rat had the opportunity to respond. Immediately following a response, a tone was presented for 1000 milliseconds to indicate accuracy, and correct responses were rewarded. (B) Trial design for the human version of the modified Flanker Task. After a short delay, flankers were presented for 100 milliseconds and then the target stimulus was presented for 50 milliseconds. After this time, the full stimulus complex was removed, and subjects had 1850 milliseconds to respond. Following the response period, there was jittered inter-stimulus interval which preceded the presentation of visual feedback to indicate accuracy and reward. (Reprinted with permission from Robble et al., 2021).

Human EEG Preprocessing

EEG data were processed offline using BrainVision Analyzer (version 2.2, Brain Products GmbH, Gilching, Germany). Raw EEG data were first visually inspected to remove gross muscle artifacts and data collected during task breaks and identify artifactual channels. Data were then filtered (0.1-30 Hz) using a second-order Butterworth zero-phase IIR filter. Next, independent component analysis was used to remove components identified as artifact (eg, eyeblinks and movements, cardiac and muscle signals). Artifactual channels were interpolated using spherical splines (Perrin et al., 1989), and data were re-referenced to the common average. Finally, data were segmented –1500 to 1500 milliseconds around the time-locking event, and epochs were rejected as artifact if any of the following conditions were met: (1) a voltage step ≥50 μV between datapoints, (2) a voltage difference >150 μV in 200-millisecond time intervals, (3) activity <0.5 μV for longer than 100 milliseconds, or (4) a maximum/minimum voltage exceeding ±75 μV.

Human ERPs

Using processed EEG data, target-locked epochs for correct congruent and incongruent trials were extracted (–250 to 700 milliseconds), baseline-corrected (–250 to 0 milliseconds) and averaged; only correct trials were extracted to align with past work investigating the N2 (Yeung et al., 2004). Using these data, the N2 component was derived as the mean amplitude 230 to 290 milliseconds post stimulus at channel 2 (approximating FCz). However, as this component was not presently or previously identified in rodents, these data are presented in the Supplement.

Response-locked epochs for correct and erroneous incongruent trials were also extracted (–800 to 700 milliseconds), baseline corrected (–800 to –700 milliseconds), and averaged; only incongruent trials were evaluated to avoid potential conflation of error- and congruency-related effects. ERN mean amplitudes were derived between 0 and 100 milliseconds post response and Pe mean amplitudes between 120 and 270 milliseconds post response from channel 9 (approximating Fz). Notably, for both target-locked and response-locked data, the selected epoch lengths, baseline correction periods, and measurement windows were selected to match those used in our previous study (Robble et al., 2021).

Human Time-Frequency Decomposition

Following artifact detection, power spectra from 1 to 30 Hz were computed in 30 logarithmic frequency steps by applying a complex Morlet wavelet transformation to both target- and response-locked epochs (–1500 to 1500 milliseconds) using a Morlet parameter of 3.5. We then calculated a percentage change baseline correction (BrainVision Analyzer 2.0 Solution by Dr. Ingmar Gutberlet; see Supplement for details) by averaging activity in the –500 to –300 millisecond prestimulus period and preresponse period for the target- and response-locked epochs, respectively. To examine changes in theta band activity, we extracted and averaged wavelet layers with center frequencies of 4.09, 4.59, 5.17, 5.81, and 6.53 Hz. Theta power values were exported from channels that align with our previous work (Robble et al., 2021); more specifically, between 300 and 500 milliseconds from channel 2 (approximating FCz) for target-locked data and between 0 and 200 milliseconds from channel 9 (approximating Fz) for

response-locked data. As with our ERP analyses, the time windows and channels selected for the time-frequency decomposition were identical to those used in our prior study (Robble et al., 2021).

Rats

Twenty-two Long-Evans rats (14 males weighing 226-250 g and 8 females weighing 176-200 g) were purchased from Charles River Laboratories (Wilmington, MA, USA). During training some animals experienced damage or disconnection of their electrodes, leading to EEG data missingness (n = 2-7 depending on the variable). Rats were maintained on a 12-hour light cycle (lights on 7:00 AM to 7:00 PM) with ad libitum access to water. During visual discrimination training (see Supplement for details) and Flanker task testing (Robble et al., 2021), the rats were food restricted, to motivate responding, via post-session feedings of either 7-10 g of rodent chow for females or 10-15 g of chow for males. Initially housed in groups of 3, the rats were singly housed following electrode implantation. All rodent-related procedures were consistent with the 2010 National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the McLean Hospital Institutional Animal Care and Use Committee.

Electrode Implantation

After training was successfully completed (see Supplement for details), rats underwent stereotaxic surgery to implant recording electrodes. For the procedure, rats were anesthetized with isoflurane (1.5%) and skull screw electrodes were bilaterally lowered to dura at a frontal site (AP: +3.7, ML: ±2.6) approximating the orbitofrontal cortex (OFC), and a single stainless-steel wire electrode was implanted unilaterally to record local field potentials from the ACC (AP: +2.7, ML: +0.8, DV: −2.1). Two skull screw electrodes, which served as reference and ground electrodes, were implanted at cerebellar sites. All electrodes were connected to an EIB-16 electrode interface board (Neuralynx, Bozeman, MT, USA) that was secured to the skull using dental acrylic. Electrode placement was confirmed post testing (see Supplement for details).

Rat Task Procedure

Once stable performance (minimum 70% accuracy for 2 consecutive sessions) was re-established post-surgery (see Supplement for details), rats were pretreated (10 minutes; s.c.) with either saline or 0.5 mg/kg or 1.0 mg/kg of MPH and completed test sessions that occurred in a mixed order across subjects using a within-subject Latin-square design. In rats, 1 mg/kg methylphenidate produces approximately 65% DAT occupancy 30 minutes after IP administration (Shimizu et al., 2019), which is equivalent to the 30-mg human dose, with peak occupancy occurring 2 minutes after administration. Between each testing session, rats were required to demonstrate successful discrimination performance (ie, at least 70% accuracy for 2 consecutive sessions); accordingly, MPH tests occurred no more than once per week.

Continuous electrophysiological recordings were obtained using the RHD-2000 recording system and supporting software (Intan Technologies, Los Angeles, CA, USA). Signals were locally digitized via a 16-channel headstage and continuously sampled at 1 kHz with a bandwidth range of 0.1-300 Hz for the duration of the session. The task consisted of 300 trials (Figure 1A) with no limited hold on responding (see Supplement for more detail). Correct responses resulted in the delivery of the previously paired correct tone and a sweetened condensed milk reward (30%; 0.1 mL/reinf). Incorrect responses were followed by the previously paired incorrect tone and no reward delivery.

Rat EEG Preprocessing

Signal analysis was performed using BrainVision Analyzer 2.0. Data were referenced offline to a cerebellar screw electrode and filtered using a Butterworth zero-phase IIR filter at 0.1 Hz (second order) and 30 Hz (eighth order). Trials were rejected if they exceeded an amplitude threshold of ±300 μV.

Rat ERPs

Target- (−1000 to 700 milliseconds) and response-locked (−500 to 2000 milliseconds) epochs were extracted, baseline-corrected (−500 to 0 milliseconds), and then averaged; response-locked epochs were only valid if responses occurred within 10 seconds of target onset. After averaging, no clear target-locked ERP component was observed (see Figure S1). However, from response-locked data we extracted ERN-like mean amplitudes between 115 and 265 milliseconds and Pe-like mean amplitudes between 300 and 600 milliseconds post response from the ACC channel for correct and erroneous incongruent trials. These epoch lengths, measurement windows, and channels were identical to those used in a previously published reported in an independent group of rats (Robble et al., 2021).

Rat Time-Frequency Decomposition

Power spectra were also derived from the rodent EEG data via complex Morlet wavelet transformation. Using a Morlet parameter of 3.5, power spectra from 0.5 to 30 Hz in 30 logarithmically distributed frequency steps were computed for both target- (−1000 to 1000 milliseconds) and response-locked (−500 to 1500 milliseconds) epochs. A percentage change baseline correction was implemented by averaging the amplitude in a −300 to −100 milliseconds prestimulus and preresponse windows. Changes in target-locked theta band activity were examined by extracting and averaging wavelet layers with center frequencies of 3.61, 4.16, 4.79, 5.51, 6.35, and 7.31 Hz between 50 and 250 milliseconds from the right frontal screw for correct congruent and incongruent trials. Changes in response-locked delta band activity were evaluated by extracting and averaging wavelet layers with center frequencies of 1.01, 1.17, 1.34, 1.55, 1.78, and 2.05 Hz between 200 and 600 milliseconds from the ACC channel for correct and erroneous incongruent trials. Again, the selected time windows and channels were identical to those used in our recent study (Robble et al., 2021).

Statistical Analyses

Power Analysis

The present sample sizes were informed by power calculations estimated using the average effect sizes previously observed (Robble et al., 2021). In humans and rats, respectively, the average $\eta p2$ value for behavioral task effects were 0.89 and 0.97, and the average neural effect was 0.68 and 0.79. As pharmacological effects were not previously observed (Robble et al., 2021), we used a $\eta p2$ value of 0.5 in our estimation. Using these effect sizes, the present cohorts of n = 24 humans and n = 22 rats estimate a power ≥.99 for detecting both task and pharmacological effects.

Modeling

Across species, linear mixed effects models were used to examine between-condition differences in measures of cognitive control. Models were estimated separately for each measure in

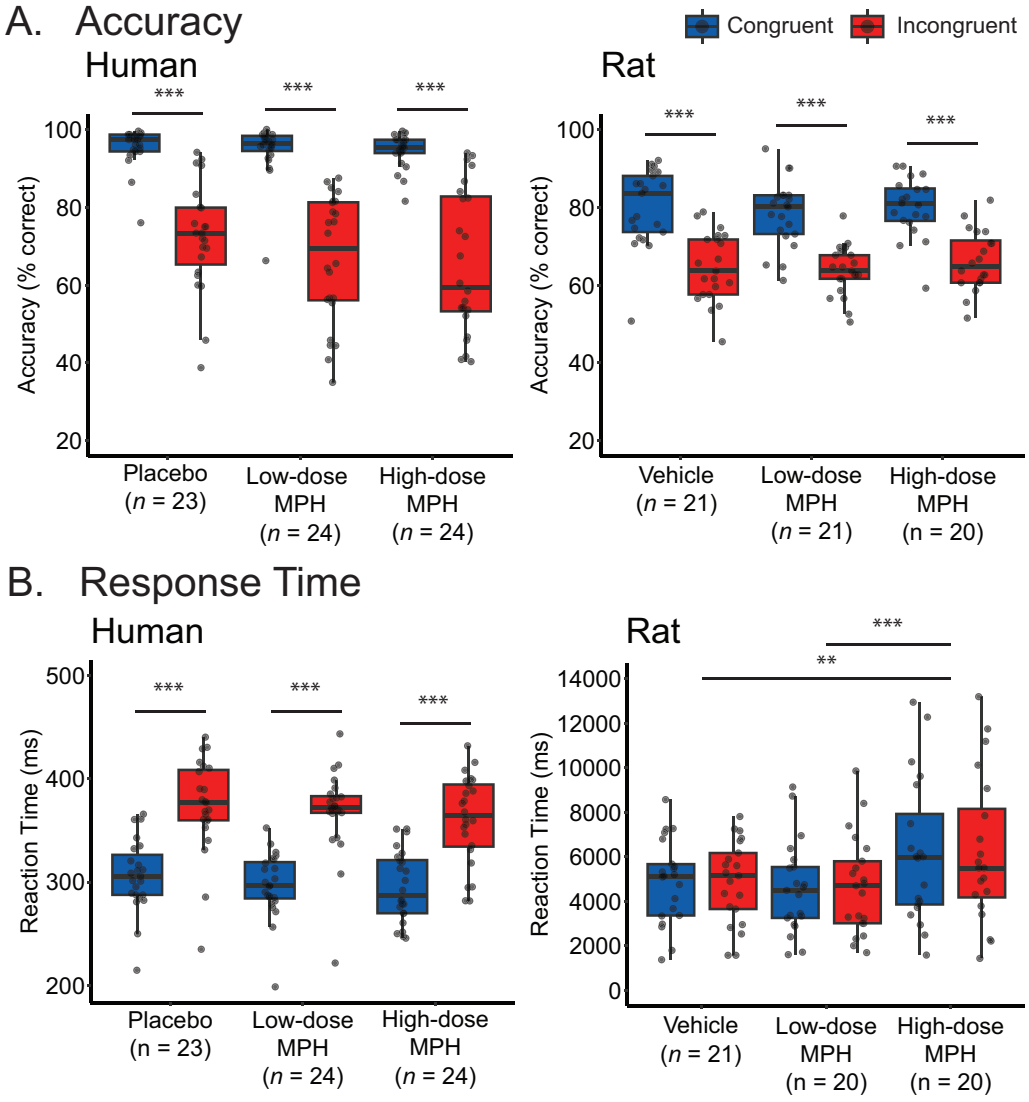

Figure 2. Behavioral Flanker data for humans and rats. (A) Both humans and rats were more accurate during congruent vs incongruent target trials across all treatment conditions. (B) Humans were faster to respond to congruent vs incongruent target trials across all treatment conditions. As in Robble et al. (2021), rats showed no congruency effect for response time (RT); rats were slower overall to respond in the high methylphenidate (MPH) condition. $^{**}P < .01$, $^{***}P < .001$.

2 analyses focusing on target- or response-locked parameters. Models focused on target-locked parameters (ie, accuracy, RT, N2 amplitude, and theta activity) and estimated each measure as a function of congruency (ie, congruent vs incongruent), treatment condition (ie, placebo, low-dose, high-dose), and the congruency × treatment condition interaction, while accommodating overall individual differences via individual-level random effects. Models focused on response-locked parameters (ie, the ERN, Pe, and either theta or delta activity) used the same structure but replaced congruency with response (ie, correct vs error). Posthoc comparisons of the estimated marginal means probed any significant effects identified in both series of models (see Supplement for control analyses considering sex).

All models were estimated in R using the *lme4* package (Bates et al., 2015), and omnibus tested and evaluated using the *stats* package (R Core Team, 2013). Post hoc Holm-adjusted comparisons were performed using the *emmeans* package (Lenth, 2022). Notably, as spectral power was quantified as a percentage change, these data were log-transformed before model estimation to help with distributional assumptions. Statistical significance was evaluated at $P < .05$.

Results

Behavior

Human accuracy and RT data are presented in the left column of Figure 2A and Figure 2B respectively. With respect to accuracy, the mixed effects model yielded a significant main effect of congruency ($F_{(1,112.14)} = 265.39$, $P < .001$, $\eta_p^2 = 0.70$), with higher accuracy for congruent than incongruent trials. Similarly, the model evaluating RT also revealed a significant main effect of congruency ($F_{(1,112.39)} = 224.11$, $P < .001$, $\eta_p^2 = 0.67$), with faster RTs for congruent than incongruent trials. Contrary to our hypotheses, there was no significant main effect or interaction term with treatment condition in either model (ts ≥ .280), indicating that Flanker interference effect was observed in all treatment conditions and not affected by any dose of MPH. Follow-up probes confirmed that individuals were between 23.0% and 28.8% less accurate (ts ≥ 8.00, Ps < .001)

and 65.5 and 71.7 milliseconds slower (ts ≤ −8.37, Ps < .001) on incongruent than congruent trials.

In turn, the right columns of Figure 2A and Figure 2B, respectively, present the rodent accuracy and RT data. Similar to humans, we observed a significant effect of congruency ($F_{(1,97.44)} = 194.54$, $P < .001$, $\eta_p^2 = 0.67$), with rats exhibiting an estimated 13.9%-15.4% greater accuracy for congruent versus incongruent trials across all treatment conditions (ts ≥ 7.52, Ps ≤ .001). In the RT model, we observed a significant effect of treatment condition ($F_{(1,99.13)} = 8.54$, $P < .001$, $\eta_p^2 = 0.15$). Posthoc tests indicated that across trial-types average RTs were slower in the high-dose MPH condition compared with both the low-dose ($t = -3.864$, $P < .001$) and vehicle conditions ($t = -3.276$, $P = .003$). Interestingly, no significant main effect or interaction with congruency (Ps ≥ .870) was observed, suggesting that, on average, RT did not differ between trial type regardless of treatment condition.

Response-Locked ERPs

Grand average response-locked ERPs waveforms for humans and rats are presented in Figure 3A and 3C, respectively. In humans, the ERN peaked at around 50 milliseconds and was followed by the Pe peaking around 200 milliseconds. For rats, negativity was observed around 200 milliseconds in error trials relative to correct trials (ie, an ERN-like component), and this was followed by an extended positivity from 300 to 600 milliseconds in error trials compared with correct trials (ie, a Pe-like component). While these components differ in appearance between species, the waveforms of both groups closely resemble those of our previous study (Robble et al., 2021).

For humans, the model examining ERN amplitude showed a significant effect of response ($F_{(1,112.47)} = 239.25$, $P < .001$, $\eta_p^2 = 0.68$), with more negative amplitudes for error versus correct trials (Figure 3B). A similar effect was observed in the Pe model, where the response effect was significant ($F_{(1,112.70)} = 61.82$, $P < .001$, $\eta_p^2 = 0.35$) (Figure 3B). Posthoc contrasts confirmed that the ERN was an estimated 6.59-7.20 μV more negative (ts ≥ 8.48, Ps ≤ .001), and the Pe was an estimated 2.58-3.45 μV more positive (ts ≤ 3.81, Ps < .001) for error than correct trials regardless of dose.

For rats, the main effect of response was trending ($F_{(1,76.16)} = 3.28$, $P = .074$, $\eta_p^2 = 0.03$) in the model examining the early negativity (ie, ERN analogue; Figure 3D), while the treatment condition ($F_{(2,77.22)} = 0.22$, $P = .804$) and interaction effect ($F_{(2,76.16)} = 1.25$, $P = .292$) were not significant. Probing this a priori trending effect revealed a response-related difference in the placebo condition ($t = 2.36$, $P = .021$), with the average ERP amplitude for error trials being 7.33 μV more negative than correct trials. Regarding the later response-locked component (Figure 3D), our model showed a significant main effect of response ($F_{(1,76.02)} = 9.97$, $P = .002$, $\eta_p^2 = 0.12$) such that, on average, error trials had more positive waveforms than correct trials. Post hoc contrasts confirmed that the late response-locked component was more positive for error trials versus correct trials in the placebo ($t = -2.27$, $P = .03$) and low-dose MPH conditions ($t = -2.34$, $P = .022$) but not the high-dose MPH condition ($P = .366$). Despite this, the main effect of treatment condition ($F_{(2,76.29)} = 0.92$, $P = .402$) and interaction effect ($F_{(2,76.02)} = 0.57$, $P = .569$) were not significant.

Target-locked Theta Activity

Grand average target-locked spectral power for humans and rats are presented in Figure 4A and 4B, respectively. The human model yielded a significant main effect of congruency ($F_{(1,113.12)} = 42.52$, $P < .001$, $\eta_p^2 = 0.27$), whereas both treatment condition ($F_{(2,113.48)} = 0.15$, $P = .858$) and congruency × treatment condition ($F_{(2,113.12)} = 0.32$, $P = .724$) were nonsignificant. As hypothesized, posthoc comparisons estimated that change in theta power was between 188% and 245% (ts ≤ −3.20, Ps ≤ .002) higher for incongruent vs congruent trials (Figure 4B). Contrary to our hypotheses, analogous rodent model observed no significant effects for congruency ($F_{(1,98.05)} = 1.36$, $P = .246$), treatment condition ($F_{(2,100.72)} = 1.32$, $P = .272$), or their interaction ($F_{(2,98.05)} = 0.98$, $P = .378$), indicating that neither the task nor MPH moderated stimulus-related theta power in rodents (Figure 4D).

Response-locked Delta/Theta Activity

Grand average response-locked spectral power for humans and rats are presented in Figure 5A and 5B, respectively. In humans there was a significant main effect of response ($F_{(1,112.88)} = 237.70$, $P < .001$, $\eta_p^2 = 0.68$), indicating greater change from baseline in theta power for erroneous versus correct trials, as hypothesized (Figure 5B). The main effect for treatment condition ($F_{(2,113.36)} = 0.17$, $P = .842$) and the interaction term ($F_{(2,112.88)} = 0.91$, $P = .405$) were nonsignificant. Posthoc tests confirmed that this effect was present for all doses (ts ≤ −7.87, Ps ≤ .001). The analogous model examining response-locked delta power in rats showed no significant effects for response ($F_{(1,76.80)} = 0.41$, $P = .525$), treatment condition ($F_{(2,79.52)} = 0.57$, $P = .570$), and their interaction term ($F_{(2,76.79)} = 1.24$, $P = .294$), indicating that neither the task nor MPH moderated response-related delta power of rodents (Figure 5D).

Discussion

The primary goals of this study were to replicate our previous work examining cognitive control in rats and humans using a modified Flanker task (Kangas et al., 2021; Robble et al., 2021) and extend this work by examining putative modulatory effects of the DA-enhancing drug MPH (Volkow et al., 2001, 2002). We successfully replicated all previous behavioral and EEG findings in humans, as well as the Flanker effect on accuracy and response-locked ERPs, observing greater *ERN-like* and subsequent *Pe-like* components following errors in rats. While these ERPs differ in appearance between species, their presence aligns with research implicating the ACC in cognitive control across species (Yeung et al., 2004; Newman et al., 2015; Warren et al., 2015). Moreover, we also replicated the absence of task-related RT effect in rodents. As previously suggested (Robble et al., 2021), this most likely reflects choices made to ensure the task's cross-species validity (eg, a primary focus on accuracy over response latency) and rodent training (eg, no imposed limited hold for responses).

In contrast to our prior report (Robble et al., 2021), we did not observe any task-related changes in target-locked theta or response-locked delta power in rats. It is worth noting that while the delta effect (ie, greater delta power in correct trials) was observed across treatment conditions, the theta effect (ie, greater theta power in incongruent trials) only emerged in the vehicle condition, perhaps limiting its robustness. Not observing either effect in a larger sample (n = 19 for theta activity and n = 15-17 for delta activity) under identical conditions was unexpected, especially given that task effects were observed in humans. It could be that frequency band definitions are not analogous across species and should be tailored to individual species. Alternatively, as processes underlying response-locked indices may differ between species, that is, error avoidance in humans and reward in rodents (Robble et al., 2021), and it could be that rodent response processing is unaffected by the task and hence delta power does not change. Nonetheless, further study into what general and

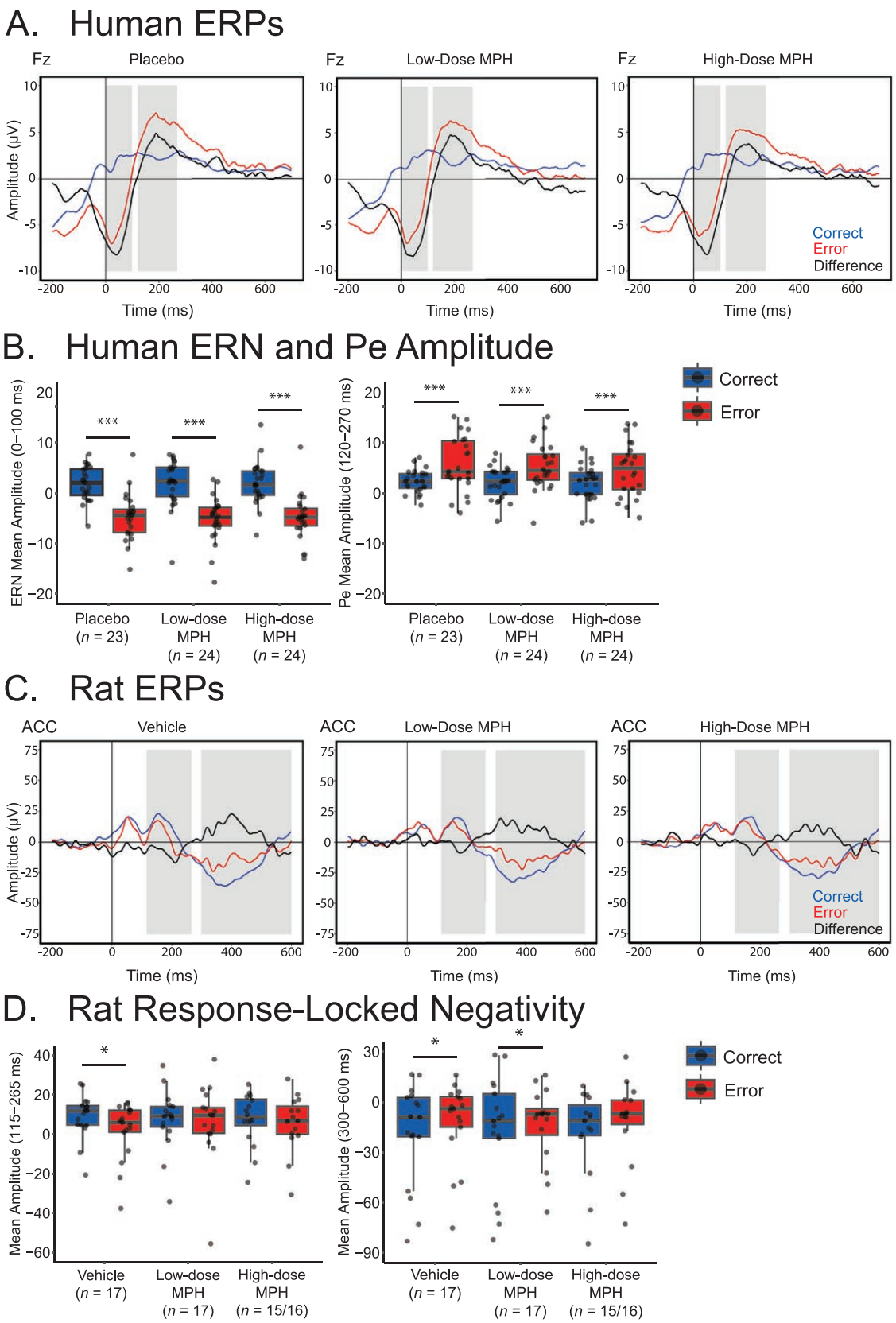

Figure 3. Response-locked event-related (ERP) data from error and correct Flanker trials in humans and rats. In both species, responses were made at time 0. (A) Grand-average response-locked ERP waveforms for human participants across all 3 treatment conditions at channel Fz. (B) Human participants exhibited significantly greater error-related negativity (ERN) and error-positivity (Pe) responses following error vs correct trials across all 3 treatment conditions ($P < .001$). (C) Grand-average response-locked ERP waveforms for rats across all 3 treatment conditions for the anterior cingulate cortex (ACC) local field potential electrode. (D) Rats exhibited a nonsignificant difference in early response-locked negativity that trended toward significance ($P = .074$) and exhibited significantly greater late response-locked negativity on correct versus error trials ($P = .002$). Gray shaded regions highlight the time windows used to measure mean amplitudes for ERP components. *$P < .05$, ***$P < .001$.

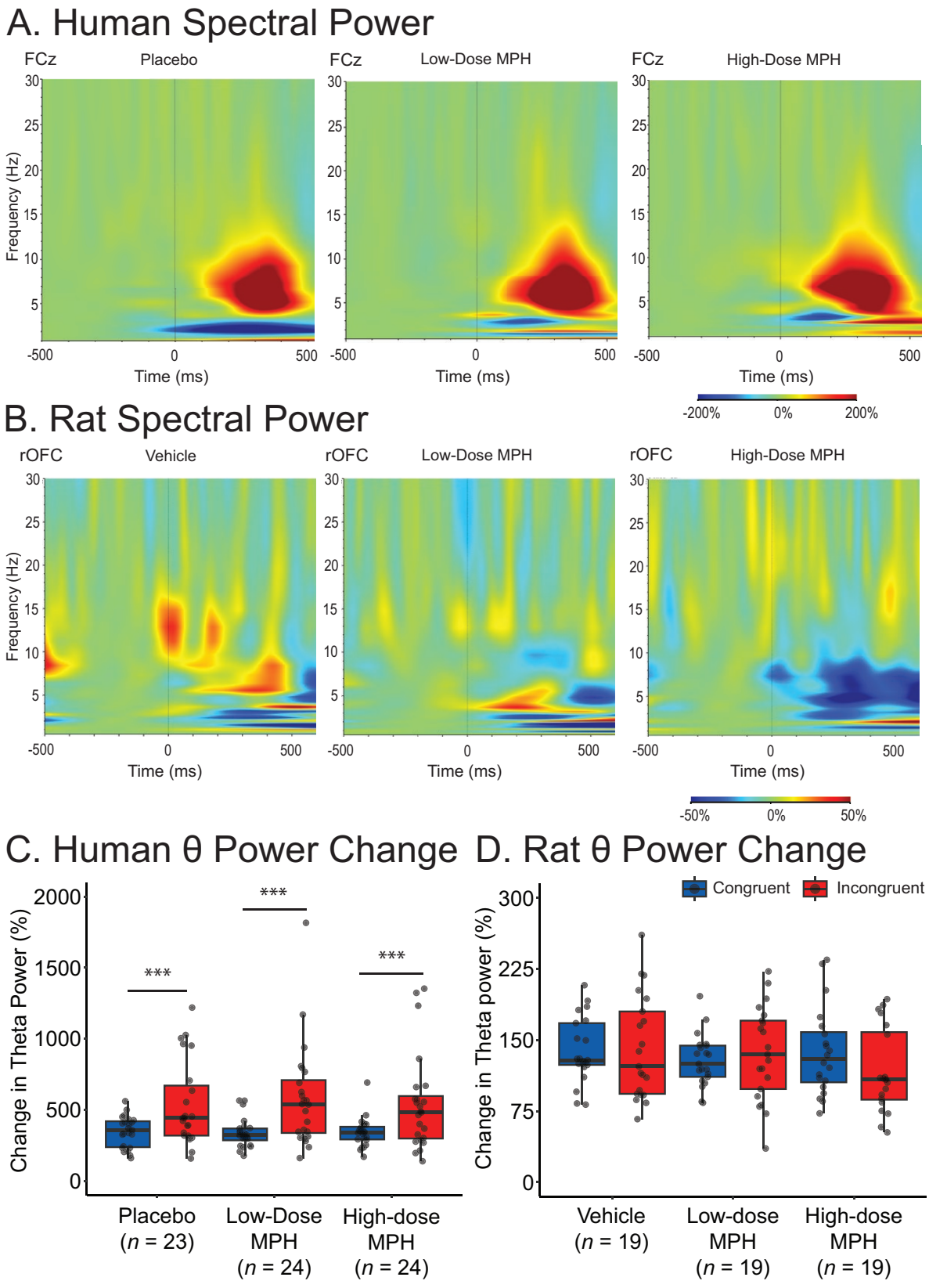

Figure 4. Target-locked spectral power, plotted as the difference between incongruent and congruent target trials. Target stimuli were presented at time 0. Data were calculated as percent change from baseline. (A) Target-locked spectral power for human participants across all 3 treatment conditions at channel FCz. (B) Target-locked spectral power for rats across all 3 treatment conditions at the anterior cingulate cortex (ACC) local field potential (LFP) electrode and the right orbitofrontal (OFC) screw. (C) Human participants exhibited significantly greater theta power (θ; 4.09-6.53 Hz) from 300 to 500 milliseconds post-target presentation for incongruent vs congruent trials across all 3 treatment conditions ($P < .001$). (D) Rats exhibited nonsignificant changes in rOFC theta power (θ; 3.61-7.31 Hz) 50 to 250 milliseconds post-target presentation for incongruent vs congruent trials across all 3 treatment conditions. ***$P < .001$.

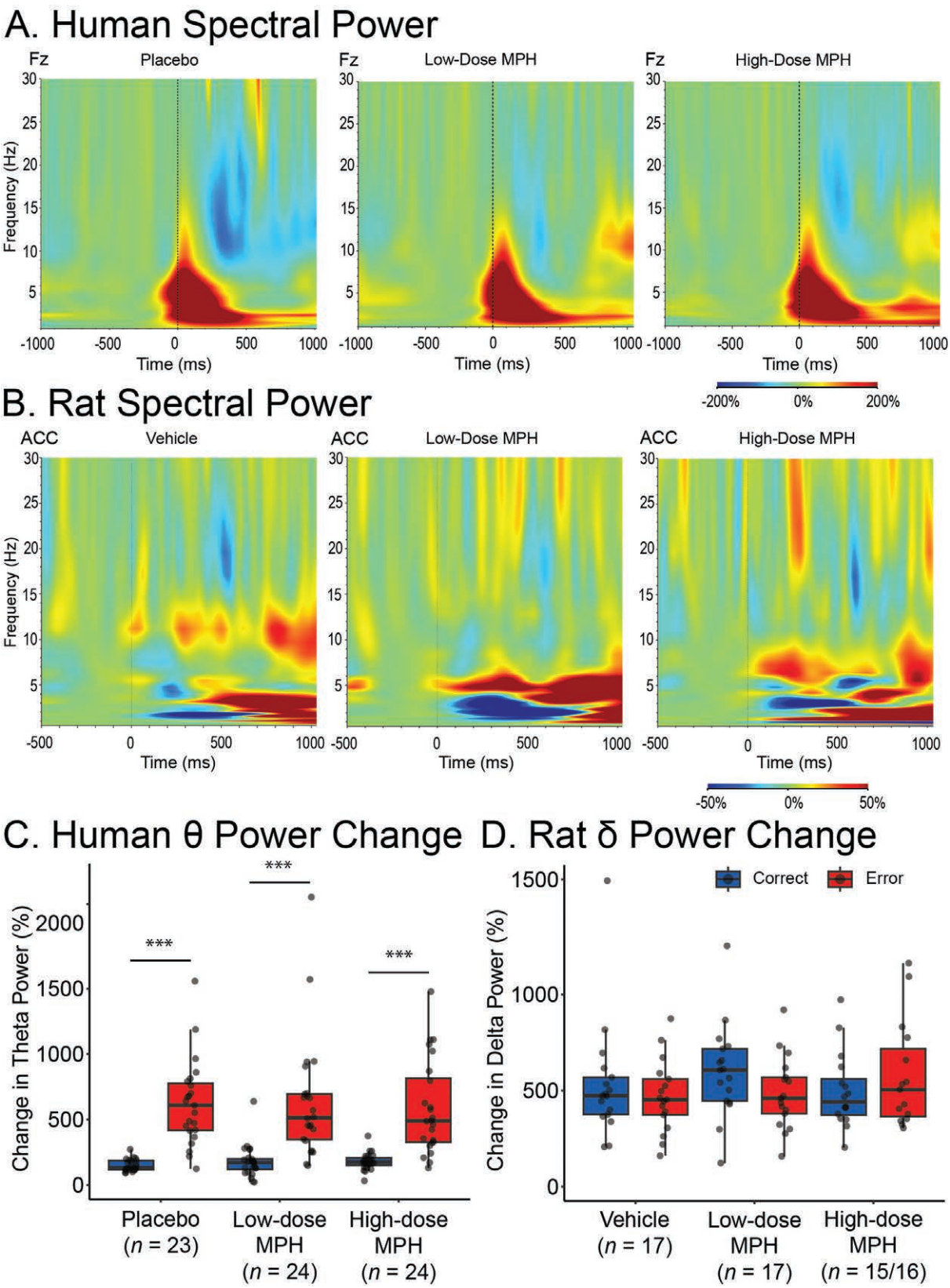

Figure 5. Response-locked spectral power, plotted as the difference between error and correct trials. Responses were made at time 0. Data were calculated as percent change from baseline. (A) Response-locked spectral power for human participants across all 3 treatment conditions at channel Fz. (B) Response-locked spectral power for rats across all 3 treatment conditions at the anterior cingulate cortex (ACC) local field potential electrode. (C) Human participants exhibited significantly greater theta (θ) power (4.09-6.53 Hz) from 0 to 200 milliseconds post response for error versus correct trials across all 3 treatment conditions ($P < .001$). (D) Rat delta power (δ; 1.01-2.05 Hz) from 200 to 600 milliseconds post response did not differ for error versus correct trials, and there was no effect of treatment condition. ***$P < .001$.

species-specific factors might moderate these measures and lead to these discrepancies is needed.

Contrary to our hypothesis, MPH did not modulate any behavioral or EEG measure in humans. These null findings contrast with prior reports indicating that MPH potentiates ERN amplitude of adults (Barnes et al., 2014) and ERN/Pe amplitude in children with attention-deficit/hyperactivity disorder (Groom et al., 2013), as well as improves behavioral response inhibition (Nandam et al., 2014). Instead, our findings are consistent with our previous study (Robble et al., 2021) that observed that modafinil, a drug known to inhibit striatal DA transporter (Madras et al., 2006; Volkow et al., 2009; Kim et al., 2014) and improve cognitive performance in humans and inhibitory control in rats (Turner et al., 2003; Morgan et al., 2007; Müller et al., 2013; Pringle et al., 2013), also did not moderate behavioral or EEG measures. Furthermore, the absence of MPH effects in the present study also aligns with the lack of modulation of human ERPs by methamphetamine (Haggarty et al., 2024), which similarly acts on DA transporter to increase cortical DA (Xie and Miller, 2009). Alternatively, it may be that the absence of MPH effects reflects limiting features of the current study. First, behavioral performance was high, particularly in humans, and so there may have been a limit to how much MPH could further improve performance. This is especially relevant as MPH effects may be moderated by task performance such that lower performance accompanies greater effects (Agay et al., 2014). Similarly, it may be that the DA levels of our healthy cohorts were already optimal, and hence any possible MPH effect was minimized. Last, it could be that the specific MPH doses used in humans were too subtle to affect brain and behavior; while some past work has used similar doses (eg, Groom et al., 2013), others have used higher doses (eg, Clatworthy et al., 2009). As such, future studies could focus on replications with increased task difficulty, controlling baseline performance, participants who are hypothesized to have reduced DA signaling (eg, depressed individuals), and/or with different doses of MPH to further investigate where effects may emerge.

Interestingly, some MPH modulation was observed in rats. Behaviorally, on average, RT was slower following the higher dose of MPH compared with both the vehicle and the lower dose of MPH. While this effect might reflect impairment related to altered DA signaling due to MPH exposure, given the lack of congruency effect for rats' RT, the results should be interpreted cautiously. Future studies should consider using higher MPH doses to probe if there is a threshold dose at which effects may emerge. Additionally, it appears that MPH may modulate between trial-type differences (ie, error vs correct) in response-locked ERP amplitude, with this difference being significant only in the vehicle condition for the early ERN-like component and in the vehicle and low-dose condition for the late Pe-like component. ERN- and Pe-like components are often invoked as indices of error detection (Nieuwenhuis et al., 2001; Folstein and Van Petten, 2008) and awareness (Wessel et al., 2011), and while MPH may potentiate error processing (Groom et al., 2013; Barnes et al., 2014), the present results, where error versus correct differences in amplitude are diminished post-MPH exposure, are consistent with a DA-related blunting of error processing. It has been postulated that MPH's effect on performance might follow an inverted U-shape function (Repantis et al., 2010), and thus, it may be that our doses for rodents were outside the range that improves error processing and instead impaired performance.

There were several challenges associated with this cross-species work. First, there were considerations regarding how to best align cross-species measurements, for example, frequency range and time window selection. While using difference waveforms to identify peaks and select measurement windows provides a robust analysis, the extension of methods like collapsed localizers and global field power peaks/troughs across species would provide additional precision in future research. Second, while human participants remained seated throughout the task, the rats' movements were not restricted. This meant that movement-related activity was present in the rodent recordings and likely added noise to the EEG data. It is also worth noting that while independent component analysis based artifact removal is common in human EEG studies, comparable approaches in rodent research are rare. Future research extrapolating independent component analysis procedures for artifact detection/removal to rodent electrophysiology could prove extremely beneficial to cross-species studies, improving data quality and potentially enhancing their translational utility. Last, while rodent behavioral accuracy was high, the rats required an extensive training period to successfully complete the Flanker task. Specifically, training sessions of rats in this study ranged from 123 to 290 days, which may present logistical and resource challenges.

Despite limitations, the current study successfully used a modified Flanker task to examine behavioral and EEG indices of cognitive control in humans and rats. We replicated several effects, including the expected Flanker interference effect on accuracy, response time, and response-locked ERPs in response to errors, providing continued support that similar neural mechanisms regulate cognitive control in both species. Interestingly, while we observed that MPH did not modulate behavioral and neural indices in humans, there were dose-specific effects on the RTs of rodents. Moreover, trial-type differences in the rodent ERN- and Pe- like components were observed in the vehicle condition and not after MPH exposure, although these effects should be interpreted cautiously. Finally, the null task effects on the spectral activity of rats identifies challenges to using these EEG measures as cross-species markers of neural activation that remain to be addressed.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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None.

Author Contributions

Samantha Linton (Data curation [Equal], Formal analysis [Equal], Visualization [Equal], Writing—original draft [Equal], Writing—review and editing [Equal]), Ty Lees (Formal analysis [Equal], Visualization [Equal], Writing—original draft [Equal], Writing—review and editing [Equal]), Genevieve Nowicki (Data curation [Equal], Investigation [Equal], Writing—review and editing [Equal]), Rachel Lobien (Data curation [Equal], Investigation [Equal], Writing—review and editing [Equal]), Gordana Vitaliano (Investigation [Equal], Writing—review and editing [Equal]), Jack Bergman (Conceptualization [Equal], Methodology [Equal], Writing—review and editing [Equal]), Diego Pizzagalli (Conceptualization [Equal], Funding acquisition [Equal], Methodology [Equal], Project administration [Equal], Supervision

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Conflict of Interest

Over the past 3 years: D.A.P. has received consulting fees from Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Sage Therapeutics, Sama Therapeutics, and Takeda; he has received honoraria from the American Psychological Association, Psychonomic Society, and Springer (for editorial work) and Alkermes; he has received research funding from the Bird Foundation, Brain and Behavior Research Foundation, Dana Foundation, DARPA, Millennium Pharmaceuticals, the National Institute of Mental Health, and Wellcome Leap; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software. B.D.K. has had sponsored research agreements with BlackThorn Therapeutics, Compass Pathways, Delix Therapeutics, Engrail Therapeutics, Neurocrine Biosciences, and Takeda Pharmaceuticals. W.A.C. has received consulting fees from Psy Therapeutics and has sponsored research agreements with Cerevel and Delix. No funding or any involvement from these entities was used to support the current work, and all views expressed are solely those of the authors. All other authors have no conflicts of interest or relevant disclosures.

Data Availability

The data used in the present work are available at: https://nda.nih.gov/edit_collection.html?id=2567

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