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ARTICLE

Concordant neurophysiological signatures of cognitive control in humans and rats

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Progress towards understanding neural mechanisms in humans relevant to psychiatric conditions has been hindered by a lack of translationally-relevant cognitive tasks for laboratory animals. Accordingly, there is a critical need to develop parallel neurophysiological assessments of domains of cognition, such as cognitive control, in humans and laboratory animals. To address this, we developed a touchscreen-based cognitive (Eriksen Flanker) task in rats and used its key characteristics to construct a novel human version, with similar testing parameters and endpoints across species. We obtained continuous electroencephalogram (EEG) recordings, including local field potentials in rats, and compared electrophysiological signatures locked to stimulus onset and responses across species. We also assessed whether behavioral or physiological task effects were modulated by modafinil, which enhances aspects of cognitive function in humans. In both species, the task elicited expected flanker interference effects (reduced accuracy) during high-conflict trials. Across homologous neuroanatomical loci, stimulus-locked increases in theta power during high-conflict trials as well as error-related negative potentials were observed. These endpoints were not affected by modafinil in either species. Despite some species-specific patterns, our findings demonstrate the feasibility of a rat Flanker task as well as cross-species behavioral and neurophysiological similarities, which may enable novel insights into the neural correlates of healthy and aberrant behavior and provide mechanistic insights relevant to treatment.

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INTRODUCTION

The prevalence of psychiatric illness in the United States continues to increase [1]. Despite longstanding promises that a better understanding of the biological basis of complex behavior would hasten the development of new therapeutics for neuropsychiatric illness, there has been limited success in the last 50 years [2]. Although myriad factors can explain this modest progress, a lack of convergence between human and animal models is often implicated. Indeed, there is a widely acknowledged disconnect between preclinical and clinical cognitive neuroscience [3], and discoveries made in laboratory animals have often failed to provide the basis for new therapeutics. Such failures have called into question the utility of animal models in psychiatric drug discovery, particularly in domains related to cognition [4]. A new approach to the study of cognition in laboratory animals—one informed by task features and neural endpoints used in humans—is needed to reduce this translational gap. Consistent with the principles of the research domain criteria (RDoC) initiative [5], the development of translationally-relevant behavioral and neurophysiological assessments of cognition would be transformative for promoting a new understanding of brain function in healthy populations and dysfunction associated with neuropsychiatric illness.

Cognitive control refers to the ability to guide goal-directed behavior and includes conflict detection and error correction. In humans, one of the most common methods to evaluate cognitive control is the Eriksen Flanker task [6], which requires subjects to respond to a set of stimuli containing non-conflicting (e.g., "<<<<<") or conflicting (e.g., "<<><<") elements as quickly and accurately as possible. Human electroencephalogram (EEG) studies have found that the Flanker task reliably elicits midfrontal cortical signals, including a type of event-related potential (ERP) known as the error-related negativity (ERN; [7]) and increased theta power [8]. The midfrontal cortex, and in particular the anterior cingulate cortex (ACC), is considered a neural "hub" critically implicated in integrating cognitive, motor, and emotional control functions [9–12]. Aberrant neural activity in the midfrontal cortex has been associated with a range of psychopathologies, including depression, schizophrenia, and anxiety disorders [13–15]. Though the clinical investigation of cortical function via the Flanker task has been substantial, direct cross-species comparisons in an analogous task have been lacking.

There are several ongoing efforts to develop translationally-aligned cognitive tasks in humans and rats, including time-estimation tasks, foraging decision-making tasks, probabilistic reversal learning tasks, and aspects of the CANTAB task battery [16–19], which continue to yield valuable insights into the neural basis of cognition. While these tasks are designed to examine several distinct domains of cognition, to the best of our

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knowledge, a rodent version of the Erikson Flanker task has never been developed. The Flanker task has ideal characteristics for cross-species evaluations of cognitive control, as it provides the opportunity to assess neurophysiological responses during both conflicts [20] and response evaluation [21, 22]. Here, we developed a novel touchscreen-based cross-species Flanker task, enabling us to compare electrophysiological responses in both rats and humans. After extensive piloting and optimizations, we first identified visual stimulus parameters under which the rats could perform the task reliably and that yielded expected behavioral patterns, and then applied these parameters to a parallel version in humans. We then assessed ERPs and spectral changes following both conflict and errors and determined whether modafinil, a drug that enhances some aspects of cognitive function in humans [23], would dose-dependently increase several of these responses including the N200, ERN, and frontal theta power. Notwithstanding some species-specific characteristics, our findings highlight substantial qualitative similarity in behavioral and electrophysiological signatures of cognitive control.

MATERIALS AND METHODS

Humans

Thirty right-handed volunteers were recruited and a total of 26 subjects (14 male, 12 female, mean ± SD age: 23.81 ± 4.82) were retained for final data analyses ($N = 4$ dropped due to having fewer than six artifact-free ERP trials; [24]). Subjects were free of any psychiatric history, as determined by the Structured Clinical Interview for DSM-5 (SCID-5; [25]) administered by a clinician. Subjects were compensated $452 for participation. All procedures were approved by the Partners Healthcare Institutional Review Board, and subjects provided written informed consent in the presence of a medical doctor prior to participation.

Procedure

The study comprised four sessions, separated by at least one week. Using a double-blind, within-subjects, placebo-controlled design, subjects were administered 0 mg (placebo), 100 mg, or 200 mg modafinil (2 h pretreatment; [26]). Continuous electroencephalographic (EEG) activity was recorded from a customized 96-channel actiCAP system using an actiCHamp amplifier (Brain Products GmbH, Gilching, Germany). The EEG assessment consisted of an 8-min baseline recording of resting EEG (4 min eyes open, 4 min eyes closed), and a randomized assignment to either a Flanker task or a probabilistic reversal learning task (the results of which will be reported separately). Analyses examining the effects of task order revealed no significant differences.

Subjects completed a modified version of the Eriksen Flanker task ([6, 27]; Fig. 1) that was first optimized for rats and then forward-engineered for humans. Subjects were seated ~70 cm in front of a computer monitor inside an acoustically and electrically shielded booth. All stimuli were presented on a 22.5-in. (diagonal) VIEWPixx monitor (VPixx Technologies, Saint-Bruno, Canada) using PsychoPy software [28]. Subjects were instructed to indicate the color of a center image (target) within a three-image display using one of two buttons (counterbalanced) on a Cedrus response pad (model RB-740m, Cedrus Corporation, San Pedro, CA). Violet flowers and green leaves (identical to the stimuli used in rats) constituted the images in the task and flanker images could either match (congruent trial) or not match (incongruent trials) the center image. During each trial, the two flanking stimuli were presented 100 ms prior to target onset, and all three images remained on the screen for 50 ms. A feedback message with the words "TOO SLOW!!!" was displayed if subjects responded slower than 600 ms in the first block, or outside of the 85th percentile of their own RTs in the previous block for blocks 2 through 5. After each response, subjects were shown a blank screen for 1000–1250 ms before receiving a feedback stimulus (1000 ms)

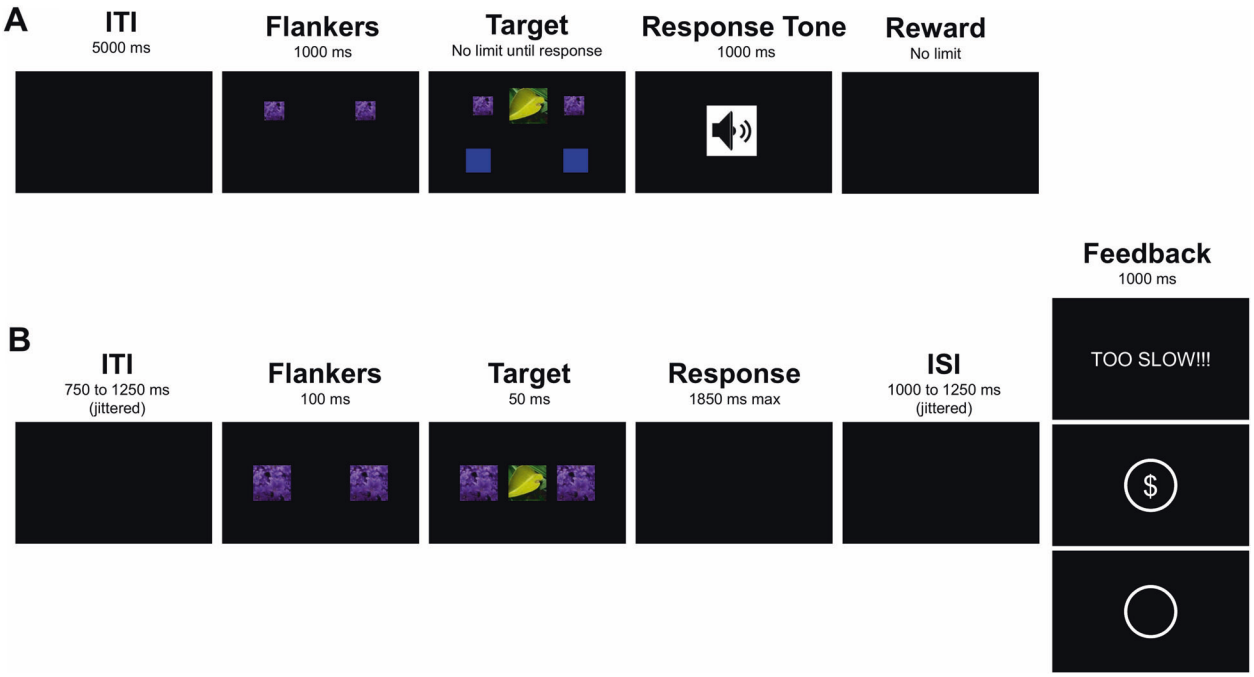

Fig. 1 Flanker task design. A Rat task design. Rats underwent 300 trial Flanker task test sessions. In each trial, the flankers appeared on the screen 1000 ms prior to the target stimulus presentation. Target presentation coincided with the appearance of two response boxes (shown in blue) and the opportunity to respond. Immediately following a response, a 1000 ms tone was presented to indicate the accuracy, and correct responses were rewarded. **B** Human task design. The flankers were presented for 100 ms prior to the target presentation. The target stimulus was presented for 50 ms, after which time the full stimulus complex was removed and subjects had 1850 ms to respond. Following the response period, there was jittered inter-stimulus interval which preceded the presentation of visual feedback.

displaying correct (dollar sign enclosed in an empty circle) or incorrect (empty circle) (Fig. 1B).

Rats

Six male (226–250 g) and six female (176–200 g) Long-Evans rats were purchased from Charles River Laboratories (Wilmington, MA). One male rat was euthanized following head cap assembly failure and excluded from all analyses. Rats were initially housed in groups of three and then singly housed following electrode implantation surgery. Rats were maintained on a 12 h light/dark cycle (lights on 7:00 a.m. to 7:00 p.m.) with ad libitum access to food and water and were mildly food-restricted during visual discrimination training and Flanker Task testing. All procedures were approved by the McLean Hospital Institutional Animal Care and Use Committee and consistent with the 2010 National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Electrode implantation surgery

Rats were initially trained in a visual discrimination task (see Supplemental methods) and then underwent stereotaxic surgery to implant recording electrodes. Rats were anesthetized with isoflurane (1.5%) and skull screw (EEG) electrodes were lowered to dura bilaterally at a frontal site (AP: +3.7, ML: ±2.6), unilaterally over an occipital site (AP: −7.0, ML: −3.5), and two cerebellar sites which served as reference and ground electrodes. Single tungsten wire electrodes were implanted unilaterally into the ACC (ACC; AP: +2.7, ML: +0.8, DV: −2.1), the nucleus accumbens core (NAcC; AP: +1.3, ML: −1.3, DV: −7.1), and primary visual cortex (V1; AP: −7.0, ML: +3.5, DV: −1.6) contralateral to the occipital screw to record local field potentials. All dorsal-ventral calculations were made from the skull surface. Finally, a single 2 mm Ag/AgCl disk was placed on the skull (AP: +2.5, ML: +0.8) immediately posterior to the ACC LFP wire to collect EEG signals in a less invasive manner (Supplemental Fig. 1). Electrodes were connected to an EIB-16 electrode interface board (Neuralynx) and the assembly was secured to the skull using dental acrylic.

Procedure

Following a 7-day recovery period, rats were given additional discrimination training to re-establish stable performance (70% accuracy for two consecutive sessions). These sessions were conducted in the electrophysiological recording environment, a Faraday cage (MED-PC) that housed a custom-built, fully plexiglass operant box designed to optimize recording quality. Once the stable performance was re-established, a series of test sessions were conducted (Fig. 1A) after rats were pretreated (30 min; i.p.) with 0 mg (DMSO vehicle), 16 mg, 32 mg, or 64 mg/kg modafinil using a Latin-square repeated measures design. Under similar testing conditions, DMSO has no effect on locomotion, attention, or motivation in rats [29, 30].

Immediately prior to testing, a head stage cable (Intan Technologies) was connected to an RHD 16 channel amplifier board (Intan Technologies) and secured to the head-mounted electrode interface board. Rats were then placed in the operant chamber and the head stage cable was attached to a commutator held in place above the chamber by a balance arm (MED-PC) to allow unrestricted movement inside the chamber. Continuous EEG and LFP data were recorded during each Flanker task test session using the RHD-2000 recording system and supported data acquisition software (Intan Technologies). Visual stimuli (green leaves/violet flowers) were used in the human task and were presented on a touchscreen. The task consisted of 300 trials on an FR1 schedule of reinforcement with no limited hold on responding. Correct responses resulted in the delivery of a sweetened condensed milk reward (30%; 0.1 ml/reinf) and the previously paired correct tone, while incorrect responses resulted in no reward delivery and the previously paired incorrect tone. To increase the saliency of target presentation and improve accuracy on incongruent trials, the flanking stimuli were each 50% of the size of the target stimulus (Fig. 1A). Between testing sessions, rats were required to regain criteria for successful discrimination, resulting in a minimum of two days between each drug test.

Histology

Upon completion of testing, rats were euthanized, and brains were removed and fixed in 4% paraformaldehyde for at least 14 days. Brains were then sliced into 40 µm sections, mounted, stained with cresyl violet, and coverslipped. Representations of electrode placements [31] are shown in Supplemental Fig. 2.

Cross-species data analysis

To analyze response latencies, data in both species were natural log-transformed, as response latencies were not normally distributed. Outlier trials were identified and removed using ±3 standard deviations from the mean as a threshold. Statistical analyses were performed on the transformed data, while untransformed values were used to generate figures.

To enable cross-species comparisons, all data were analyzed with BrainVision Analyzer 2.0. Given the differences in electrode sensitivity across species, species-specific artifact rejection criteria were used. In humans, epochs were rejected if any of the following criteria were met: (1) a voltage step exceeding 50 µV in 200-ms time intervals, (2) a voltage difference of more than 150 µV within a trial, or (3) a maximum voltage difference of less than 0.5 µV within a trial. In rats, epochs were rejected as artifactual if any voltage step exceeding 300 µV occurred in 200-ms time intervals. For the LFP channels, the range was extended to 400 µV given the enhanced sensitivity to local voltage fluctuations.

Data were band-pass filtered from 0.1 to 30 Hz. Stimulus-locked and response-locked data were segmented into individual epochs spanning from 1500 ms before and after the event (segments were 3000 ms in length), baseline-corrected (described below), and averaged. For the stimulus-locked data in both species, only data from stimuli that preceded a correct response were considered for further analysis [32]. For response-locked data in humans, trial segments were only considered if the responses fell within an individually-determined 95% confidence interval of incongruent-trial response times (RTs). For response-locked data in rats, trial segments were only considered if the responses fell within 10 s following target stimulus onset.

In humans, stimulus-locked ERPs were quantified as the average activity within the 230–290 ms time window following the target stimulus onset on correct trials at channel 2, which corresponds roughly to electrode FCz, and were computed in reference to a −250 to 0 ms pre-stimulus window. In rats, data were baseline corrected from −500 to 0 ms pre-target stimulus presentation. Stimulus-driven deflections in rats were not apparently different by condition (incongruent vs. congruent) on correct trials in any relevant time window and thus, all-time points were compared (see statistical analyses).

In humans, the ERN was quantified as the average amplitude between 0 and 100 ms following response onset, and subsequent error-related positivity (Pe) was quantified as the average amplitude between 120 and 270 ms post-response at channel 9, which corresponds to electrode Fz. The resulting averages were then baseline-corrected by the 800–700 ms pre-response time window. In rats, post-response negativity and subsequent positivity were baseline corrected by −500 to 0 ms pre-response time and were quantified between 115–265 ms and 300–600 ms, respectively. In both species, response-locked ERPs were evaluated on incongruent trials only to disentangle error- and congruency-related effects.

Theta power was isolated using a complex Morlet wavelet transformation. Pre-processing steps were similar to those completed in the time domain. Following artifact rejection with

the parameters specified above, a complex Morlet wavelet transformation was implemented using a Morlet parameter *c* of 3.5 applied to the data from 1 to 30 Hz in 30 frequency steps distributed on a logarithmic scale. A percentage change baseline correction (BVA 2.0 Solution by Dr. Ingmar Gutberlet, 2014) was implemented by first averaging the amplitude in a −500 to −300 ms pre-stimulus window for the stimulus-locked data and −500 ms to −200 ms pre-response window for the response-locked data. Thus, subsequent power values reported below are calculated based on the percentage change of power relative to the baseline period according to the formula: percentage change (time-frequency) = activity (time-frequency − baseline frequency)/baseline frequency [33].

In humans, total power values on individual trials were exported in the 300–500 ms post-target window for stimulus-locked data and the 0–200 ms post-response time window for response-locked data and averaged. In rats, total power values on individual trials were exported in the 50–250 ms post-target time window for stimulus-locked data and the 200–600 ms post response time window for response-locked data and averaged. In humans, for both stimulus- and response-locked theta calculations, wavelet layers were extracted corresponding to the theta frequency band (4.09–6.53 Hz). Frequency power was maximal at frontal central electrode sites and thus exported at channel 2 (roughly corresponding to FCz) for stimulus-locked theta and channel 9 (Fz) for response-locked theta. In rats, stimulus-locked theta power was quantified by extracting wavelet layers corresponding to the theta frequency band at electrodes with apparent differences in theta power between trial types (frontal EEG screw: 3.61–7.31 Hz). The rat theta band analyzed here lies well within the previously defined range of 3–12 Hz 3 [34, 35] and approximated the analysis band in humans. Similarly, response-locked delta power was quantified by extracting wavelet layers corresponding to the delta frequency band in the ACC LFP channel, where we observed an apparent difference in delta power between errors and correct responses (1.01–2.05 Hz).

Experimental design and statistical analyses

In two rats, signals from the frontal EEG screws appeared to be cross-contaminated (shorted) and data from these electrodes were excluded from analyses. Thus, the final sample size was 11 rats (5 male, 6 female); however, for frontal EEG channels only, the final sample was 9 rats (4 male, 5 female). This smaller sample was used for evaluation of target stimulus-locked ERPs and spectral power, as these signals were assessed at frontal EEG channels. The full sample-sized was available for all other behavioral and physiological measures. Statistical analyses were designed to enable three determinations: (1) whether expected Flanker task effects were detectable in either species, (2) whether these effects were modulated by modafinil treatment, and (3) whether task effects were similar across species. Relevant dependent measures considered for analysis were accuracy and reaction time, as well as stimulus-locked and response-locked ERPs and changes in spectral power.

To determine the effects of congruency and modafinil treatment on cognitive control variables, species-specific repeated measures ANOVAs were used with *Congruency* (congruent, incongruent) and *Dose* (humans: placebo, 100 mg, 200 mg modafinil; rats: vehicle, 16 mg, 32 mg, and 64 mg/kg modafinil) as within-subject factors and *Sex* as a between-subject factor. Significant main effects or interactions were further examined using Bonferroni's post-hoc comparisons. When no significant main effects or interactions were observed, a paired *t*-test in the placebo/vehicle condition was used to determine whether expected task effects were present in a drug-free state. To quantitatively assess cross-species similarity, significant effects were compared using univariate analysis with *Species* and *Sex* as between-subject factors (see Supplemental methods). Bayes Factor analyses were performed in JASP 0.14 (see Supplemental Methods and Table S1; University of Amsterdam; Amsterdam, the Netherlands) and all other statistical analyses were performed in SPSS 24 (IBM; Armonk, NY).

RESULTS

Behavior

In humans, accuracy in all treatment conditions was lower on high-conflict incongruent trials compared to low-conflict congruent trials ($F(1,24) = 110.64$, $p < 0.001$, $\eta^2_p = 0.82$, $BF_{10} = 3.45 \times 10^{28}$; Fig. 2A), and this effect was observed in all subjects in all treatment conditions (binomial $p(26/26) < 0.001$). In the placebo condition, accuracy on incongruent trials was significantly reduced compared to congruent trials ($t(50) = 14.74$, $p < 0.001$, Cohen's $d = 4.17$; note that for analyses of placebo/vehicle data, degrees of freedom take into consideration Bonferroni post hoc comparisons). In rats, accuracy was lower on incongruent trials compared to congruent trials in all treatment conditions ($F(1,9) = 254.99$, $p < 0.001$, $n^2_p = 0.966$, $BF_{10} = 1.71 \times 10^{14}$; Fig. 2B), and reduced accuracy on incongruent trials was observed in each subject (binomial $p(11/11) < 0.001$). In the vehicle condition, accuracy on incongruent trials was significantly reduced compared to congruent trials ($t(30) = 7.65$, $p < 0.001$, Cohen's $d = 2.79$). In both species, these results are consistent with the well-characterized flanker interference effect [9]. Contrary to our hypotheses, modafinil treatment did not affect accuracy in humans ($Fs < 2.60$, $ps > 0.09$, $BF_{10} = 0.15$) or rats ($Fs < 1.7$, $ps > 0.18$, $BF_{10} = 0.17$). To examine cross-species similarity, we conducted a repeated-measures ANOVA using Flanker Interference difference in accuracy scores (congruent accuracy—incongruent accuracy) as a dependent variable, and *Drug* (placebo, low, and high dose modafinil) as within-subjects factors, and *Sex* and *Species* as between-subjects factors. There was a significant main effect of *Species* ($F(1,33) = 5.64$, $p = 0.024$, $n^2_p = 0.146$), indicating that, while both species showed a significant interference effect, the effect was larger in humans (Fig. 2C). Critically, there was no *species* × *drug* interaction ($p = 0.394$), indicating cross-species similarity in performance across drug conditions.

In humans, reaction time was slower on incongruent trials relative to congruent trials in all treatment conditions ($F(1,24) = 439.02$, $p < 0.001$, $\eta^2_p = 0.95$, $BF_{10} = 2.32 \times 10^{44}$; Fig. 2D), an effect that was observed in all subjects (binomial $p(26/26) < 0.001$). In the placebo condition, reaction time was significantly slower on incongruent compared to congruent trial types ($t(50) = 29.77$, $p < 0.001$, Cohen's $d = 8.42$). In rats, reaction times were similar on incongruent and congruent trials ($F(1,9) < 1.4$, $p > 0.27$, $BF_{10} = 0.22$; Fig. 2E). Modafinil treatment did not affect reaction time in either humans ($Fs < 1.18$, $ps > 0.31$, $BF_{10} = 0.1$) or rats ($Fs < 2.3$, $ps > 0.1$, $BF_{10} = 3.55$). The two species were not directly compared because rats did not show an interference effect on reaction time. Together, these results demonstrate cross-species concordance for the Flanker interference effect on accuracy (which was, however, statistically larger in humans than rats), and similar (null) effects of modafinil in both species.

Electrophysiological results

Stimulus-locked ERPs. In humans, we found a larger negative voltage deflection 230–290 ms post-stimulus presentation on incongruent relative to congruent trials across treatment conditions, with the maximal signal detected at FCz ($F(1,24) = 63.9$, $p < 0.001$, $\eta^2_p = 0.727$, $BF_{10} = 1.31 \times 10^{11}$; Fig. 3A, C). This deflection was observed in nearly all subjects in the placebo condition (binomial $p(23/26) < 0.001$), was significantly greater on incongruent trials in the placebo condition ($t(50) = 7.71$, $p < 0.001$, Cohen's $d = 2.18$), and is consistent with the stimulus-conflict N200 component observed in Flanker tasks [36]. There was no effect of modafinil treatment on the N200 ($F < 1.0$, $p > 0.4$, $BF_{10} = 0.11$). To

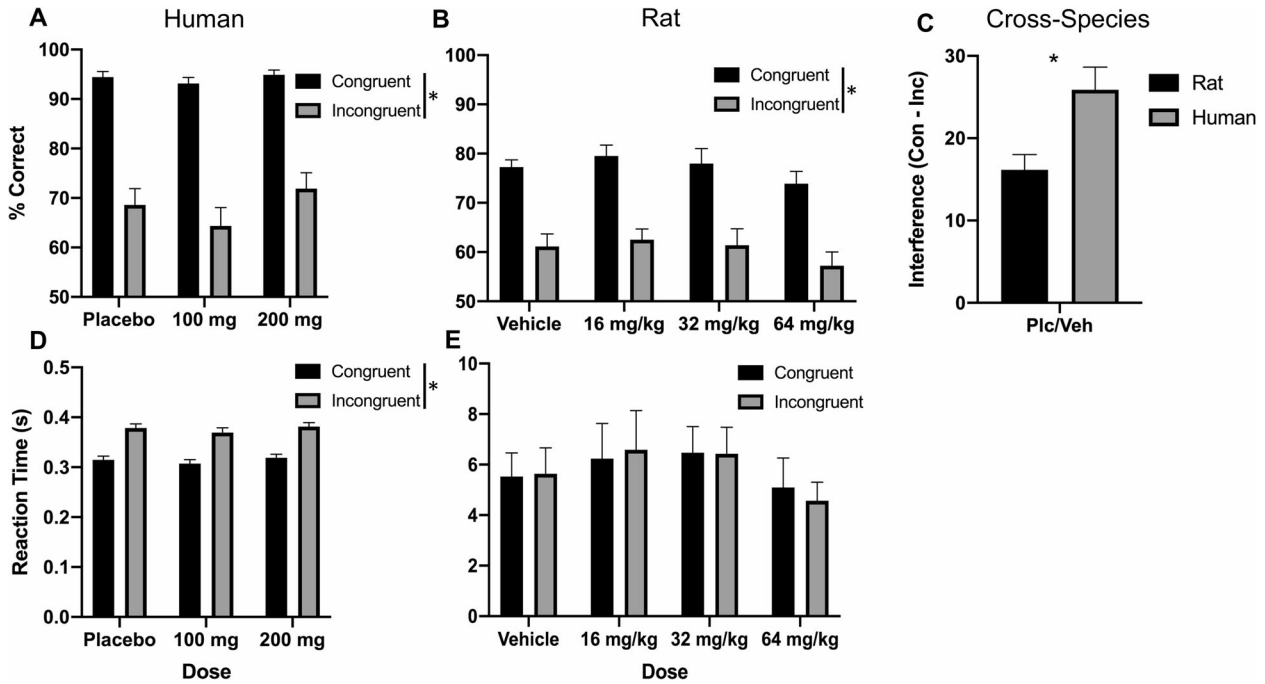

Fig. 2 Behavioral results. A Human response accuracy. Average response accuracy is shown as a percentage of correct trials ($n = 26$). **B** Rat response accuracy. Average response accuracy is shown in the percentage of correct trials ($n = 11$). **C** Cross-species comparison of the interference effect on accuracy. The difference between accuracy on congruent and incongruent trials (*y*-axis) is significantly larger in humans. **D** Human reaction time. Average reaction time shown in seconds. **E** Rat reaction time. Average reaction time shown in seconds. The significant main effect of congruency indicated by figure legend "*". Data are presented as mean ± standard error of the mean.

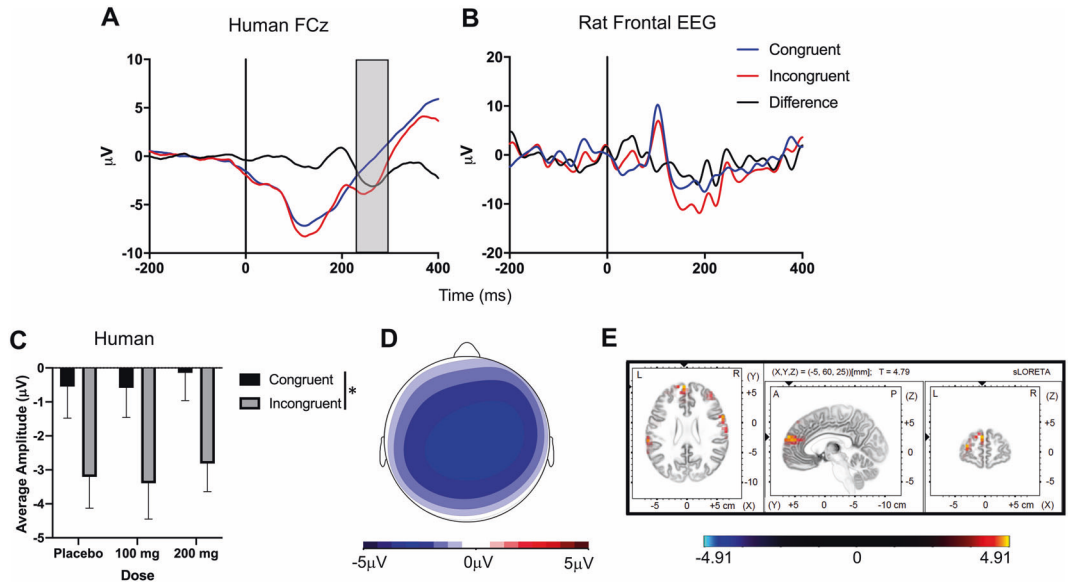

Fig. 3 Stimulus-locked event-related potentials. Congruent target presentation is shown in blue, incongruent target presentation in red, and the difference wave (incongruent−congruent) in black. Target stimulus presentation is indicated by the vertical line at time 0. **A** Human FCz placebo condition ($n = 26$). Trial types were compared in the 230–290 ms time window as indicated by the shaded box. **B** Rat frontal EEG vehicle condition ($n = 9$). In rats, ERPs did not differ by trial types, so all points were compared. **C** Human data across drug treatment. Modafinil had no effect on the N200 component. **D** Human scalp distribution of the N200 (incongruent minus congruent) from 230 to 290 ms post target stimulus presentation. **E** Source localization of the N200 computed by sLORETA. The peak voxel was located in the Precentral Gyrus (BA 6; $X = 59$, $Y = 2$, $Z = 32$; $t = 6.80$, $p < 0.05$, corrected), and the cluster surviving correction for multiple comparisons encompassed prefrontal and anterior cingulate cortices. BA Brodmann area. *X*, *Y*, *Z* coordinates are based on Talairach coordinates. A Anterior, P Posterior, L Left, R Right. The significant main effect of congruency indicated by figure legend "*".

determine a potential source of the N200 in the placebo condition, we used sLORETA [37]. As expected, we found that congruency (incongruent minus congruent) resulted in significant activation ($p <$ 0.05, corrected for multiple comparisons) in areas in the middle frontal lobe, including medial frontal gyrus (Brodmann area (BA) 6, BA 9, BA 10; Fig. 3D, E, Table S2). Given that there were no discernable N200-like ERPs in the stimulus-locked rodent data (Fig. 3B), data were entered into a TANOVA using sLORETA. The

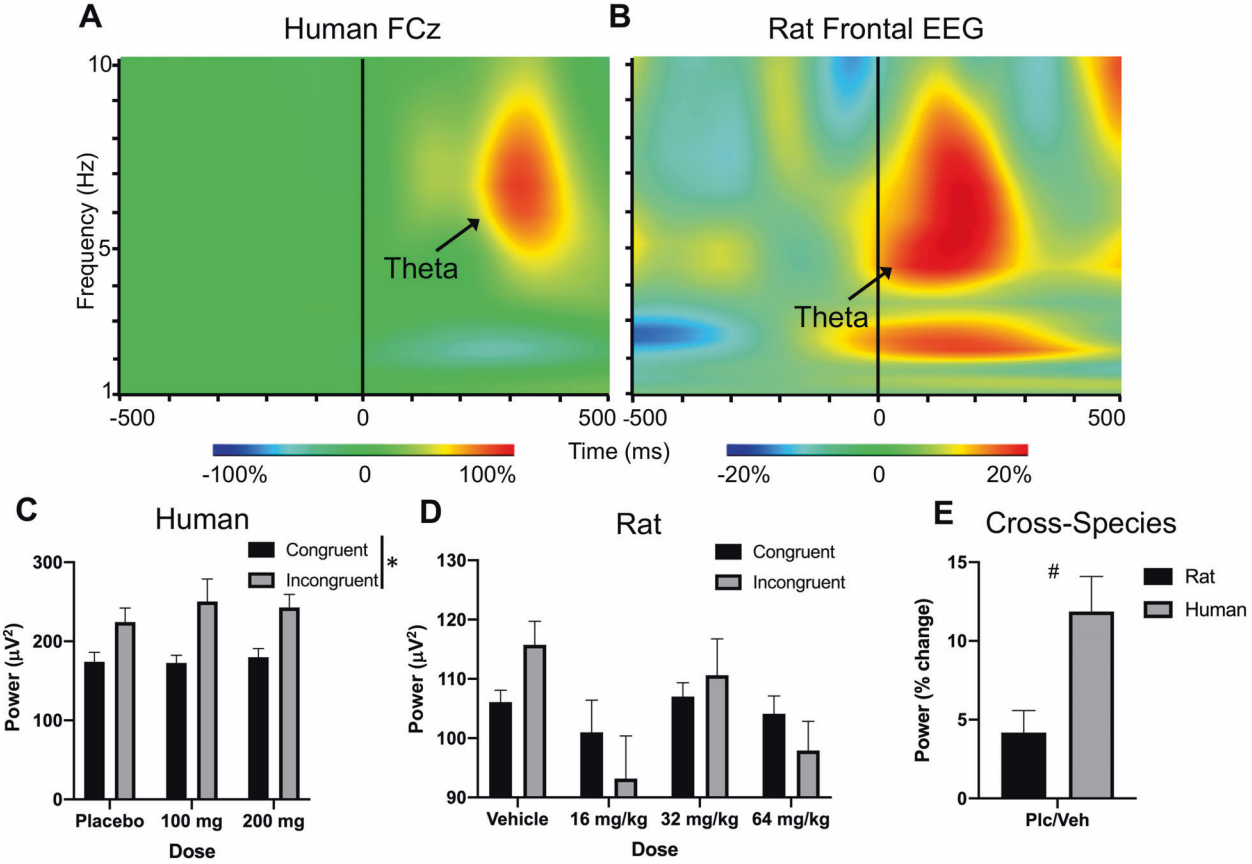

Fig. 4 Stimulus-locked wavelets. Color plot data are plotted as the difference between incongruent and congruent target stimulus presentation. Data are presented as percent change from baseline. Target stimulus presentation occurred at time 0. **A** Human FCz placebo condition. Increased frontal theta power (4.09–6.53 Hz) from 300 to 500 ms post target stimulus presentation. **B** Rat frontal EEG vehicle condition. Increased frontal theta power (3.61–7.31 Hz) from 50 to 250 ms post target stimulus presentation. **C** Human theta power across drug treatment. **D** Rat theta power across drug treatment. Modafinil had no effect on conflict-induced changes in theta power in either species. **E** Cross-species comparison of conflict-evoked theta power. Data were normalized as percent change [(incongruent−congruent)/(incongruent + congruent)] for cross-species comparison. The task elicited a trending ($p = 0.052$) larger conflict-evoked frontal theta signal in humans than rats, indicated by "#". The significant main effect of congruency indicated by figure legend "*". Boxes indicate time-frequency ranges exported for analysis.

congruency effect (incongruent minus congruent) was computed via paired-samples *t*-tests. Using this method and the resulting critical *t* value ($t > 5.66$), we detected no significant differences between congruent and incongruent trials in rats (all *ps* > 0.05). In the absence of a stimulus-locked N200-like deflection in the rats, the two species were not directly compared.

Stimulus-locked spectral power (theta). Frontal theta power in humans was greater following incongruent than congruent target stimulus presentation across treatment conditions ($F(1,24) = 39.32$, $p < 0.001$, $\eta^2_p = 0.61$, $BF_{10} = 2.34 \times 10^7$; Fig. 4A, C). Theta power on incongruent trials was significantly greater than congruent trials in the placebo condition ($t(50) = 3.66$, $p = 0.0018$, Cohen's $d = 1.03$), and this effect was observed in nearly all subjects (binomial $p(22/26) < 0.001$). In rats, theta power did not differ between congruent and incongruent trial types across drug conditions ($F < 0.01$, $p > 0.9$, $BF_{10} = 0.25$). However, in the vehicle condition, theta power was larger on incongruent trials than congruent trials at the right frontal EEG electrode ($t(8) = 3.07$, $p = 0.015$, Cohen's $d = 1.02$; Fig. 4B, D), an effect that was observed in nearly all rats (binomial $p(8/9) < 0.02$). Notably, as can be seen in Fig. 4A, B, frontal theta in rats peaked earlier (~200 ms) than theta in humans (~350 ms). Modafinil treatment did not affect theta power in humans ($F < 0.6$, $p > 0.5$, $BF_{10} = 0.10$) or rats ($F < 2.6$, $p > 0.08$, $BF_{10} = 6.11$). Notably, the large Bayes factor in rats, coupled with the lack of significant effect of modafinil, implies that the sample may have been underpowered to detect a drug effect on frontal theta. Because increases in frontal theta in the placebo/vehicle condition were observed in both species, we examined cross-species similarity directly. There was no significant effect of *Species*, however, we found a trend towards greater theta power in humans ($F(1,31) = 4.08$, $p = 0.052$, $\eta^2_p = 0.116$; Fig. 4E).

Response-locked ERPs. In humans, a negative voltage deflection (i.e., ERN) peaked between 0 and 100 ms after incorrect responses and was larger than the negative deflection following correct responses across treatment conditions ($F(1,24) = 123.56$, $p < 0.001$, $\eta^2_p = 0.837$, $BF_{10} = 2.91 \times 10^{31}$; Fig. 5A, C). In the placebo condition, the negative deflection was significantly larger after incorrect responses ($t(50) = 15.58$, $p < 0.001$, Cohen's $d = 4.41$). This effect was present in nearly all subjects (binomial $p(25/26) < 0.001$), and is thought to reflect automatic error detection [21]. Similar difference waves in the response-locked ERP emerged in rats in the ACC local field potential ($F(1,9) = 48.66$, $p < 0.001$, $\eta^2_p = 0.844$, $BF_{10} = 168.37$; Fig. 5B, D). Relative negativity in the difference between incorrect and correct responses was present in nearly all subjects (binomial $p(10/11) < 0.006$) and was significantly different in the vehicle condition ($t(30) = 3.32$, $p < 0.001$, Cohen's $d = 1.21$). While the relative negativity in rats, unlike in humans, was driven by an increased positivity on correct

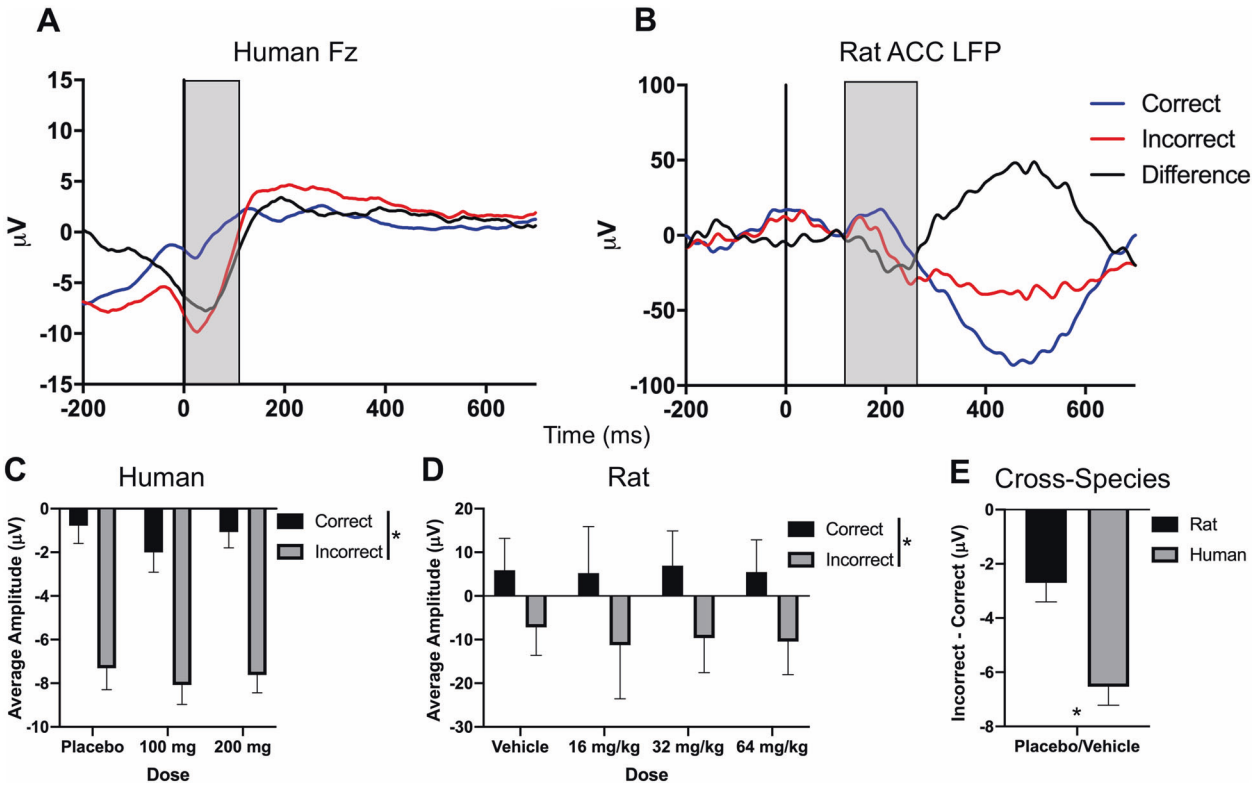

Fig. 5 Response-locked event-related potentials. Correct responses are shown in blue, incorrect responses in red, and the difference wave (incorrect−correct) in black. The response occurred at time 0 as indicated by the vertical line. **A** Human FCz placebo condition ($n = 26$). Errors and correct responses were compared in the 0–100 ms time window as indicated by the shaded box. **B** Rat ACC LFP vehicle condition ($n = 11$). In rats, errors and correct responses were compared in the 115–265 ms time window as indicated by the shaded box. **C** Human amplitudes across drug treatment. **D** Rat amplitudes across drug treatment. Modafinil had no effect on response-locked ERPs in either species. **E** Cross-species comparison of the difference between incorrect and correct responses. Data were normalized using the ratio of trial type-specific standard deviations between the species to enable cross-species comparison. The task elicited a difference between incorrect and correct responses in humans than rats. The significant main effect of accuracy indicated by figure legend "*".

responses and occurred slightly later, the cross-species qualitative similarity in difference waves, an essential consideration in ERPs [38], is notable. Modafinil did not affect the error-related response in humans ($F < 2.7$, $p > 0.07$, $BF_{10} = 0.13$) or in rats ($F < 0.2$, $p > 0.8$, $BF_{10} = 0.36$). Because both species showed response-locked negativity in the difference between incorrect and correct responses in the placebo/vehicle conditions, we compared them directly. We found a significant effect of *Species* ($F(1,33) = 10.85$, $p = 0.002$, $\eta^2_p = 0.247$), indicating that, while both species showed a negative difference between incorrect and correct responses, this difference was larger in humans (Fig. 5E). To determine a potential source of the human ERN, we used sLORETA. As expected, errors were associated with significant ($p < 0.05$, corrected for multiple comparisons) activation in the medial frontal gyrus (BA 9, BA 6; Supplemental Fig. 3A–C, Table S2).

In humans, immediately following the ERN, incorrect responses were associated with a larger positive deflection (i.e., Pe) compared to correct responses across treatment conditions ($F(1,24) = 22.61$, $p < 0.001$, $\eta^2_p = 0.485$, $BF_{10} = 6.42 \times 10^8$; Fig. 5A). In the placebo condition, the Pe (which is thought to reflect attention allocation to the error; [39]) was significantly larger following errors ($t(50) = 5.86$, $p < 0.001$, Cohen's $d = 1.66$) and was observed in the majority of subjects (binomial $p(19/26) < 0.01$). Rats also exhibited a positive deflection in the error minus correct difference wave, although this was driven by a large negative deflection in the correct response across treatment conditions ($F(1,9) = 57.68$, $p < 0.001$, $\eta^2_p = 0.865$, $BF_{10} = 8.47 \times 10^7$; Fig. 5B). In the vehicle condition, the Pe was significantly larger following errors ($t(30) = 6.70$, $p < 0.001$, Cohen's $d = 2.45$), and this effect was observed in nearly all subjects (binomial $p(10/11) < 0.006$). Modafinil treatment did not affect the Pe humans ($F < 0.6$, $p > 0.5$, $BF_{10} = 0.09$) or rats ($F < 0.6$, $p > 0.6$, $BF_{10} = 0.12$). Because both species exhibited a significant Pe in the placebo/vehicle condition, we compared them directly. We found a significant effect of *Species* ($F(1,33) = 8.826$, $p = 0.006$, $\eta^2_p = 0.211$), indicating that, while the task elicited a Pe-like deflection in both species, the effect was larger in rats. Together, these results demonstrate that the Flanker task elicited similar difference wave components to response-locked ERPs, although the timing and constituent deflections to error and correct trials differed between species.

Response-locked spectral power. In human subjects, frontal theta power was significantly increased following incorrect compared to correct responses on incongruent trials across treatment conditions ($F(1,24) = 67.518$, $p < 0.001$, $\eta^2_p = 0.738$, $BF_{10} = 3.52 \times 10^{26}$; Fig. 6A, C). In the placebo condition, theta power was significantly larger following incorrect responses ($t(50) = 11.83$, $p < 0.001$, Cohen's $d = 3.35$). Such error-related increases in frontal theta are commonly detected in Flanker tasks [8] and were observed in nearly all subjects (binomial $p(25/26) < 0.001$). In contrast, rats did not exhibit error-related theta power but did exhibit a pronounced response-locked change in delta power, such that delta power in the ACC local field potential was greater following correct than incorrect responses across treatment conditions ($F(1,9) = 16.79$, $p = 0.003$, $\eta^2_p = 0.651$, $BF_{10} = 2.19 \times 10^5$; Fig. 6B, D). In the vehicle condition, the suppression of delta power was

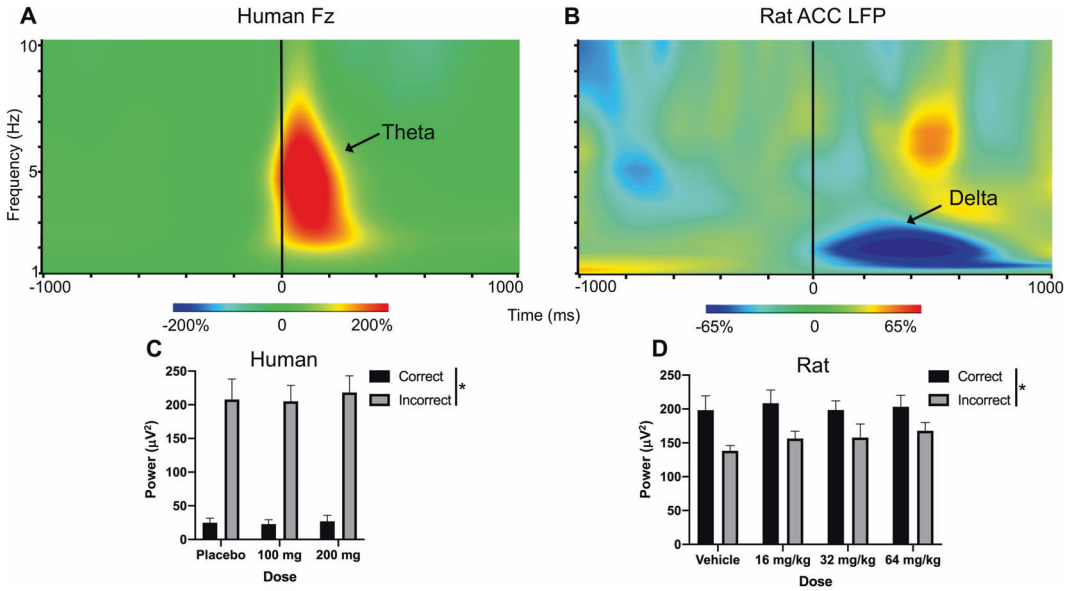

Fig. 6 Response-locked wavelets. All data are plotted as the difference between incorrect and correct responses on incongruent trials. Data are presented as percent change from baseline. The response occurred at time 0. **A** Human Fz placebo condition. Increased frontal theta power (4.09–6.53 Hz) from 0 to 200 ms post response. **B** Rat ACC LFP vehicle condition. Reduced delta power (1.01–2.05 Hz) 200–600 ms post response. **C** Human theta power across drug treatment conditions. **D** Rat delta power across drug treatment conditions. The significant main effect of accuracy indicated by figure legend "*". Boxes indicate time-frequency ranges exported for analysis.

significantly greater following errors ($t(30) = 4.78$, $p < 0.001$, Cohen's $d = 1.53$) and was observed in all subjects (binomial $p(11/11) < 0.001$). Modafinil treatment did not affect response-locked changes in spectral power in humans ($F < 0.4$, $p > 0.7$, $BF_{10} = 0.07$) or rats ($F < 1.1$, $p > 0.3$, $BF_{10} = 0.12$). Because the two species show different changes in response-locked spectral power, they were not directly compared. These data indicate that, while the task elicited response-evoked changes in spectral power in both species, these effects had species-specific characteristics.

DISCUSSION

The overarching goals of this work were to (1) develop a novel cross-species task to probe cognitive control and (2) assess similarities in neurophysiological responses during this task between humans and rats. We used prior work in humans to develop a novel version of the Eriksen Flanker task that rats could perform via touchscreen and validated this new procedure in humans to ensure that it produced the same general outcomes as traditional versions. We then used these procedures to collect task-aligned endpoints in rats and humans. We found that, in both humans and rats, the task elicited an interference effect on accuracy, conflict-induced increases in frontal theta power, and relative negativity and subsequent positivity in the ERP following errors. By comparing task effects observed in each species directly, we found that the task elicited larger effects on Flanker interference (accuracy), and relative negativity following responses in humans, and a larger post-error positivity in rats (driven by the large negative deflection following correct responses). Collectively, the current data suggest that the neural mechanisms that regulate cognitive control in rats may overlap with those in humans.

A cross-species Flanker task enables the systematic testing of hypotheses about basic cognitive control function, as well as the ways in which alterations in neurotransmitter signaling affect specific cognitive domains. For example, dopamine has been consistently implicated in midfrontal cortex-mediated cognitive control [40, 41], suggesting that increases in dopamine might influence these measures. We tested this possibility with modafinil, a dopamine reuptake inhibitor that has been shown to increase extracellular levels of dopamine [22]. Based on a large literature [42, 43], we had predicted that modafinil would dose-dependently increase several signals, including N200, ERN, and frontal theta power. Surprisingly, none of these signals were modulated with modafinil in either species, though we observed a trend in stimulus-locked theta power in rats ($p = 0.08$) that may bear out in future studies. While modafinil has pro-cognitive effects in humans [23], there are no reports describing modafinil effects on conflict and response monitoring; as such, our data suggest that that the drug might affect cognitive domains other than conflict and response monitoring. Further evaluation of how other, more efficacious dopaminergic drugs modulate these activities will provide a critical context for the present results with modafinil.

We found that both humans and rats exhibited increases in theta power after high-conflict (incongruent) trials, with rats showing earlier differentiation in the theta band than humans. These findings align with earlier human source localization studies indicating that these conflict-related signals originate in the ACC [36], as well as with rodent studies demonstrating conflict-evoked increases in ACC activity [44]. Indeed, we found the ACC to be a source of conflict-induced ERPs in humans (Fig. 5E and Table S1). Frontal theta power has emerged as an important index of cognitive control after incorrect responses, increased conflict, and negative feedback suggesting that it reflects a common mechanism of cognitive control [8, 45]. Conflict-potentiated theta power in humans, like the corresponding N200, reflects successful inhibition of prepotent responses or the resolution of competing response choices [32]. A prior study demonstrated increases in frontal theta power in rats following correct trials after premature errors in a time-estimation task [16]. While time estimation tasks provide important insights on cognitive function, they are not widely used to study cognitive deficits in human clinical populations. Our observation of conflict-evoked frontal theta power in both rats and humans extends this prior work and further underscores the utility of frontal theta power in the study of healthy behavior and psychopathology.

Though we observed differences in magnitude and timing across species, the presence of ERN-like and Pe-like signals in rodent ACC extends models of ACC function and suggests that response-monitoring signals are fundamental and evolutionarily conserved aspects of cognitive control. We note that the individual ERP waveforms differed from rodents to humans; in contrast to the well-established initial negativity and subsequent positivity after errors, rodents demonstrated an initial positivity and subsequent negativity on correct trials. Although the components differed, the ERP difference waves appeared similar between the species. In addition, we cannot rule out the possibility that the post-response negativity in rats was driven by immediate auditory feedback indicating response accuracy. Though few studies have examined post-response negativity in rats and compared these signals to humans, post-response negativity has been observed in the rat ACC local field potential in a probabilistic reward task [46]. Consistent with our findings, the onset of this signal was delayed in rats relative to humans in an analogous task [47]. While further research is required to fully understand timing differences in error-related ERPs between humans and rats, it has been shown that other ERPs, such as auditory responses, have a more rapid onset in rodents [48]. Despite timing differences between the species, auditory ERPs have been previously shown to be delayed by a similar amount in human pathology and rodent models of pathology [49]. Though the present study did not find modulation of the post response negativity with modafinil, future studies will use other pharmacological and nonpharmacological challenges to further assess potential similarity across species.

Unlike the observed similarity in response-locked ERPs, response-locked spectral changes diverged between species. As expected, humans exhibited a well-characterized error-evoked increase in frontal theta power. However, rats showed an error-evoked suppression of delta power in the ACC local field potential (i.e., increased delta power for correct responses). Such species-specific features of spectral data are not surprising, based on prior studies in rats. For example, instrumental responding for reward has been shown to increase delta power in the prefrontal cortex, ventral tegmental area, and CA1 region of the hippocampus in rats [50], and free access to food has been shown to increase delta power in the orbitofrontal cortex [51]. Thus, it is most likely that the current data represent a point of functional divergence between humans and rats, whereby responses are processed through the engagement of distinct neural circuitry underlying conditions that maintain behaviors (e.g., rewards in rats, the proclivity to avoid mistakes in humans). Understanding such species-specific characteristics, as well as cross-species similarities, of neural responses should improve the translational utility of response-locked spectral power changes in studies of cognitive function.

While humans showed the expected Flanker interference effect on reaction time (reflected in longer response latencies on incongruent compared to congruent trials), the task did not elicit the expected effect on reaction time in rats. One possible explanation for these dissimilar results may lie in important differences in timing between the two versions of the task. While humans were required to respond within a limited time, no such requirement was in effect for rats. Further, while humans can be instructed to pay close attention and, indeed, were prompted to speed up if response latencies increased to the maximum allowable time, the conditions required to instruct or train rats to attend to response latency likely would have resulted in considerable divergence between cross-species task structure. Whereas this initial version of the rat task was not specifically designed to quantify differences in reaction time between incongruent and congruent trial types—in fact, *accuracy* was our benchmark while developing, piloting, and optimizing the rodent task—further task development to align response latencies across species might yield additional important points of comparison and insight.

We also did not detect differences in ERPs between incongruent and congruent target stimulus presentation in rats. One potential explanation for this null finding may be related to the limitations of the rat visual system. Although the observation of increases in target-locked theta power suggests that the rats are indeed capable of detecting the presence of the stimulus, it is possible that the punctuated presentation of the target stimulus did not drive a consistent (time-locked) difference in ERPs. Theta power may be more sensitive to this type of stimulus presentation in rats. Alternatively, it is possible that the effect was not detected due to a lack of electrode coverage. While we have the capability to record from human subjects using 96 separate electrodes, the size and contour of the rat skull substantially reduce the maximum number of implantable surface electrodes, which were used in this study to maximize translational relevance. Future studies of stimulus-locked ERPs in the rat would benefit from increased electrode coverage of the forebrain area and, potentially, the use of multichannel local field potential probes.

In summary, cross-species comparisons of neurophysiological activity during cognitive tasks may enable advances in the understanding of common mechanisms of neural processing. Here, we developed a novel Flanker task to assess similarities in humans and rodents in neurophysiological responses to cognitive control. Similarities across species include not only behavioral responses but extend to discrete neural events and oscillatory patterns that index cognitive control and decision making. The observation of neurophysiological responses in rats that are qualitatively similar to well-characterized effects in humans serves as validation for this novel task and highlights its potential utility going forward. Investment in translationally-relevant models, like the Flanker task, may enhance the utility of laboratory animals in the context of psychiatric illness, enabling novel insights into the neural basis of healthy and aberrant behavior and thereby hastening the development of innovative treatments.

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AUTHOR CONTRIBUTIONS

MAR—design of the work. Acquisition, analysis, and interpretation of data. Drafting of manuscript. HSS—design of the work. Acquisition, analysis, and interpretation of data. Drafting of manuscript. BDK—design of the work. Interpretation of data. Revision of the manuscript. SN—design of the work. Acquisition, analysis, and interpretation of data. MB—acquisition and analysis of data. AMI-M—analysis and interpretation of data. SP—acquisition of data. EC—acquisition of data. AD-A—design of work. Interpretation of data. Revision of the manuscript. SAB—interpretation of data. Revision of the manuscript. SL—design of work. Interpretation of data. VBR—design of work. Interpretation of data. Revision of the manuscript. GV—acquisition of data, medical evaluations. Revision of the manuscript. JB—design of work. Interpretation of data. Revision of the manuscript. WAC Jr.—design of work. Interpretation of data. Revision of the manuscript. DAP—design of work. Analysis and interpretation of data. Revision of the manuscript. Secured funding.

ADDITIONAL INFORMATION

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