Cognitive, Affective, & Behavioral Neuroscience (2024) 24:269–278
https://doi.org/10.3758/s13415-023-01150-z

SPECIAL ISSUE/PRECLINICAL ASSAYS

Amphetamine increases motivation of humans and mice as measured by breakpoint, but does not affect an Electroencephalographic biomarker

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Accepted: 15 December 2023 / Published online: 2 January 2024

Abstract

Translation of drug targets from preclinical studies to clinical trials has been aided by cross-species behavioral tasks, but evidence for brain-based engagement during task performance is still required. Cross-species progressive ratio breakpoint tasks (PRBTs) measure motivation-related behavior and are pharmacologically and clinically sensitive. We recently advanced elevated parietal alpha power as a cross-species electroencephalographic (EEG) biomarker of PRBT engagement. Given that amphetamine increases breakpoint in mice, we tested its effects on breakpoint and parietal alpha power in both humans and mice. Twenty-three healthy participants performed the PRBT with EEG after amphetamine or placebo in a double-blind design. C57BL/6J mice were trained on PRBT with EEG (n = 24) and were treated with amphetamine or vehicle. A second cohort of mice was trained on PRBT without EEG (n = 40) and was treated with amphetamine or vehicle. In humans, amphetamine increased breakpoint. In mice, during concomitant EEG, 1 mg/kg of amphetamine significantly decreased breakpoint. In cohort 2, however, 0.3 mg/kg of amphetamine increased breakpoint consistent with human findings. Increased alpha power was observed in both species as they reached breakpoint, replicating previous findings. Amphetamine did not affect alpha power in either species. Amphetamine increased effort in humans and mice. Consistent with previous reports, elevated parietal alpha power was observed in humans and mice as they performed the PRBT. Amphetamine did not affect this EEG biomarker of effort. Hence, these findings support the pharmacological predictive validity of the PRBT to measure effort in humans and mice and suggest that this EEG biomarker is not directly reflective of amphetamine-induced changes in effort.

Keywords Dextroamphetamine · Cognition · Biomarker · Progressive ratio breakpoint

Introduction

The will to expend effort underlies a person's everyday functioning; yet intrinsic motivation remains poorly understood from a neurobiological perspective. Deficits in motivation are a hallmark of several psychiatric disorders, including schizophrenia and depression (Kirkpatrick et al., 2006; Laughren & Levin, 2011; Marder et al., 2011). Further investigation into the mechanisms underlying motivation and its role in these disorders is hindered by the shortcomings of the currently available tools. For example, depression treatment development has been guided by animal studies of behaviors with little connection to depression as manifested in humans (e.g., forced swim test or deficits in sucrose preference (Barkus et al., 2012; Distler et al., 2012; Karlsson et al., 2009; Vardigan et al., 2010), quantifying abnormalities that

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are not reliably observed in the human phenotype (Berlin et al., 1998). To address this gap, recent efforts have focused on the development of tasks with cross-species predictive validity, specifically in the context of assessing amotivation (Horan et al., 2015; Reddy et al., 2015, 2016). Recent initiatives from the National Institute of Mental Health (NIMH) aim to close this cap, including Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) (Barch et al., 2009; Carter & Barch, 2007) and the Research Domain Criteria (RDoC) framework (Cuthbert, 2014). The focus on task features and potential biomarkers across species offers a more precise way to understand cognitive and behavioral disturbance in psychiatric disorders.

One of the behavioral tasks recommended by CNTRICS is the progressive ratio breakpoint task (PRBT), which measures effortful motivation. Broadly, the PRBT requires a participant to perform a specific action (lever presses, nose pokes, joystick rotations, etc.) a set number of times to receive a reward, at which point a new trial begins with an increased number of needed actions. The highest number of actions committed within a session to obtain a reward is termed the breakpoint and is interpreted as a measurement of the motivational state of the participant. The potential contribution of effortful motivation to global cognition (Markou et al., 2013) is supported by our finding that breakpoint as measured by the PRBT predicted 24% of the variance of global cognitive functioning in people with schizophrenia (Bismark et al., 2017). PRBT has already been widely used in animals, originally to assess drug-addicting effects in mice (Drew et al., 2007; Markou et al., 2004; Romoli et al., 2019), rats (Higley et al., 2011; Orio et al., 2009; Paterson et al., 2004), primates (Cooper et al., 2013), and humans (Barrett et al., 2008; Stoops et al., 2005). More recently, PRBT has been used to ascertain the motivation for natural rewards in rodents (Amitai et al., 2019; Bensadoun et al., 2004; Heath et al., 2019; Young & Geyer, 2010, 2013), and humans (Bismark et al., 2017; Wolf et al., 2014). Human PRBT variants are designed to be either physically or cognitively challenging, but both paradigms have provided evidence for decreased motivation in schizophrenia (Bismark et al., 2017; Wolf et al., 2014) and depression (Hershenberg et al., 2016). Hence, the PRBT provides a degree of face validity and clinical sensitivity (Young, 2023; Young et al., 2010), although to-date limited data have been generated to support neurobiological, pharmacological, or predictive validity.

Recently, our group investigated the potential neurobiological and predictive validity of the PRBT by utilizing electroencephalographic (EEG) recordings in both mice and humans while they performed the task. Such EEG recordings are beneficial, because unlike other neural recording (e.g., functional magnetic resonance imaging), they can be conducted in awake behaving animals (Young & Light, 2018). We demonstrated that a PRBT EEG biomarker—an increase in parietal alpha power during the PRBT session as a participant reached their breakpoint not simply linked to time on task—was seen in both mice and humans (Cavanagh et al., 2021). However, the pharmacologic predictive validity and sensitivity of this EEG biomarker have not yet been assessed. Following this observation, the present study sought to test the pharmacological predictive validity of: 1) behavioral outcomes (breakpoint), and 2) parietal alpha power as a biomarker of changes in motivation state, within the PRBT. This approach is the first to conduct such cross-species validation in both mice and humans. Given that amphetamine increased breakpoint in mice (Bensadoun et al., 2004; Heath et al., 2015), we tested whether amphetamine would increase breakpoint in both mice and humans, in addition to altering the parietal alpha biomarker of motivation. Hence, we hypothesized that amphetamine would: 1) increase breakpoint in both humans and mice; and 2) that parietal alpha power would shift in concert with breakpoints across species.

Methods

Human study

Participants

Twenty-three healthy participants (HP; 48% female) aged 18–35 years were recruited from the community via public advertisements and monetarily compensated for study participation. First, subjects underwent phone screening to assess current and past medical and psychiatric history, medication, and recreational drug use and family history of psychosis. Participants who passed the phone screen were invited for a screen day. At screening visits, participants signed study consents and completed the structured clinical interview (SCID-NP; First et al., 2002), self-reporting questionnaires about caffeine intake and handedness, a hearing test, physical examination, an electrocardiogram (EKG), urine toxicology screen, urine pregnancy test for females as per our established screening protocol (Chou et al., 2013), and a Wide Range Achievement Test (WRAT) for IQ assessment, confirming physical and mental health. Study inclusion criteria were described previously (Bhakta et al., 2022). This study was conducted at the UCSD Medical Center, with approval from the UCSD Human Subject Institutional Review Board. See Table 1 for further demographic details.

Progressive Ratio Breakpoint Task (PRBT) assessment in humans

Consistent with previous reports (Bismark et al., 2017), participants were given instructions to complete the task. It was made clear that they could stop the study and leave as soon as they chose to do so. Participants were required

Table 1 Characterization of the human cohort. *WRAT* Wide Range Achievement Test; *MCCB* MATRICS Comprehensive Cognitive Battery

Age (mean (SD))	22 (4.82)
Race (%):	
Caucasian	39
Asian	26
Pacific Islander/Native Hawaiian/Alaskan	17
Mixed race	15
Gender: M:F	12:11
Education (mean (SD))	14.26 (1.74)
Smokers: nonsmokers	0:23
WRAT score (mean (SD))	108.13 (11.61)
Caffeine intake in mg/day (mean (SD))	165 (231.6)
MCCB composite T-score (mean (SD))	48.17 (9.06)

to rotate the same arcade joystick handle in the indicated direction to be "rewarded" (told that they achieved the next level and received 50 "points"). The number of rotations needed to achieve each level was preset on a progressive ratio schedule (5, 15, 35, 70, 120, rotations, etc.). Ultimately, participants were asked to earn as many points (that had no value) as possible, but it was made clear that they could quit any time, which would end the entire testing session, and they could go home. The breakpoint was quantified as the largest number of levels completed before the subject chose to disengage with the task.

Human drug design

A double-blind, randomized, placebo-controlled, counterbalanced, within-subject design was utilized. Healthy participants received either placebo (PBO) or one of two active doses of d-amphetamine (10 or 20 mg) orally on each of the 3 test days, which were separated by 1 week (MacQueen et al., 2018). Briefly, participants arrived at 8:30 AM after overnight fasting with exception of water, completed a urine toxicology screen and a urine pregnancy test in females, and ate a standardized breakfast. Vital signs (VS) and subjective symptom rating scale (SRS) scores (Swerdlow et al., 2003) were obtained at specific intervals pre- and post-pill [see (Bhakta et al., 2022; Cavanagh et al., 2022)]. Starting 120 minutes post-pill, subjects completed cognitive neuroscience tests finishing with PRBT assessment with simultaneous EEG recording (approximately 150 minutes post-pill).

Human electrophysiological recording and pre-processing

Continuous electrophysiological data were recorded in direct current (DC) mode from 64 scalp leads using a BioSemi Active Two system (http://www.biosemi.com). During data acquisition, the electrode impedances were kept below 25 mV, and all channels were referenced to the system's internal loop (CMS/DRL electrodes). Four electrooculograms (EOG) recorded at the superior and inferior orbit of the left eye and outer canthi of each eye, and one nose and two mastoid electrodes were used for offline re-referencing. All data were collected by using a 1048 Hz sampling rate utilizing a first-order anti-aliasing filter. Custom Matlab scripts and EEGLab (Cavanagh et al., 2021) functions were used for all data processing. As in our previous study (Cavanagh et al., 2021), EEG data were grouped into one second epochs; alpha band power was then averaged for the first and last 50 seconds of the task. Bad channels and bad epochs were identified and were subsequently interpolated and rejected, respectively; then blinks were removed following independent component analysis.

Human drug doses chosen

Amphetamine was administered at 0-, 10-, or 20-mg doses. These doses were chosen because they are used to treat attention-deficit hyperactivity disorder and can improve attention and shift EEG signaling in healthy participants (MacQueen et al., 2018).

Animal subjects

Female and male C57BL/6J mice were obtained from The Jackson Laboratory (Bar Harbor, ME) at 8 weeks of age, housed in same sex groupings of two to four per cage in a temperature- and humidity-controlled vivarium under a reverse 12-h light/dark cycle (lights off 0800 h) and tested during the dark phase. Mice were food restricted to 85% of their free feeding weight for the duration of the study. Mice were first acclimated to the testing chamber and receiving rewards and were considered to be habituated when they consumed 30 rewards in a 30-min session. Following habituation, mice were trained to touch a single illuminated square for reward and were considered trained when they touched the square 30 times within a 30-min session. After touch training, mice were fitted with EEG caps consisting of skull screws (0.078" 57 stainless steel machine screws) fitted and silver wire leads soldered to the pins of Omnetics connectors wrapped securely around each corresponding screw and secured to the skull by using dental cement. Screws were targeted to medial prefrontal cortex (mPFC: AP +2.80, ML +0.00) posterior parietal cortex (PPC: AP −1.46, ML +1.50) and primary motor (M1: AP +0.75, ML 1.50) with a cerebellar ground. Mice were allowed 1 week recovery and then were allowed to reacquire touch criteria before PRBT training.

In cohort 1, 24 mice (50% female) were tested in the PRBT and intraperitoneally were injected with amphetamine (0, 0.1, 0.3, or 1.0 mg/kg) 30 min before testing

(doses that include those that affect activity, in addition to lower doses improving attention in mice (MacQueen et al., 2018)), randomized via Latin square design, with concomitant EEG recording. Test sessions were 2 hr. Mice were given a 72-hr washout period between tests sessions.

In cohort 2, 40 mice (50% female) were trained in the PRBT and treated with amphetamine (0 or 0.3 mg/kg only, see *Results*) but were not tethered (thus there were no EEG recordings during performance) to test whether such tethering might have impeded drug effects. Drug administration was identical to the first cohort (again within-subjects), aside from the use of a 48-hr washout period, instead of a 72-hr period. All experimental procedures were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the University of New Mexico Health Sciences Center Institutional Animal Care and Use Committee (see Cavanagh et al., 2021 for information on touchscreen pretraining). All rewards included the delivery of an auditory tone signaling the availability of strawberry milkshake.

Progressive Ratio Breakpoint Task (PRBT) assessment in mice

Mice pressed a single illuminated square in the center of the touchscreen for strawberry milk rewards. The stimulus remained on the screen until the required response number was made, consistent with human testing. The number of touches required for a reward increased by a step every three trials (e.g., 1, 1, 1, 2, 2, 2, 4, 4, 4, 7, 7, 7, etc.), consistent with earlier studies (Bensadoun et al., 2004; Milienne-Petiot, Kesby et al., 2017b; Young et al., 2011, 2015). The breakpoint was the last (and therefore highest) ratio completed at the end of the 2-hr session. Mean choice latency (MCL, the average time between trial initiation and response) and mean reward latency (MRL, the average time between reward delivery and reward collection) also were measured. As in our previous study (Cavanagh et al., 2021), data were epoched around the stimulus presentation; alpha band power was then averaged for the first and last five epochs (5 s) of the task.

Mouse drug doses chosen

Amphetamine was administered at 0, 0.3, or 1.0 mg/kg. These doses include those that induce hyperactivity (1.0 mg/kg) and those that do not (0.1 and 0.3), which also improve operant task performance in mice (Heath et al., 2015; MacQueen et al., 2018).

Statistical analysis

Mixed linear models (MLMs) were run by using MIXED command in SPSS 26 (IBM, Chicago, IL) to analyze individual differences in PRBT and EEG across doses in the human and mouse EEG studies, with sex included as a factor. Alpha power was quantified by using a priori time-frequency region of interest of 8–12 Hz from 0 to 200 ms (poststimulus for mice, arbitrarily around the time locking 1-s marker for humans), as in Cavanagh et al. (2021). The individual difference in alpha power (last minus first) was used for statistical analysis. Given the absence of parametric variation, the performance of the second cohort of mice was analyzed by ANOVA, accounting for dose, sex, and baseline PRBT performance. Alpha for all hypotheses was set at 0.05. We report linear trends, which had the best fit to the data.

Results

Human

Amphetamine increased breakpoint in humans ($F(2,42) = 7.3$, $p < 0.005$; Fig. 1A). *Post hoc* analyses revealed that amphetamine increased breakpoint at both 10-mg and 20-mg doses relative to placebo ($p < 0.05$). No effect of sex was seen ($F(1,31) = 0.5$, $p = 0.493$), nor was there a sex*drug interaction on breakpoint ($F(1,30) = 0.3$, $p = 0.599$). To test for main effect of time on EEG responsivity, an MLM was used with time as a factor. This analysis revealed a main effect of time across all drug conditions (time $F(1,28.24) = 33.4$, $p < 0.001$) but no interaction with other variables. Consistent with previous reports, larger alpha power was observed in the late versus early time window. Given the size of this effect, the lack of interactions, and the size of the model relative to the size of the data, subsequent analyses used the difference score in time (last minus first) to reduce the model size and complexity. There was no effect of amphetamine on the alpha power difference ($F(2,59) = 0.3$, $p = 0.76$), nor sex ($F(1,59) = 0.0$, $p = 0.94$), nor interaction ($F(2,59) = 0.71$, $p = 0.50$; Fig. 1B, C).

Cohort 1 Mice—EEG tethered

In mice, during concomitant EEG, amphetamine significantly decreased breakpoint ($F(3,56) = 49.9$, $p < 0.001$; Fig. 2A). *Post hoc* analyses revealed that it was the highest dose of amphetamine (1 mg/kg) that significantly reduced breakpoint relative to vehicle-treated mice ($p < 0.05$). This dose of amphetamine reduced the number of trials, and therefore, this condition was not analyzed for alpha power, because there were not enough trials to estimate a

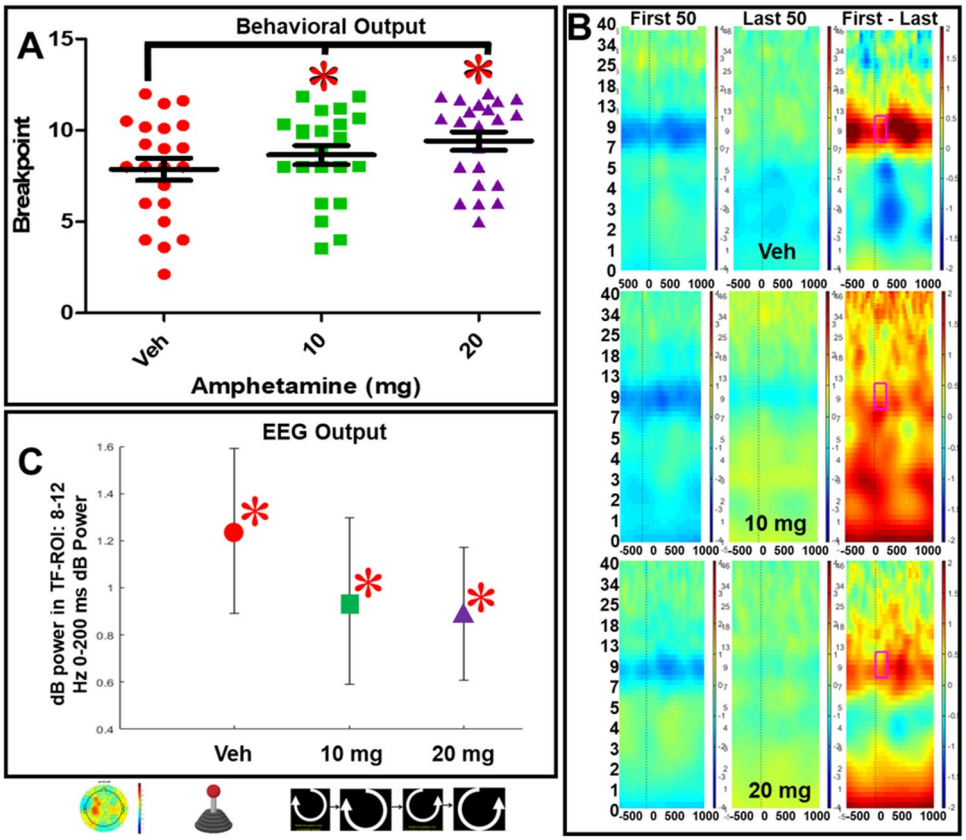

Fig. 1 Effects of amphetamine on motivation in humans as measured via progressive ratio break point task (PRBT) and EEG. **A** Amphetamine significantly increased the break point (joystick rotation) in humans at both doses (10 mg, 20 mg) compared with control. **B** Participants showed elevated parietal alpha power just before reaching break point when given placebo (Veh), as shown by time frequency plots comparing activity in the last vs. first block of trials. **C** This effect was reduced when subject was given amphetamine, although without significant effect. Data presented as individual data-points as well as means ± S.E.M. *$p < 0.05$ as indicated; *$p < 0.05$ relative to 0 db Power

beginning and end set. In the remaining three conditions (placebo, 0.1 mg/kg, 0.3 mg/kg), no main effect of sex on breakpoint was observed ($F(1,28) = 0.110$, $p = 0.743$), nor was there an observed drug*sex interaction ($F(1,37) = 2.8$, $p = 0.102$). For EEG analysis (Fig. 2B, C), the MLM with time revealed a main effect of sex ($F(1,149) = 6.59$, $p = 0.01$; males were higher than females) but not time ($F(1,149) = 1.70$, $p = 0.19$) nor drug ($F(1,149) = 2.45$, $p = 0.09$) and no significant interactions. For simplicity, a reduced MLM was used with the difference score in time (last minus first), with no effect of amphetamine on the alpha power difference ($F(2,49.3) = 1.4$, $p = 0.26$). Given that there was little difference of the alpha power between first and last blocks in 0.1 and 0.3 mg/kg treated mice, we conducted a Wilcoxon signed-rank test for zero median within vehicle-treated mice, observing that they exhibited a significant difference between first and last blocks ($z = 2.0$, $p = 0.045$), consistent with previous observations.

Cohort 2 Mice—Drug treatment alone

Given this unexpected finding of a null effect of amphetamine on breakpoint in mice, we ran a separate cohort to determine whether the presence of the recording tether was a determining factor of their task motivation. This cohort used only the 0.3-mg/kg dose, as this was the highest dose that did not impair performance in the previous cohort and does not induce hyperactivity. This difference enabled us to specifically test the effect of the absence of the tether without other factors possibly affecting motor behavior. This untethered mouse study demonstrated a main effect of amphetamine on breakpoint ($F(1,30) = 11.4$, $p = 0.002$). Thus, amphetamine (0.3 mg/kg) increased breakpoint consistent with the human study (Fig. 3A). Mean choice latency was not affected by amphetamine ($F(1,30) = 0.7$, $p = 0.418$, Fig. 3B), nor was mean reward latency ($F(1,30) = 1.6$, $p = 0.211$, Fig. 3C). As in cohort 1, no main effect of sex was observed in breakpoint

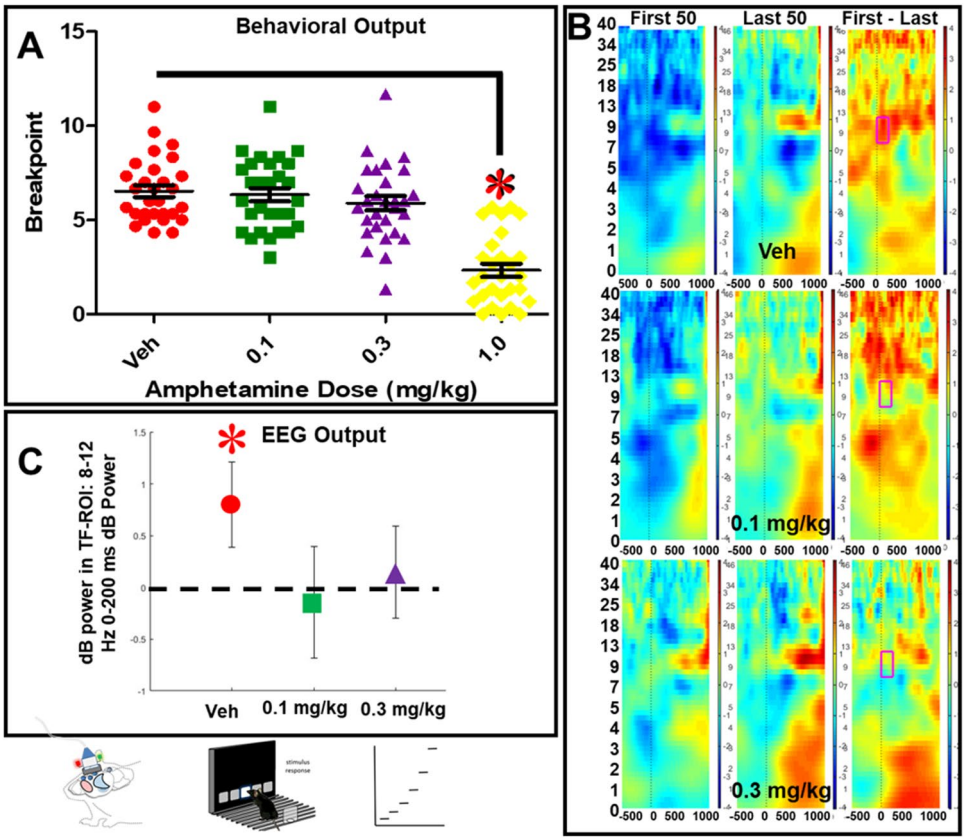

Fig. 2 Effects of amphetamine on motivation in mice as measured via progressive ratio break point task (PRBT) and EEG. **A** The highest dose of amphetamine (1.0 mg/kg) significantly decreased the break point (nose poke) of mice, whereas the other doses (0.1, 0.3 mg/kg) did not show a significant effect compared with control. **B** Mice showed elevated parietal alpha power in the last block of trials relative the first block before reaching breakpoint when given vehicle (Veh) as shown by time frequency plots. **B, C** This effect was reduced in mice treated with 0.1 and 0.3 mg/kg of amphetamine, although without significant effect, with vehicle-treated mice exhibiting significantly higher parietal alpha power in the last – first block of trials. Data presented as individual data-points as well as means ± standard error of the mean. *$p < 0.05$ as indicated; *$p < 0.05$ relative to 0 db Power

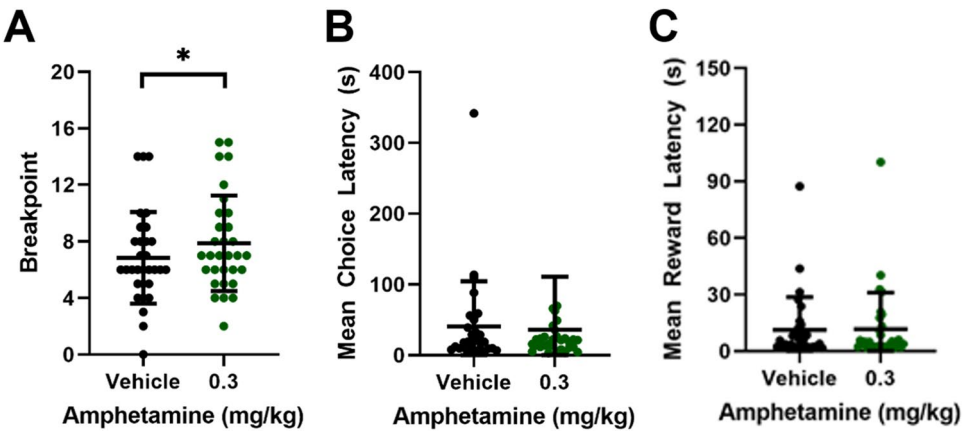

Fig. 3 Amphetamine-induced increase in effortful motivation in the PRBT. After being treated with 0.3 mg/kg of amphetamine, mice exhibited significantly higher breakpoint, the primary outcome measure in the PRBT (**A**). No effect of amphetamine was observed on mean choice latency (**B**), or mean reward latency, with no interaction on baseline level of performance (**C**). Data presented as individual data plots, with mean ± standard error of the mean. *$p < 0.05$ relative to vehicle-treated mice

($F(1,30) = 0.6$, $p = 0.445$), mean choice latency ($F(1,30) = 1.660$, $p = 0.208$), or mean reward latency ($F(1,30) = 0.491$, $p = 0.489$). No drug*sex interactions were for any measure (breakpoint: $F(1,30) = 0.017$, $p = 0.897$; mean choice latency: $F(1,30) = 0.798$, $p = 0.379$; or mean reward latency: $F(1,30) = 0.791$, $p = 0.381$).

Discussion

We provide evidence for the pharmacologic predictive validity of the PRBT, given that amphetamine increased breakpoint in both humans and mice. Furthermore, we provide evidence that both humans and mice exhibit an increase in parietal alpha power, peaking just before subjects desist from responding ("give up"), as seen in all human participants and vehicle-treated mice. Although amphetamine lowered this EEG biomarker, it did not exert significant effects, nor did amphetamine increase breakpoint during EEG tethering in mice. The lack of amphetamine effect on tethered mice may reflect potential limitations of EEG headgear in mice while performing this physical effort task. That amphetamine did not shift the EEG biomarker in mice or humans casts doubt on its suitability as a pharmacologically sensitive biomarker of physical effort, as it may reflect trait responsiveness. Further tests should assess if parietal alpha change reflects global arousal, which is similar to but mechanistically distinct from effortful engagement (Klimesch et al., 1998).

These studies provide two key findings: 1) the pharmacologic predictive support of the PRBT as a means to measure motivation given that amphetamine increased breakpoint in both species; and 2) the observation that a rise in parietal alpha power is reproducible across humans and untreated mice, as previously seen (Cavanagh et al., 2021). This PRBT study was based on previous studies that showed amphetamine-induced breakpoint increases in mice (Bensadoun et al., 2004). This study is the first to demonstrate that amphetamine also increases breakpoint in humans in the PRBT with natural rewards as used in mice, thus demonstrating pharmacological predictive validity of the task. Stimulants, particularly those that inhibit dopamine transporters as does amphetamine, have long-been used to increase effort in people and rodents. For example, the dopamine transporter inhibitors GBR12909 and modafinil increase breakpoints in mice, potentially mediated by dopamine D1 receptors (Young & Geyer, 2010). Other dopamine transport inhibitors, such as beta-phenylethylamine (Ryu et al., 2021) and the dopamine D1 receptor antagonist SCH 23390 (Milienne-Petiot, Groenink et al., 2017a, Milienne-Petiot, Kesby et al., 2017b), increased breakpoint in rodents. One surprising finding in the current study was the failure of amphetamine (0.3 mg/kg) to increase breakpoint in mice that were EEG-tethered unlike in previous publications and our second cohort. We hypothesize that this lack of effect at 0.3 mg/kg may be due to the effort required to complete the task while physically tethered to the EEG, despite the use of commutators to reduce tangling and to make ambulation as unencumbered as possible. Previous studies have utilized a multiday training approach to acclimate animals to movement while tethered, as done in the current study. However, our current data suggest that movement in tethered mice will be hindered to a degree that masks the effects of amphetamine on PRBT performance. Additionally, the inability of our system to measure motor activity during PRBT via beam breaks limited our ability to gauge the interaction between potential motor effects of both EEG tethering and high-dose amphetamine, which can induce hyperactivity in previous studies. Future technology minimizing the size of such headgear may make it possible to demonstrate stimulant-induced PRBT changes and their relationship to EEG biomarkers. The significant decrease in breakpoint following 1 mg/kg of amphetamine was unexpected given previous reports that this dose increased breakpoint (Heath et al., 2015), although in mice that had been previously trained to stability in PRBT. This decrease may be an artifact of the EEG tethering, but similar decreases in breakpoint following high doses of amphetamine have been previously reported in marmosets (Cilia et al., 2001). Therefore, it is possible that our observed decrease was a typical response to high-dose amphetamine in PRBT-naïve mice rather than an effect of EEG tether. Importantly however, this work provides support for a long history of research of stimulant-induced increases in effort that we now quantified in humans using the same PRBT as used in mice.

These data also support the reproducibility of the EEG biomarker of PRBT performance-induced change in parietal alpha power as both humans and mice desist from responding, consistent with previous findings (Cavanagh et al., 2021). While amphetamine increased effort in humans, without altering subjective effects on drowsiness or happiness (data not shown), it did not affect this EEG biomarker significantly. Given that amphetamine improved attention in the 5-choice continuous performance test in this same cohort, with concomitant changes in P3b amplitude and frontal theta power (Bhakta et al., 2022), this study was not hindered by limitations of amphetamine-induced changes in EEG. In further support, amphetamine boosted the reward positivity component of this group of humans and a separate group of mice without affecting learning during a task (Cavanagh et al., 2021); thus, it is possible to detect drug-induced changes in EEG without concomitant changes in behavior. Given that amphetamine shifted the EEG biomarker signal of mice performing a learning (Cavanagh et al., 2021), but not effort task, it is possible for drug-induced changes in EEG signals during behavior to be measured. Future studies should utilize improved technology

and/or use an effort-based choice task that can be conducted across species (Cocker et al., 2012; Green et al., 2015), given evidence for amphetamine-induced increases in effortful choices in humans (Wardle et al., 2011). Such a decision-making approach would enable the detection of the choice of effort, without the requirement of continuously increasing repeated effort, potentially revealing effects on effort and EEG biomarkers.

Other attempts at identifying EEG biomarkers of effortful motivation have been conducted. For example, another group identified changing EEG responses over time when performing a PRBT, albeit elevated P300 amplitude after rewards (Klawohn et al., 2022). The clinical sensitivity of this EEG measure was in evidence where people with depression had an attenuated increase in their P300 responses despite reaching a comparable breakpoint (Klawohn et al., 2022). A potential link to outcome is seen whereby P300 amplitudes during a monetary incentive delay task positively predicted therapy completion in people with depression (White et al., 2021). Although total rewards received in the current study precludes such a P300 analysis here (at least 15 per person would be needed), future studies will endeavor to reduce requirements in this PRBT, thereby resulting in more rewards. Hence, given potential links to psychiatric conditions, the impact of amphetamine on P300 during reward presentation will be determined in future analyses.

Conclusions

The results from these studies support the translatability of PRBT findings across species. The amphetamine-induced increased breakpoint observed in humans and mice, here and previously, support the pharmacological predictive validity of the task across species. Moreover, the change in parietal alpha power before ending the task is reproducible, as seen in humans and mice. It has yet to be determined whether this biomarker is sensitive to changes in breakpoint however, and further study is required. Future studies to investigate translatable biomarkers will address the limitations encountered in this study, including the potential effects of EEG recording equipment on mouse task performance. The pharmacologic predictive validity and clinical sensitivity of the PRBT warrant its continued investigative use as a means to quantify effort across species.

Acknowledgments The authors thank Dr. Mark A. Geyer, Ms. Mahalah R. Buell, and Mr. Richard F. Sharp for their support on these studies.

Author contribution MN: Manuscript writing, Data Curation, Data Analysis, Investigation.

SGB: Methodology, Investigation, Data curation, Supervision, Project Administration, Editing.

JAT: Investigation, Data curation, Supervision, Project Administration.

JEK: Investigation, Data curation, Supervision, Project Administration.

LB: Investigation, Data Curation.

BZR: Investigation, Data curation, Supervision, Project Administration.

JAN: Investigation, Data curation.

GAL: Conceptualization, Methodology, Resources, Writing—Review & Editing, Funding acquisition.

NRS: Conceptualization, Methodology, Writing—Review & Editing, Investigation, Data curation, Medical Monitoring of Test Subjects, Supervision, Project Administration, Funding acquisition.

JLB: Conceptualization, Methodology, Resources, Writing—Review & Editing, Funding acquisition

JFC: Conceptualization, Methodology, Software, Formal analysis, Writing, Funding acquisition.

JWY: Conceptualization, Methodology, Writing—Review & Editing, Funding acquisition.

Funding These studies were funded by NIMH UH3MG109168.

Data Availability Data are made available upon request.

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Open Practices The data and materials for all experiments are available upon request.