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Model-based planning is unaffected by ketamine, antidepressant and internet delivered cognitive behavioural therapy treatments in depression

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Cognitive impairments have been observed in patients with depression. These include deficits in inhibition, shifting, and updating; cognitive processes that are critical for goal-directed control over behavior ('model-based planning'). Nevertheless, results of model-based planning in depression have been mixed. We aimed to address this by taking a within-person approach, examining model-based planning before and after a range of effective treatments for depression. Across two parallel studies, participants completed a two-step reinforcement learning paradigm before and after antidepressant medication, internet-based cognitive behavioral therapy (iCBT) or intravenous (IV) ketamine infusion. In experiment 1, 93 patients with treatment-resistant depression were randomized to a single dose of IV ketamine (0.5 mg/kg) or IV saline (50 mL 0.9% NaCl). In Experiment 2, 781 participants were followed for four weeks of antidepressant (N = 83), or iCBT (N = 611) treatment. N = 87 participants without any psychiatric diagnosis were followed as a control group. In both experiments, depressive symptoms significantly improved in treatment groups compared to their corresponding control groups, but we did not find evidence of changes in model-based planning. Moreover, we failed to find associations between individual differences in model-based planning and differential response to ketamine, iCBT or antidepressant treatments. Individual differences in model-based planning at baseline were associated with compulsivity, but not with depression symptoms. These findings suggest that model-based planning is not necessarily compromised in depression and does not improve following treatments. This result provides evidence for the trait-like nature of model-based planning and underscores the specificity of its relation to disorders of compulsivity.

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INTRODUCTION

Depression is a prevalent, debilitating and potentially life-threatening condition and one of the world's leading causes of disability [1]. A range of effective treatments exist, but none are universally effective. Response to first line treatments such as antidepressant medication or cognitive behavioural therapy (CBT) is estimated at around 50% [2, 3], and up to 30% of patients do not respond to available forms of treatment [4]. Newer treatments such as intravenous (IV) ketamine have shown great promise for patients who are characterised as 'treatment resistant' to first line therapies, but response rates are still not adequate [5]. One potential explanation for the variability seen in treatment response is the heterogeneity that exists in clinical presentation and impairments. One aspect of this heterogeneity are cognitive impairments which are present in 20–50% of patients with depression [6–8]. Research has shown that cognitive problems persist into remission and are associated with poor treatment outcomes overall [9, 10]. Meta-analysis of cognitive dysfunctions in depressed patients suggest pronounced deficits in inhibition (overriding dominant or prepotent responses), shifting (switching between mental sets or tasks), and updating (adding or discarding working memory contents) [11]. Cognitive problems also include deficits in memory, executive functioning, cognitive flexibility (ability to adapt to changing circumstances or update beliefs based on new information) [7, 12, 13], as well as subjective difficulties in concentration and decision-making listed as DSM-5 diagnostic criteria [14]. These attenuated cognitive processes are critical for goal-directed behavior, crucial for navigating and adapting to complex environments.

Goal-directed behavior uses planning, simulation, and reflection to achieve a desired outcome [15, 16]. Inspired by computational theories of reinforcement-learning, the two-step decision-making

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task [17] formalizes goal-directed control as a construct called 'model-based planning'. Model-based planning is quantified as the extent to which decision-makers use a mental model of action-state relationships to guide choices. Prior studies examining goal-directed planning in depression are surprisingly few. Most studies to date have used general population samples, rather than depressed patients, and have not revealed any cross-sectional associations between individual differences in depression and model-based planning [18–20]. However, one study showed that individuals high in depression were more sensitive to the deleterious effects of stress on model-based planning [21]. Another found a similar negative association between anxious-depression and model-based planning, but only when the task had low stakes [22]. More recently, researchers compared diagnosed patients with depression to healthy controls and found no differences in model-based planning [23], but sample size was likely too small (N = 23) to make definitive conclusions. No study has yet tested if model-based planning improves following treatments for depression, or indeed how heterogeneity in this cognitive capacity within a depressed sample might differentially relate to treatment response. Understanding how different therapeutic interventions impact goal-directed planning in depression could reveal (or refute) plausible treatment mechanisms and help tailor treatments to address specific cognitive impairments.

Our understanding of the effect of treatment on cognitive deficits in depression is growing, but remains incomplete. For example, some studies showed procognitive effects of antidepressant medications such as improvement in verbal memory [24], delayed recall [25] and working memory [26, 27]; others have shown no changes in domains such as executive functioning and cognitive control [25]. In a large randomised longitudinal clinical trial (iSPOT-D) of N > 1000 unmedicated patients with depression, Shilyansky and colleagues [28] found no effect of three types of antidepressant medication on a range of cognitive domains including cognitive flexibility. Studies examining cognitive changes following CBT have similarly yielded inconclusive results. A systematic review of 19 studies found preliminary evidence of improved executive functioning following evidence-based psychotherapy for depression [29]. Studies examining the effects of IV ketamine on cognitive dysfunction are still in their infancy. A recent systematic review [30] found that from the 14 studies examined, more than half of them reported positive cognitive outcomes post IV ketamine treatment, including improvements working memory, verbal and visual memory, executive function, attention, and auditory verbal episodic memory; while the rest of the studies showed no improvement or in one case reporting negative effects on verbal memory.

Building on this work, in this study, we administered the two-step task across two parallel studies concerning IV ketamine infusion, antidepressant medication, and internet-based CBT (iCBT). Experiment 1 was a randomized controlled trial of ketamine in patients with treatment resistant depression. Experiment 2 was a longitudinal observational study following patients receiving antidepressant medication or iCBT for 4 weeks, along with a non-treatment control group used to control for practice effects. In all cases, our primary hypothesis was to test for within-person changes in model-based planning across each treatment group. We also examined whether the extent of clinical improvement was associated with the degree of cognitive improvement.

MATERIALS AND METHODS

Experiment 1

Data were collected as part of a double-blind placebo-controlled randomized clinical trial of IV ketamine for treatment resistant depression (Fig. 1A). A detailed description of the methods used can be found in Price et al., [31]. The protocol was ethically approved by the University of Pittsburgh Institutional Review Board. All participants provided written consent prior to participation.

Participants

Individuals between 18–60 years of age with treatment resistant unipolar depression were recruited from the community and outpatient clinical settings through website advertisements, clinical referrals, or a local research registry. Treatment resistant depression was defined as at least one unsuccessful adequate trial of an antidepressant medication approved by the U.S. Food and Drug Administration in the current depressive episode. All participants met DSM-5 criteria for major depressive disorder and reported moderate to severe levels of depression (a score ≥25 on the Montgomery-Åsberg Depression Rating Scale (MADRS); [32]). Further details and full inclusion and exclusion criteria are available at ClinicalTrials.gov: NCT03237286. Baseline demographics are reported in Supplementary Table 1. There were no significant age ($p = 0.580$), sex assigned at birth ($p = 0.650$) or education attainment ($p = 0.688$) differences observed between the ketamine and saline-control groups.

Study procedures

Participants were randomized to a single dose of IV ketamine (0.5 mg/kg) or IV saline (50 mL 0.9% NaCl) administered over a 40-minute infusion, followed by 4 hours of clinical monitoring. All infusions were administered by blinded, licensed nurses in a medical hospital setting. Pre-infusion participants provided psychological, clinical, and cognitive data in the larger parent study. A subset of those measures were analyzed as secondary data analysis. At both pre-infusion and 24-hour post-infusion, participants' depressive symptoms were assessed using MADRS, and a subset of participants, enrolled during later stages of the parent trial, completed the two-step reinforcement learning task. After exclusion criteria, there were N = 65 participants in the ketamine group and N = 28 participants in the saline group that had both task and clinical data at both time points. A 2:1 ketamine:saline condition was used due to the additional comparator groups used to test primary aims of the parent study (see Price et al., [31] for primary clinical trial findings).

Two-step reinforcement learning task. Participants completed 100 trials [33] of an adapted version of the two-step reinforcement learning task [17] (Fig. 1C). In the first step, participants had to choose between two rockets which probabilistically traveled to one of two planets. Each rocket traveled to a preferred planet 70% of the time ('common' transition) or to the other planet 30% of the time ('rare' transition). Next, participants had to choose between two aliens, each with a unique probability of being rewarded. The probability of being rewarded drifted slowly and independently for each alien over the course of the task. In both stages, participants had up to 2500 ms to respond. In this task, model-based and model-free learning have distinctive behavioural signatures. A pure model-based learner takes into account estimates of how rewarding each alien is and how likely each rocket is to travel to the planet where that alien resided. Behaviourally, this is expressed by an interaction between reward and transition. By contrast, a pure model-free learner only considers previous reinforcement and is behaviourally characterised by a main effect of reward.

Clinical outcome measure. The primary clinical outcome measure was the Montgomery-Åsberg Depression Rating Scale (MADRS) [32]. The MADRS is a 10-item clinician-administered scale, designed to be particularly sensitive to antidepressant treatment effects in patients with major depression. The MADRS used in present analyses was collected at two timepoints: a pre-infusion baseline visit (completed approximately 1 hour prior to infusion) and at a 24-hr post-infusion visit, and was administered by a single, blinded, Master's-level study rater.

Experiment 2

Data were collected as part of the Precision in Psychiatry Study (PIPS), an observational study which followed individuals through their first four weeks of treatment with iCBT or antidepressant medication (Fig. 1B). The protocol obtained ethical approval from the Research Ethics Committee of School of Psychology, Trinity College Dublin and the Northwest-Greater Manchester West Research Ethics Committee of the National Health Service, Health Research Authority and Health and Care Research Wales. All participants provided electronic informed consent prior to participation.

Participants

Individuals commencing iCBT on the SilverCloud platform within ±2 days were recruited for this study. They were invited through an NHS mental health service after being prescribed iCBT or if they elected to avail of iCBT

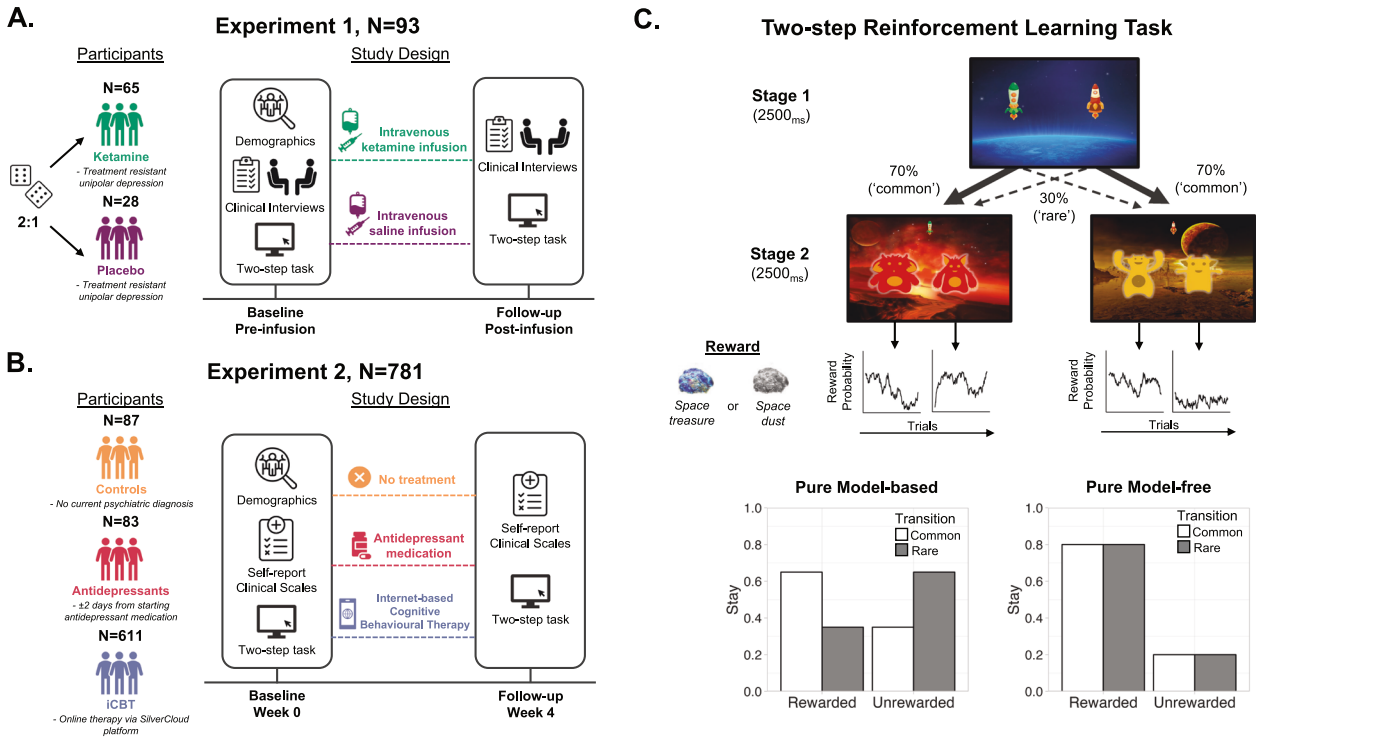

Fig. 1 Overview of study procedures. A Experiment 1 collected data from a double-blind placebo-controlled randomized clinical trial of ketamine-infusion therapy for treatment resistant depression. Participants were randomly assigned to either the ketamine or saline (placebo) group in a ratio of 2:1. Pre-infusion, or at baseline, participants self-reported on sociodemographics, completed a clinician-administered scale for assessing depression severity, and the two-step task. Participants then received either a single dose of intravenous ketamine-infusion or saline-infusion. 24-hours post-infusion, participants were reassessed on the clinician-administered scale and completed the two-step task. **B** Experiment 2 consisted of an observational study design where participants were followed during their first four weeks of antidepressant or internet-based cognitive behavioural therapy treatment. At baseline, participants reported on sociodemographics and a battery of mental health questionnaires used to derive transdiagnostic scores of anxious-depression and compulsivity and intrusive thought. They also completed the two-step task. Following four weeks, the participants re-engaged with the mental health questionnaires and completed the two-step task. An additional group of individuals who reported no current psychiatric illness completed the same procedure in the same time frame to serve as a control group. **C** Schematic of the two-step reinforcement learning task participants completed. In the first stage, participants first choose between two stimuli, and are probabilistically transitioned to one of two second stage states (70% preferred planet, 30% alternative planet). Participants choose again between two stimuli, being rewarded with space treasure or unrewarded with space dust. The probability of being rewarded drifts slowly and independently for each stimulus. In this task, model-based learners will use an internal model of the structure to maximise the amount of space treasure collected while model-free learners will base their decision on previous reinforcement.

provided by an Irish-based mental health charity, Aware. An antidepressant group was also recruited ±2 days from beginning their treatment, they were recruited through physical e.g., pharmacies, and online advertisements. An age and gender-matched control group were included if they reported to not be undergoing current psychiatric treatment and did not have a current psychiatric diagnosis. Participants in all groups were excluded if they were not between 18–70 years of age, were not fluent in English or did not have computer access. The active treatments group had to score over 10 on the Work and Social Adjustment Scale, while the control group had to score below 10. After exclusion criteria, there were $N = 611$ participants in the iCBT group, $N = 83$ participants in the antidepressant group and $N = 87$ participants in control group that had both task and clinical data at both time points. The control group was younger ($M = 28.5$, $SD = 11.9$) than the iCBT group ($M = 31.5$, $SD = 10.8$), Tukey HSD, $p = 0.040$ (Supplementary Table 1), but there were no significant gender ($p = 0.474$) or education attainment ($p = 0.121$) differences.

Study procedures

A detailed description of the study design published in Lee et al., [34]. Participants completed a baseline assessment, three brief weekly check-in assessments and a final assessment at a 4-week follow-up. At baseline, participants completed the two-step task along with a battery of clinical questionnaires which were repeated at a 4-week follow-up. Participants completed the entirety of the procedure online, which included additional assessments not pertinent to the present study.

Two-step task. The same paradigm was used as described in Experiment 1, except that participants in this experiment completed 150 trials.

Self-report questionnaires. We focus on a subset of self-report data gathered from the PIP study including age, gender and educational attainment and a transdiagnostic measure of 'anxious-depression' and 'compulsivity and intrusive thought' [18]. These transdiagnostic dimensions were used in favour of the independent clinical measures to reduce multicollinearity between clinical scales. Here, 'anxious-depression' reflects items related to anxiety and depression, and not an anxious subtype of depression, while 'compulsivity and intrusive thought' reflects items related to OCD, disordered eating, impulsivity and schizotypy. Additional information about the derivation of these scores is provided in the online supplement.

Data analysis

Quantifying model-based planning. Data were analysed using a hierarchical logistic regression model implemented by the lme4 R package [35]. The model explains stay or switch (coded 1,0) behaviour, from the type of transition on the last trial (coded common=1, rare = −1), whether that trial was rewarded (coded rewarded=1, unrewarded=0), and their interaction. Reward, transition and their interaction were included as random effects. The outcome of interest, model-based planning, is quantified by the interaction between reward and transition. The model also quantifies other indices of task performance such as choice preservation (the model's intercept) and a model-free index (the main effect of reward). To test the

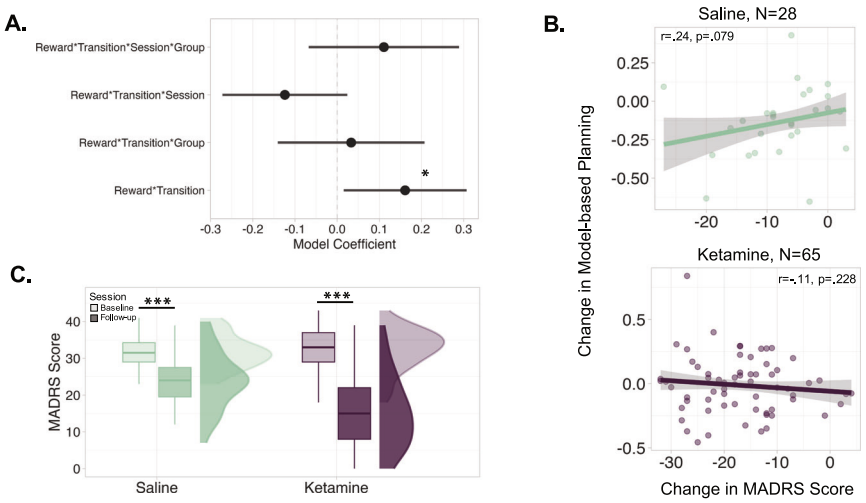

Fig. 2 Results from Experiment 1: A Randomized Clinical Trial of Ketamine for Treatment Resistant Depression. A Regression beta coefficients of the hierarchical model on stay behaviour explained by reward, transition, group, session and their interactions. There was an overall effect of model-based planning (reward*transition interaction). No other significant interactions were observed suggesting model-based did not change from pre- to post-infusion in either group. Error bars reflect 95% confidence interval. **B** Correlation between changes in depression severity MADRS Change and change in model-based planning per group (saline, ketamine). Each dot represents a participant, the line represents the line of best fit while the shaded areas represent 95% confidence interval. **C** Distribution and boxplot of values of MADRS scores across (ketamine vs saline control) and within (pre- vs post-infusion) groups. A significant group*session interaction was observed with both groups demonstrating reductions of depressive symptoms from pre- to post-infusion however this effect was steeper in the ketamine group. Central line reflects median values. For all panels: *p < 0.05, **p < 0.01, ***p < 0.001.

influence of individual differences in model-based planning, we use subject-level reward*transition coefficients as regressors or in correlation analyses. For analyses involving continuous outcomes, linear mixed-effects models were fitted using the lme4 and lmerTest R packages, with degrees of freedom and significance tests for fixed effects estimated through the default Satterthwaite's approximation. All analyses were performed using R (version 4.2.3 and version 4.0.4 for studies 1 and 2).

RESULTS

Experiment 1

Does ketamine treatment improve model-based planning? A hierarchical mixed effects model ($stay_t$ ~$reward_{t-1}$*$transition_{t-1}$*infusion group*session) was used to test for within-group differences from pre-infusion to 24 hours post-infusion, between group differences in the ketamine vs saline group, and their interaction on model-based planning (Supplementary Table 3, Fig. 2A). As expected, there was an overall tendency to repeat choices trial-to-trial ($\beta = 1.40$, $SE = 0.225$, $p < 0.001$), and a main effect of reward ($\beta = 0.45$, $SE = 0.12$, $p < 0.001$), indicative of model-free learning, and an interaction between reward and transition ($\beta = 0.16$, $SE = 0.07$, $p = 0.030$), reflecting model-based learning. Observed stay probabilities as a function of reward and transition for each group at each time point are presented in Supplementary Figure 1. Crucially, we failed to find differences in model-based planning between ketamine and saline group (reward*transition*group interaction: $\beta = 0.03$, $SE = 0.09$, $p = 0.708$), or between pre-infusion and 24-hours post-infusion (reward*transition*session interaction: $\beta = -0.12$, $SE = 0.08$, $p = 0.10$). We also observed no significant interaction between group and session on model-based planning (reward*transition*infusion group*session: $\beta = 0.11$, $SE = 0.09$, $p = 0.222$), suggesting model-based planning did not change from pre- to post-infusion differently across the groups. To formally quantify evidence for the null effects of infusion group and session, we compared the full model (including infusion group and session) against a reduced model without these terms in a Bayesian linear mixed effects model using the *brms* package in R. We calculated the Bayes factor comparing the two models by using the *bayes_factor()* function in the *brms* package 100 times. This function approximates the marginal likelihood for each model after bridge sampling. The resulting Bayes Factors were less than 1 ($M = 0.000035$, $SD = 0.000017$) suggesting that the data strongly favored the null model, providing more support for the lack of group and session effects on model-based planning.

We then tested whether changes in depressive symptoms were associated with changes in model-based behavior. In other words, we examined whether those who experienced the biggest therapeutic benefit (i.e., greater MADRS change score), also have the biggest change in model-based learning. A linear mixed effect model was used to explain model-based planning from interactions between session*MADRS change scores from pre-infusion to 24-hours post-infusion, controlling for MADRS score at baseline. There were no significant associations between model-based planning and change in depression scores in any of the infusion groups (Session*MADRS change score: Saline group: $\beta = 0.01$, $SE = 0.01$, $p = 0.226$, Ketamine group: $\beta = -0.00$, $SE = 0.00$, $p = 0.399$, Supplementary Table 4). This was supported by non-significant simple correlations between changes in model-based scores and changes in depression severity measured by the MADRS in each group (Saline group: $r = 0.24$, $p = 0.079$, Ketamine group: $r = -0.11$, $p = 0.228$, Fig. 2B).

Are individual differences in model-based planning associated with response to ketamine treatment? A linear mixed effect model was used with the MADRS scores as dependent variables and session, infusion group, baseline model-based scores, and their interaction as regressors. We observed a main effect of session ($\beta = -7.89$, $SE = 1.57$, $p < 0.001$, suggesting depression severity reduced in both groups from pre to post 24-hour infusion, and a significant interaction effect between session and infusion group ($\beta = -9.14$, $SE = 1.87$, $p < 0.001$, Supplementary Table 5). This was confirmed by simple effects within each group and found those in the ketamine group exhibited a greater decrease in the MADRS score ($t = -15.65$, $p < 0.001$) compared to the saline group ($t = -5.86$, $p < 0.001$, Supplementary Table 6, Fig. 2C). To test if clinical improvement was moderated by baseline model-based planning, we examined the interaction between baseline model-based scores, session and infusion group which was non-significant ($\beta = 2.40$, $SE = 1.79$, $p = 0.183$, Supplementary Table 5).

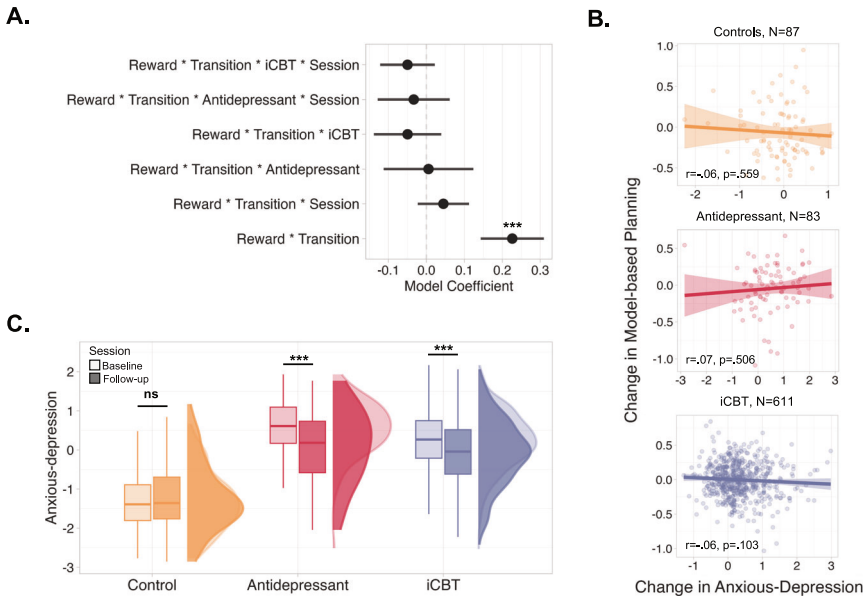

Fig. 3 Results from Experiment 2: Precision in Psychiatry Study. A Regression beta coefficients of the hierarchical model on stay behaviour explained by reward, transition, group (Control, Antidepressant and iCBT), session (baseline, follow-up) and their interactions. For illustrative purposes, only model-based results are presented. There was an overall effect of model-based planning (reward*transition interaction). No other significant interactions were observed suggesting model-based did not change from baseline to follow-up infusion and in any group (control as reference group). Error bars reflect 95% confidence interval. **B** Correlation between changes in anxious-depression (AD) and change in model-based (MB) planning per group. Each dot represents a participant, the line represents the line of best fit while the shaded areas represent 95% confidence interval. **C** Distribution and boxplot of values of anxious-depression scores across control and treatment groups (Antidepressant, iCBT) and within (baseline, 4-week follow up) groups. Anxious depression scores reduced from baseline to follow-up in the treatment groups only. Central line reflects median values. For all panels: ns $p > 0.05$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Experiment 2

Does model-based planning improve following antidepressant medication or iCBT? A hierarchical mixed effects model ($stay_t$ ~ $reward_{t-1}$ * $transition_{t-1}$ * group (iCBT, antidepressant, control as the reference) * session) was used to test for group differences in model-based planning, improvement pre-post treatment, and their interactions. Full model results are presented in Supplementary Table 7; here, we focus only on the key results in text. First, looking at basic task behaviour in the reference group at baseline, we identified the model-free effect of reward on stay behaviour ($\beta = 0.30$, $SE = 0.05$, $p < 0.001$), a model-based reward*transition interaction ($\beta = 0.23$, $SE = 0.04$, $p < 0.001$), and a tendency to stay with the same choice on subsequent trials ($\beta = 1.26$, $SE = 0.10$, $p < 0.001$) (see Supplementary Figure 1 for stay probabilities for each trial condition for each group). Crucially, the effect of model-based planning at baseline did not differ by group (reward*transition*antidepressant: $\beta = 0.01$, $SE = 0.06$, $p = 0.925$; reward*transition*iCBT: $\beta = -0.05$, $SE = 0.05$, $p = 0.274$, Fig. 3A). There was no change from baseline to follow-up in model-based planning in controls (reward*transition*session: $\beta = 0.05$, $SE = 0.03$, $p = 0.193$, Fig. 3A) and there were no differences between the control group and the antidepressant or iCBT groups in this regard (ps > 0.176). This was confirmed by the results of simple effects within each group. Model-based planning did not significantly improve from baseline to 4-week follow-up in the control group ($\beta = 0.05$, $SE = 0.03$, $p = 0.174$, Supplementary Table 8), antidepressant treatment group ($\beta = 0.01$, $SE = 0.03$, $p = 0.722$, Supplementary Table 8), or in the group of individuals who received 4-weeks of iCBT treatment ($\beta = -0.01$, $SE = 0.01$, $p = 0.687$, Supplementary Table 8). We formally evaluated evidence for the null through a Bayesian linear mixed effects model comparing a full model with all interaction terms (i.e., including group and session) to a null model without these terms. As in Experiment 1, we calculated Bayes Factor 100 times resulting in $BF > 1$ ($M = 0.0147$, $SD = 0.0088$), favoring the null model, suggesting model-based planning did not vary as a function of treatment or time.

To test if intra-individuality in treatment response might explain this, we examined if changes in model-based planning were evident in those who had the largest improvement in symptoms. This was tested using a repeated measures model with model-based scores as the dependent variable and independent variables of session, change in anxious-depression and group. The critical interaction between change in anxious-depression scores, group and time was not significant (ps >0.284, Supplementary Table 9). For completion, we also ran this separately in each of the groups (session*AD change – all ps >0.133, Supplementary Table 10). Finally, this was additionally confirmed by non-significant simple correlations between changes in model-based scores and changes in anxious-depression in each group (Control: $r = -0.06$, $p = 0.559$, Antidepressant: $r = 0.07$, $p = 0.506$, iCBT: $r = -0.06$, $p = 0.133$, Fig. 3C).

Are individual differences in model-based planning at baseline associated with response to antidepressants or iCBT treatment? A linear mixed effects model was used with anxious-depression (AD) scores serving as the dependent variable and main effects of session, group (iCBT, antidepressant, control as the reference), model-based scores at baseline, and their interaction as regressors (Supplementary Table 11). There was a main effect of antidepressant group, indicating that anxious-depression scores were higher in the antidepressant group, compared to the control group ($\beta = 1.84$, $SE = 0.15$, $p < 0.001$), and similarly they were higher in the iCBT compared to the control group ($\beta = 1.52$, $SE = 0.15$, $p < 0.001$). There was no main effect of session in the control group ($\beta = 0.10$, $SE = 0.08$, $p = 0.217$). There was an interaction between session and the antidepressant ($\beta = -0.62$, $SE = 0.13$, $p < 0.001$) and the iCBT group ($\beta = -0.45$, $SE = 0.09$, $p < 0.001$), such that both groups showed larger reductions in symptoms at follow-up. Simple effects within each group confirmed that both

groups had a reduction in anxious-depression from baseline to follow-up (Antidepressants: $\beta = -0.59$, $SE = 0.11$, $p < 0.001$; iCBT: $\beta = -0.40$, $SE = 0.03$, $p < 0.001$), while the control group did not ($\beta = 0.12$, $SE = 0.08$, $p = 0.103$, Supplementary Table 12). There was no main effect of model-based scores at baseline on anxious-depression in the control group ($\beta = -0.22$, $SE = 0.23$, $p = 0.337$, Supplementary Table 11) and this did not differ across the treatment groups ($p > 0.595$). Finally, there was no interaction between baseline model-based scores and treatment response, reflected by the non-significant interactions between session, group and model-based planning at baseline (ps > 0.433).

Compulsivity and model-based planning. Prior research has consistently shown that individual differences in compulsivity (CIT) are related to model-based planning. As a validation step, we sought to replicate these associations here. At baseline, we identified a significant association in all three groups (Antidepressant: $\beta = -0.08$, $SE = 0.04$, $p = 0.053$, Controls: $\beta = -0.12$, $SE = 0.06$, $p = 0.031$, iCBT: $\beta = -0.05$, $SE = 0.02$, $p = 0.002$, Supplementary Table 13). There were no significant changes in this association from baseline to follow-up in any group, reward*transition*CIT*session, all $p < 0.23$ (see Supplementary Table 14 for full results).

Test-retest reliability. Using the control group, we estimated the 4-week test-retest reliability of model-based estimates to understand if issues with task reliability may have reduced our ability to detect changes. We did this within the control group, which underwent no treatment. An intraclass correlation coefficient of $ICC = 0.59$, $p < 0.001$ was observed suggesting model-based estimates were moderately reliable over 4 weeks.

DISCUSSION

The present study found that model-based planning did not improve following three evidence-based treatments for depression: ketamine-infusion, antidepressant medication, or internet-based cognitive behavioral therapy. Experiment 1 was one of the largest randomized-control ketamine trials in depression to date. In line with the previous literature, we found rapid reductions in mood symptoms in the ketamine group compared to saline-control [36, 37]. Importantly, these improvements were not accompanied by increases in model-based planning. While considerable attention has been paid to ketamine's effects on mood, its impact on cognitive functions is less understood. Some have suggested that ketamine reverses neuroplasticity deficits in depression, as measured by increase of BDNF release and synapse number as well as the stimulation of mTOR signaling in the PFC [38] and that this might produce cognitive enhancements. In line with this, some preclinical and clinical studies have found improvements in cognitive flexibility following ketamine administration, as indexed by performance in neurocognitive tests such as set-shifting task or Stroop interference test following the administration of ketamine [39–41]. But many studies show no improvements, and in general, studies have been limited by small sample sizes and a lack of rigorous control groups [30, 42]. Our null findings, from a large-scale randomized control trial, suggest that the enhanced neuroplasticity induced by a single dose of ketamine might not include an effect on model-based planning.

We observed a consistent null result in Experiment 2, in patients following 4-weeks of antidepressant and iCBT treatments. As with ketamine, these treatments were effective in reducing anxious-depression from baseline to follow-up, but this did not translate to changes in model-based planning. These findings add to a growing body of literature examining cognitive changes following these treatments, which largely operate on the premise that iCBT and antidepressant medications could improve cognition by alleviating depressive symptoms that potentially interfere with cognitive functions. Although the lack of baseline differences between the antidepressant and control group complicates interpretation, our primary focus was to test for within-person treatment changes. Moreover, this null finding is consistent with outcomes of the iSPOT-D study, which failed to identify cognitive improvements in >1000 individuals randomised to a variety of antidepressant medications [28]. Prior studies of psychotherapy have suggested that there is some preliminary evidence for executive function changes following treatment, but evidence is overall mixed, depending on sample size and the existence of pre-treatment deficits [29]. Together, the lack of change in model-based planning in both treatment groups, and the absence of an association between the improvements in anxious-depression and changes in model-based planning, suggest this cognitive capacity may not be directly targeted by these treatments. Moreover, the effect sizes for these groups and time interactions were uniformly small, reinforcing the interpretation that the lack of statistical significance reflects negligible effects.

Leveraging the large sample size in the iCBT group, we also tested for cross-sectional associations with depression symptomatology. We found that a dimension of anxious-depression was not associated with individual differences in model-based planning while the "compulsivity and intrusive thought" dimension was associated with reduced model-based planning, consistent with prior research [18–20]. This dimension captured behaviours and traits observed across disorders such as OCD, eating disorders, impulsivity, alcohol misuse and schizotypy [18]. The lack of association with depression is consistent with what has been previously observed in general population studies [18–20], and more recently in a small patient sample [23] - extending these findings to a large treatment-seeking sample. Although compulsivity symptoms also reduced before and after iCBT and medication treatments in Experiment 2, like depression, there was no association with improvements in compulsivity and any improvement in model-based planning. This mirrors the findings of a prior study examining model-based planning after exposure and response prevention for OCD, where model-based planning did not improve despite substantial reductions in OCD scores following treatment [43]. Another study found that a single session of theta burst stimulation did not alter model-based planning, in spite of significant clinical improvements among patients with clinical compulsive behaviors [44]. More recently, a study followed a general population sample over 3 and 12 months and also found that model-based planning remained relatively stable and did not fluctuate with changes in compulsivity within-person over time [45]. These findings together suggest that model-based planning has a trait-like quality. Moreover, both the cross-sectional and longitudinal findings of the present study provide convergent evidence that current (i.e. 'state') levels of distress, anxiety or generalized impairment are not a likely explanation for the reductions in model-based planning consistently reported in compulsivity. Nonetheless, we cannot determine from these data whether reduced model-based planning reflects a casual risk factor for compulsivity or merely a correlational trait marker. While our findings suggest stability across time and treatment, longer timescales and randomized controlled designs are necessary to establish directionality or developmental primacy.

This study had some limitations. In Experiment 1, patients were given a single dose of IV ketamine. It is possible that repeated ketamine administrations (e.g., 6 infusions over 2–3 weeks, as is the typical induction phase in TRD treatment) might have an effect on model-based planning. Moreover, we did not assess other measures of cognitive function at baseline to determine their relationship with depressive symptoms or their improvement post induction. Of note, cognitive impairments at baseline are not a pre-requisite for testing for within-subject improvements following successful treatment of depression, as cognition can

be improved even in healthy samples, and treatment mechanisms can be based on patients' strengths rather than their weaknesses. Experiment 2 was an observational and not a randomized-controlled design and so causal inferences about different treatments cannot be made; however, this limitation is mitigated given our principal analysis depends on within-person changes. The iCBT treatment was self-paced and modules varied across participants (see Lee et al., [34] for further details), this means that participants received different effective doses of the intervention. We therefore cannot exclude the possibility that a more potent and regimented intervention may incur larger clinical improvements and potentially translate to changes in model-based planning. Finally, it is possible that 4 weeks of treatment is insufficient to achieve the sort of sustained clinical gains required to see knock-on improvements in cognition. However, the consistency of our findings to the longer duration iSPOT-d study suggest this is likely not the case.

CONCLUSION

This study provides convergent evidence that model-based planning is not linked with within-person changes in depression symptoms following a range of treatments, or with individual differences in depression in a large treatment-seeking sample. These data provide support that model-based planning is a relatively stable trait-like cognitive process, with specific relevance to a transdiagnostic dimension of compulsivity and not with mood-related psychopathology.

DATA AVAILABILITY

Data for Experiment 2 is available at https://osf.io/6pztf/.

CODE AVAILABILITY

Code to reproduce the main finding and figures of this manuscript are available at https://osf.io/6pztf/.

REFERENCES

1. Friedrich MJ. Depression is the leading cause of disability around the world. JAMA. 2017;317:1517.
2. Cuijpers P, Miguel C, Harrer M, Plessen CY, Ciharova M, Ebert D, et al. Cognitive behavior therapy vs. control conditions, other psychotherapies, pharmacotherapies and combined treatment for depression: a comprehensive meta-analysis including 409 trials with 52,702 patients. World Psychiatry. 2023;22:105–15.
3. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163:28–40.
4. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023;22:394–412.
5. Price RB, Kissel N, Baumeister A, Rohac R, Woody ML, Ballard ED, et al. International pooled patient-level meta-analysis of ketamine infusion for depression: In search of clinical moderators. Mol Psychiatry. 2022;27:5096–112.
6. Hack LM, Tozzi L, Zenteno S, Olmsted AM, Hilton R, Jubeir J, et al. A cognitive biotype of depression and symptoms, behavior measures, neural circuits, and differential treatment outcomes: a prespecified secondary analysis of a randomized clinical trial. JAMA Netw Open. 2023;6:e2318411.
7. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, et al. Cognitive deficits and function outcome in major depressive disorder: determinants, substrates, and treatments interventions. Depress Anxiety. 2013;30:515–27.
8. Liu J, Chen Y, Xie X, Liu B, Ju Y, Wang M, et al. The percentage of cognitive impairment in patients with major depressive disorder over the course of the depression: a longitudinal study. J Affect Disord. 2023;329:511–8.
9. LeMoult, Gotlib. Depression: a cognitive perspective. Clin Psychol Rev. 2019;69:51–66.
10. Douglas KM, Porter RJ. Longitudinal assessment of neuropsychological function in major depression. Aust N. Z J Psychiatry. 2009;43:1105–17.
11. Snyder HR, Miyake A, Hankin BL. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. Front Psychol. 2015;6:328.
12. Conradi HJ, Ormel J, de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. Psychol Med. 2011;41:1165–74.
13. Levens SM, Gotlib IH. Updating emotional content in recovered depressed individuals: evaluating deficits in emotion processing following a depressive episode. J Behav Ther Exp Psychiatry. 2015;48:156–63.
14. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013.
15. Dolan RJ, Dayan P. Goals and habits in the brain. Neuron. 2013;80:312–25.
16. Dickinson A. Actions and habits: the development of behavioural autonomy. Philos Trans R Soc Lond B, Biol Sci. 1985;308:67–78.
17. Daw ND, Gershman SJ, Seymour B, Dayan P, Dolan RJ. Model-based influences on humans' choices and striatal prediction errors. Neuron. 2011;69:1204–15.
18. Gillan CM, Kosinski M, Whelan R, Phelps EA, Daw ND. Characterizing a psychiatric symptom dimension related to deficits in goal-directed control. eLife. 2016;5:e11305.
19. Seow TXF, Benoit E, Dempsey C, Jennings M, Maxwell A, O'Connell R, et al. Model-based planning deficits in compulsivity are linked to faulty neural representations of task structure. J Neurosci. 2021;41:6539–50.
20. Donegan KR, Brown VM, Price RB, Gallagher E, Pringle A, Hanlon AK, et al. Using smartphones to optimise and scale-up the assessment of model-based planning. Commun Psychol. 2023;1:31.
21. Heller AS, Ezie CEC, Otto AR, Timpano KR. Model-based learning and individual differences in depression: The moderating role of stress. Behav Res Ther. 2018;111:19–26.
22. Patzelt EH, Kool W, Millner AJ, Gershman SJ. Incentives boost model-based control across a range of severity on several psychiatric constructs. Biol Psychiatry. 2019;85:425–33.
23. Knolle F, Sen P, Culbreth A, Koch K, Schmitz-Koep B, Gürsel DA, et al. Investigating disorder-specific and transdiagnostic alterations in model-based and model-free decision-making. J Psychiatry Neurosci. 2024;49:E388–E401.
24. Keefe RS, McClintock SM, Roth RM, Doraiswamy PM, Tiger S, Madhoo M. Cognitive effects of pharmacotherapy for major depressive disorder: a systematic review. J Clin Psychiatry. 2014;75:864–76.
25. Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int J Neuropsychopharmacol. 2015;19:pyv082.
26. Baune BT, Renger L. Pharmacological and non-pharmacological interventions to improve cognitive dysfunction and functional ability in clinical depression – A systematic review. Psychiatry Res. 2014;219:25–50.
27. Dam VH, Stenbæk DS, Köhler-Forsberg K, Ip C, Ozenne B, Sahakian BJ, et al. Hot and cold cognitive disturbances in antidepressant-free patients with major depressive disorder: a NeuroPharm study. Psychol Med. 2021;51:2347–56.
28. Shilyansky C, Williams LM, Gyurak A, Harris A, Usherwood T, Etkin A. Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. Lancet Psychiatry. 2016;3:425–35.
29. Groves SJ, Douglas KM, Milanovic M, Bowie CR, Porter RJ. Systematic review of the effects of evidence-based psychotherapies on neurocognitive functioning in mood disorders. Aust N. Z J Psychiatry. 2021;55:944–57.
30. Grasso V, Gutierrez G, Alzbeidi N, Hernandorena C, Vázquez GH. Cognitive changes in patients with unipolar TRD treated with IV ketamine: a systematic review. Prog Neuro-Psychopharmacol Biol Psychiatry. 2024;135:111095.
31. Price RB, Spotts C, Panny B, Griffo A, Degutis M, Cruz N, et al. A Novel, brief, fully automated intervention to extend the antidepressant effect of a single ketamine infusion: a randomized clinical trial. Am J Psychiatry. 2022;179:959–68.
32. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382–9.
33. Decker JH, Otto AR, Daw ND, Hartley CA. From creatures of habit to goal-directed learners: tracking the developmental emergence of model-based reinforcement learning. Psychol Sci. 2016;27:848–58.
34. Lee CT, Palacios J, Richards D, Hanlon AK, Lynch K, Harty S, et al. The Precision in Psychiatry (PIP) study: testing an internet-based methodology for accelerating research in treatment prediction and personalisation. BMC Psychiatry. 2023;23:25.
35. Bates D, Machler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015;67:1–48.
36. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, et al. Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. Biol Psychiatry. 2016;80:424–31.
37. Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry. 2012;71:939–46.
38. Kopelman J, Keller TA, Panny B, Griffo A, Degutis M, Spotts C, et al. Rapid neuroplasticity changes and response to intravenous ketamine: a randomized controlled trial in treatment-resistant depression. Transl Psychiatry. 2023;13:159.

39. Permoda-Osip A, Kisielewski J, Bartkowska-Sniatkowska A, Rybakowski JK. Single ketamine infusion and neurocognitive performance in bipolar depression. Pharmacopsychiatry. 2015;48:78–79.
40. Shiroma PR, Albott CS, Johns B, Thuras P, Wels J, Lim KO. Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. Int J Neuropsychopharmacol. 2014;17:1805–13.
41. Gass N, Becker R, Reinwald J, Cosa-Linan A, Sack M, Weber-Fahr W, et al. Differences between ketamine's short-term and long-term effects on brain circuitry in depression. Transl Psychiatry. 2019;9:172.
42. Gill H, Gill B, Rodrigues NB, Lipsitz O, Rosenblat JD, El-Halabi S, et al. The effects of ketamine on cognition in treatment-resistant depression: a systematic review and priority avenues for future research. Neurosci Biobehav Rev. 2021;120:78–85.
43. Wheaton MG, Gillan CM, Simpson HB. Does cognitive-behavioral therapy affect goal-directed planning in obsessive-compulsive disorder?. Psychiatry Res. 2019;273:94–99.
44. Brown VM, Gillan CM, Renard M, Kaskie R, Degutis M, Wears A, et al. A double-blind study assessing the impact of orbitofrontal theta burst stimulation on goal-directed behavior. J Psychopathol Clin Sci. 2022;131:287–300.
45. Sookud S, Martin I, Gillan CM, Wise T. Impaired goal-directed planning in trans-diagnostic compulsivity is explained by uncertainty about learned task structure. Biol Psychiatry: Cog Neurosci and Neuroim. 2025;0:0.

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AUTHOR CONTRIBUTIONS

KRD and SH contributed to formulating the research questions, analysing the data and writing the article. CMG and RBP contributed to designing the study, analysis and writing the article. BMP and VMB contributed to the analysis and editing of the manuscript. CTL, SiH, KL, CF, AKH, VOK contributed to the design and roll-out of the study. KES contributed to the design, analysis and editing of the manuscript.

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COMPETING INTERESTS

KRD, SH, KL, CF, AKH, VOK, KES, BMP and CMG have no conflicts of interest to declare. CTL and SiH are current employees of SilverCloud Health. VMB has received consulting fees from Aya Technologies. KES acknowledges core funding by the Rene and Susanne Braginsky Foundation and the ETH Foundation. RBP is the named inventor on a University of Pittsburgh–owned patent filing related to the combination intervention that was used in the parent clinical trial.

ADDITIONAL INFORMATION

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