Delay discounting correlates with depression but does not predict relapse after antidepressant discontinuation

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Running title: Trajectories of delay discounting in remitted depression

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Abstract

Background: Approximately one third of people with major depressive disorder experience a relapse within six months of discontinuing antidepressant medication (ADM), however, reliable predictors of relapse following ADM discontinuation are currently lacking. A putative behavioural predictor is delay discounting, which measures a person's impatience to receive reward. Delay discounting is linked to both depression and reduced serotonergic function, rendering it a plausible candidate predictor.

Methods: In a multi-site study we measured delay discounting in participants with remitted depression (*N*=97), before and within six months after discontinuation of ADM, and in matched controls without a lifetime history of depression (*N*=54). Using predictive models, we tested whether either baseline discounting, or an early change in discounting following ADM discontinuation, predicted depressive relapse over a six month follow up period. We also tested differences between remitted depression and control groups in delay discounting at baseline, and associations between discounting and depressive symptoms.

Results: The remitted depression group, compared to the control group, showed significantly higher ($p<0.05$; Cohen's $d=0.34$) discounting at baseline. In addition, baseline discounting was positively correlated with depression rating scores (Spearman $\varrho= 0.24$). However, delay discounting did not increase following ADM discontinuation. Neither baseline discounting nor a change in discounting following ADM discontinuation predicted subsequent depressive relapse.

Conclusions: Delay discounting remains elevated in remitted, medicated depression. However, delay discounting neither increases following ADM discontinuation, nor does it prospectively predict depressive relapse. Impulsivity in depression has little relationship with illness trajectory following ADM discontinuation.

Introduction

Depressive disorders are estimated to be among the largest contributors to years lived with disability worldwide[1,2]. This huge burden of morbidity is largely attributable to the chronic relapsing pattern[3,4] that often characterizes depression. Furthermore, although many people derive benefit from antidepressant medication, approximately one in three will experience another depressive episode within six months of antidepressant discontinuation[5]. An initially successful treatment is therefore still too often followed by a relapse.

Randomized controlled trials indicate that continual maintenance treatment with antidepressant medication reduces the risk of relapse[5–8]. Nevertheless, maintenance treatment does not completely eliminate the risk of suffering from breakthrough depression while still on treatment, or from further depressive episodes after subsequent discontinuation[9]. Additionally, many people experience unpleasant side effects of antidepressant medication, such as weight gain and sexual dysfunction[10]. Thus, not all individuals who experience a depressive episode benefit equally from continuing medication after achieving remission. There is therefore a pressing clinical need to distinguish those who can safely discontinue antidepressants from those with a higher risk of relapse following discontinuation.

Current clinical guidelines recommend continued treatment for at least six months after obtaining remission from a first episode of depression, and at least two years of treatment after remission for patients deemed to be at high risk of relapse[11,12]. The risk of relapse is assessed using one or more of different predictors, such as the number of prior episodes[11], physical and psychological comorbidities[11], ethnicity[13], a melancholic subtype[14], anxiety[15], somatic pain[16], and previous response to medication[17]. However, several of these predictors lack robust replication studies to support their relevance (for a review see[18]). Where replications do exist, these sometimes reach conflicting conclusions, for example regarding the effect of the number of previous episodes on future relapse risk[6,19]. Other predictors are difficult to reliably measure; for example, in clinical practice, previous response to treatment is often unclear[18]. This uncertainty not only calls for continued investigation into existing markers of relapse, but also motivates a search for novel relapse predictors.

In this study we evaluate delay discounting, which quantifies a person's impatience to receive reward, as a candidate behavioural predictor of depressive relapse following antidepressant discontinuation. Delay discounting can be quickly assessed, by offering participants a series of choices between immediate and delayed rewards of varying magnitude. Conventionally, such choices are used to estimate a parameter termed the 'discount rate', which captures how steeply the subjective value of reward decreases as it is delayed. Higher discount rates imply a steeper decrease in reward value with delay, and thereby greater impatience. The behavioral and neural correlates of delay discounting have been extensively studied (see e.g. [20–23]).

Existing evidence suggests that delay discounting is a plausible candidate marker of depressive relapse. Firstly, delay discount rates are observed to be higher amongst people with acute depression, when compared to either healthy controls, or unmedicated subjects with remitted repression[24]. The greater impatience observed in acute depression has been interpreted as resulting from the pessimistic future outlook which is a feature of depression[4,25–31]. Secondly, antidepressant medications are hypothesised to ameliorate depression by increasing serotonergic neuromodulation[32], while discounting is also found to be sensitive to serotonergic manipulations. Specifically, research in humans finds that discount rates increase following serotonin depletion[33–35], and are reduced by treatment with selective serotonin reuptake inhibitors[36]. Finally, rodent studies have demonstrated that stimulating serotonergic neurons in the dorsal raphe, or their projections to medial prefrontal cortex, augments an animal's willingness to wait for reward[37,38]. In summary, discounting is increased in depression, increases following serotonin depletion and decreases following enhancement of serotonin release. Thus, delay discounting is a putative marker of both depressive cognition and serotonergic function.

Based on these findings, our primary hypothesis was that patients with remitted depression who show higher delay discounting are at increased risk of relapse following antidepressant discontinuation. A secondary hypothesis was that antidepressant discontinuation results in an increase in delay discounting, and that the magnitude of this early increase in discounting predicts subsequent depressive relapse. We tested these hypotheses within the AIDA (Antidepressiva Absetzstudie) study – a two-center,

longitudinal, observational study of antidepressant discontinuation[39–41]. We also tested how delay discounting is related to depression symptom scores and other psychometric data amongst this sample of patients with remitted depression.

Methods and Materials

Participants and study design

Data from the AIDA study has been analysed previously [39–41]. However, the delay discounting data reported here have not previously been examined. The dataset consists of: i) participants treated with antidepressant medication (ADM), who decided to discontinue their antidepressant medication independently from study participation, after being diagnosed with Major Depressive Disorder, and ii) healthy control (HC) participants matched for age, sex and education to the ADM group. Healthy controls were excluded if there was a lifetime history of DSM IV Axis I or Axis II disorders, with the sole exception of nicotine dependence. Recruitment criteria for the ADM group included: (a) at least one severe[42] or multiple depressive episodes, (b) initiation of antidepressant treatment during the last depressive episode, and (c) achieving stable remission, assessed by a score of less than 7 on the Hamilton Depression Rating Scale 17[43] for 30 days. See[39–41] for detailed inclusion and exclusion criteria.

All participants gave informed written consent and received monetary compensation for their time. Ethical approval for the study was obtained from the cantonal ethics commission Zurich (BASEC: PB_2016-0.01032; KEK-ZH: 2014-0355) and the ethics commission at the Campus Charité-Mitte (EA 1/142/14), and procedures were carried out in accordance with the Declaration of Helsinki.

As shown in Figure 1, participants were assessed and compared at Main Assessment 1 (MA1) to identify features characterising the remitted, medicated state. Next, patients were randomised to either discontinue their medication at MA1 (MA1-D-MA2) or enter a waiting period approximately matched to the length of discontinuation time (group MA1-MA2-D). Patients in the waiting group discontinued their ADM after Main Assessment 2 (MA2). After discontinuation, all patients entered a six month follow-up (FU) period, wherein some patients experienced a relapse.

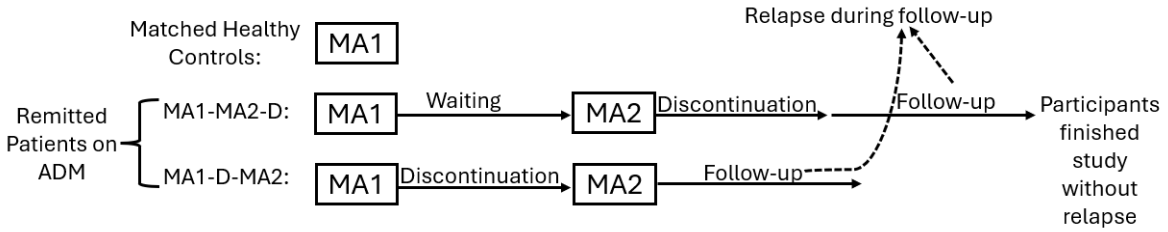

Figure 1. Study Design. We recruited remitted, medicated patients on antidepressant medication (ADM) and matched healthy controls. Patients were assessed at Main Assessment 1 (MA1) to identify features characterising the remitted, medicated state. Next, patients were randomised to either discontinue their medication before MA2 (bottom arm, "group MA-1-D-MA2" or enter a waiting period while continuing their ADM, matched to the length of discontinuation time (top arm, "group MA1-MA2-D"). Discounting was assessed at MA1 and MA2, to investigate the effects of discontinuation. Patients in the MA1-MA2-D discontinued their ADM after MA2. After discontinuation, all patients entered the follow-up (FU) period of 6 months, during which some patients relapsed.

The data analysis plan for the current study was preregistered [44], and is provided in Supplementary Table 1. All participants answered rating questionnaires, among which, the measures of prior interest for the present study were Hamilton Depression Scale (HAM-D), Emotion Regulation Questionnaire (ERQ), Brief Self-Control Scale (BSCS), Daily Hassles, Satisfaction with Life Scale (SWLS), Adverse Childhood Experience (ACE), Childhood Trauma Questionnaire (CTQ), Traumatic Life Events Questionnaire (TLEQ), and the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B).

Delay discounting tasks

Delay-discounting procedures estimate the indifference pointat which a smaller but immediately available reward, *r*, and a larger but delayed reward, *R*, have approximately the same subjective value to the participant. Here, participants completed two delay discounting tasks to estimate indifference points for rewards across a range of delays. The first task was Kirby's monetary choice questionnaire (MCQ)[45] , which consists of 27 items each asking participants to choose between an immediate and a delayed reward. In the second task, participants answered an adaptive version of the questionnaire[46], wherein a

discount rate is estimated after each choice the subject makes, and the next immediate and delayed rewards offered are provided from the currently estimated indifference point. At each step, this procedure elicits the most informative choice, based on a participant's estimated discount rate. The procedure continues until a stable estimation of the indifference point is reached[46]. Including two tasks, rather than one, was intended to bolster reliability.

Delay discounting model and model fitting procedure

We model the participants' choices using a standard hyperbolic model[47]:

$$V(R,d) = \frac{R}{1+Kd}. \qquad (1)$$

This equation describes the subjective value, V, of a reward, R, available after a delay d. K is a discount rate, estimated from participants' indifference points. Higher values of K reflect greater impulsivity and reduced tolerance for delay[48]. The hyperbolic model of delay discounting is illustrated in Figure 2. A generalization of this hyperbolic model includes an exponent on the delay term, which adjusts the curvature of the discount curve[49]. Here, since we are interested in individual differences, we omit this exponent in favour of the standard hyperbola, which captures variability in discounting with a single parameter, K.

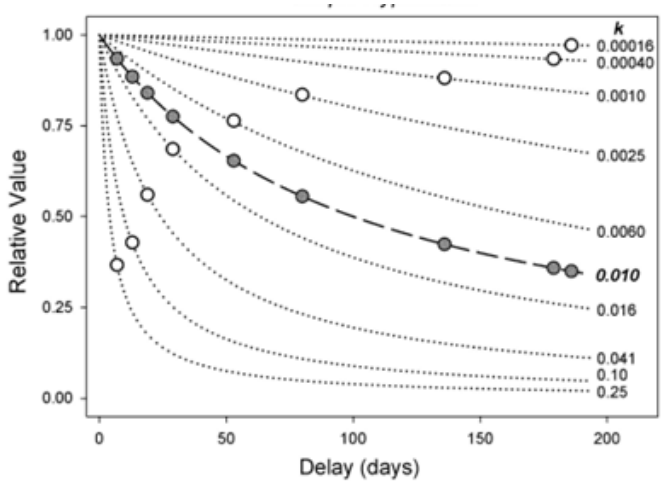

Figure 2. Hyperbolic delay discounting. Illustration of the hyperbolic model of delay discounting for a subset of nine questions from Kirby's monetary choice questionnaire (MCQ) consisting of small amount of delayed reward (25-35). Each open white circle represents one of the nine questions: its X-coordinate indicates how long one would have to wait for the delayed reward (delay, d), while its Y-coordinate indicates the value of the immediate, no delay reward relative to the delayed reward (relative value, V/R). Each dotted curve represents the hyperbolic delay discount rate, K, at which a participant would be indifferent between immediate and delayed rewards for each specific choice. The dashed curve corresponds to a discount function with $K = 0.01$. A person with this fitted value of the discount rate would choose the immediate rewards in the questions with K values larger than 0.01

(bottom four hyperbolic curves), and would choose the delayed reward on the questions with K values smaller than 0.01 (top five hyperbolic curves). Open grey circles represent the subjective values, V(R, d), predicted by the dashed curve for each value of delay (d) of the nine questions. Adapted from 45,50,51.

We fit the delay discounting model using a Bayesian hierarchical (mixed-effects) logistic regression[52]. This general procedure is widely used to fit parameters in decision making tasks, see e.g.[52–55]. In brief, estimated discount rate yields a difference in subjective value between immediate and delayed rewards for each choice. A logistic sigmoid (softmax) function, $\sigma(x) = \frac{1}{1+\exp(-x)}$, transforms this subjective value difference into a probability of choosing the immediate reward on each choice. We used an optimization procedure to find parameters that maximize the joint probability of each participant's observed choices, assuming an empirical prior distribution over discount rates. This prior distribution, which is estimated using Expectation-Maximization (EM), serves to regularise the inference and prevent parameters that are not well-constrained from taking on extreme values [52]. The reader is referred to [52] for the full technical details of the routine.

To maximize reliability, we fit the model to the concatenated answers of both the classic and the adaptive versions of the questionnaires. We estimate the goodness-of-fit of the resulting model using McFadden's pseudo-R^2, averaged across all subjects[56]. Furthermore, after fitting the model, we exclude subjects whose model accuracy is not significantly better than chance, estimated by a corresponding binomial test with a significance threshold of 0.05. Specifically, subjects for which $p = \sum_{i=k}^{n} \binom{n}{i} 0.5^i 0.5^{n-i} > 0.05$ are excluded, where p denotes the p-value of the binomial test, n is the number of questions in the questionnaire and k is the number of correctly classified answers.

Data analysis

Analyses were performed in Matlab (R2023a) according to the pre-registered analysis plan provided in Supplementary Table 1 and also in [44]. In each analysis step reported below, we refer the reader to the corresponding analysis step from Supplementary Table 1, or indicate the step was not part of the original analysis plan. In this study we report analyses of discounting choice data.

For the sake of clarity, we divide the analyses into four categories: i) prediction of relapse, ii) effect of discontinuation, and iii) discounting *in remitted depression*. We also emphasize that, since previous studies show that discount rates, *K*, are log-normally distributed[51,57] we test for differences in *log K* rather than *K*.

i) Prediction of Relapse

We started by testing for association between discount rate and relapse by using a one-tailed two-sample *t*-test to test if *log K* at MA1 was greater in patients who relapsed than in patients who did not relapse during follow-up. This test explores the potential of baseline *log K* as a predictor of future relapse. We also used a one-tailed two-sample t-test to test if the *change* in *log K* between MA1 and MA2 (gain scores) differed between subjects from the MA1-D-MA2 group who relapsed during follow-up and subjects from the MA1-D-MA2 group who did not relapse during follow-up. This test examines whether a change in *log K* following discontinuation is associated with subsequent relapse. The tests detailed in this paragraph were not part of the pre-registered analysis plan.

In addition, to test for an association between time to relapse and discount rate, we use MATLAB *coxphfit* function to fit a Cox proportional hazards model with days to relapse as the dependent variable. We fitted two such models, with independent variables as i) *log K* at MA1 (Step (4) in the analysis plan), or ii) *log K* at both MA1 and MA2 (Step (5) in the analysis plan).

To examine whether discount rates can predict subsequent relapse, we fitted a logistic regression model with an L1 regularization (known as "Lasso" [58]), as implemented by the *lassoglm* function in Matlab, with relapse as the dependent variable and either *log K* at MA1 (Step (4) in the analysis plan), or both *log K* at MA1 and *log K* at MA2 as independent variables (Step (5) in the analysis plan). Consistent with the analysis plan, the model was trained on subjects from the Zurich sample, with a view to testing on the Berlin sample. We applied tenfold cross validation with stratification to optimize the value of the L1-regularization parameter.

ii) Effect of discontinuation

We also hypothesized that discontinuation at MA1 would be associated with an increase in *log K* (between MA1 and MA2), assessed relative to the group who discontinued at MA2. To test for this, we fitted a linear mixed effects model using MATLAB *fitlme* function, with *log K* at both timepoints as the dependent variable, and group (i.e., MA1-D-MA2 or MA1-MA2-D), timepoint (i.e., MA1 or MA2) and [group x timepoint], as independent (fixed effect) variables (Step (2) in the analysis plan). We include a random slope term for each participant.

iii) Discounting in remitted depression

We used a one-tailed two-sample t-test to test the hypothesis that *log K* at MA1 was greater in patients than in controls (Step (1) in the analysis plan). We also tested for associations between *log K* at MA1 and scores on the various rating scales, using simple linear regression, with *log K* as the dependent variable. Additionally, we express pairwise associations between *log K* at MA1 and each rating scale as a Spearman correlation coefficient (Step (3) in the analysis plan).

Finally, we tested whether *log K* at MA1 was associated with a change in depression (HAM-D) scores over time, independent of discontinuation (Step (6) in the analysis plan). To do so, we fitted a linear mixed effect model, wherein the dependent variable is HAM-D score (at MA1 or MA2), the independent variables (with fixed effects) are *log K* at MA1, timepoint (MA1 or MA2), a [$log\ K_{MA1}$ x timepoint] interaction, discontinuation group (MA1-D-MA2 vs. MA1-MA2-D) and [discontinuation group x timepoint] interaction. We included a random slope for each participant. Here, the [$log\ K_{MA1}$ x timepoint] interaction term expresses the extent to which a change in depression score across time depends on *log K* at baseline, whereas the [discontinuation group x timepoint] interaction term controls for possible confounding that results from testing on two discontinuation groups that differ in the time of withdrawal. Here we hypothesized that participants with higher baseline discounting would show less improvement in depressive symptoms across time.

Complementary analysis methods and results that appear in the *a priori* analysis plan are provided in the Supplementary Material. As set out in the analysis plan, all comparisons were performed first on the Zurich sample, with a view to testing on the Berlin sample as an out-of-sample validation of predictive accuracy. However, where no significant associations

between *log K* and the variables of interest were found in either sample, we pooled both samples to maximize power. We report these pooled analyses here.

Results

Model fitting

Model accuracy met the (binomial test) accuracy criterion described above for all participants, and therefore no participants were excluded. The numbers of participants in each group and at each site are shown in Table 1. The average model accuracy was 85%; mean McFadden's pseudo-R^2 across subjects was 0.59, indicating a good fit to the data. Discount rates obtained from the adaptive discounting questionnaire and the Kirby MCQ were only moderately correlated (Spearman ϱ=0.32, $p < 0.001$).

	Zurich			**Berlin**		
	Controls	Patients		Controls	Patients	
		MA1-D-MA2	MA1-MA2-D		MA1-D-MA2	MA1-MA2-D
N	32	32	39	22	15	11

Table 1: Number of participants in each *site* and *group*. *See Figure 1 for an explanation of the study design and groups.*

In addition, no significant associations were found between *log* K at baseline and any possible confounding factors tested. The details and results are provided in Supplementary Table 2.

(i) Prediction of relapse

We found no significant difference in *log K* at MA1 between subjects treated with ADM who relapsed during follow-up and subjects treated with ADM who did not relapse ($t(78)$=0.44, p >0.25,two-tailed two-sample; Cohen's d = 0.10). Furthermore, a change in *log K* following discontinuation (i.e., between MA1 and MA2 amongst the MA1-D-MA2 group), did not differ significantly between participants who subsequently relapsed and those who did not relapse ($t(37)$=0.58, p>0.25, one-tailed; Cohen's d=0.20). In a Cox proportional hazards regression model, including *log K* at both timepoints, neither *log* K_{MA1} nor *log* K_{MA2} were

significantly associated with days-to-relapse (Coefficient *log* K_{MA1} =-0.02, p>0.25; coefficient *log* K_{MA2} =-0.08, p>0.25), nor was *log* K_{MA1} associated with relapse when entered into a separate regression model (Coefficient =-0.08, p>0.25).

In the prediction of relapse, the regularized regression weights were found to be all zero, resulting in a balanced accuracy of 0.5 and reflecting the balanced proportion of the majority class. For the sake of completeness, the distribution of baseline *log K* in the different relapse groups is shown in Supplementary Figure S1.

(ii) **Effect of discontinuation**

Contrary to our secondary hypothesis, antidepressant discontinuation was not associated with a significant increase in impulsive choice, relative to continuing medication. Specifically, in a linear mixed effects model with *log K* as the dependent variable, we found no significant [timepoint x discontinuation group] interaction ($\beta_{timepoint\ x\ group}$ =0.04, t(180)=0.15, p>0.25). In other words, discontinuation did not significantly alter a change in *log K* across time. Main effects of timepoint and group were also small and non-significant (β_{group} =-0.05, t(180)=-0.10, p>0.25 ; $\beta_{timepoint}$=0.10, t(180)=0.56, p>0.25).

We further explored this null finding in a *post hoc* analysis, by performing a one-tailed two-sample t-test on *log* K gain scores to test whether *log K* increased more in patients who discontinued at MA1 (MA1-D-MA2) than in patients who discontinued at MA2 (MA1-MA2-D). To prevent error accumulation due to the additivity of noise, in model fitting, the difference between *log K* at MA1 and *log K* at MA2 was estimated concurrently with *log K* at MA1. Again, we found no significant difference in the change in *log K* between MA1 and MA2, among the MA1-D-MA2 group compared with the MA1-MA2-D group (t(82)=0.19, p >0.25; Cohen's d = 0.04).

(iii) Discounting *in remitted depression*

Group comparison of *log K* between healthy controls and patients with remitted depression (treated with ADM) at MA1 revealed significantly higher discount rates in the patient group (t(149)=2.03 and p =0.022, one-tailed; Cohen's d = 0.34).

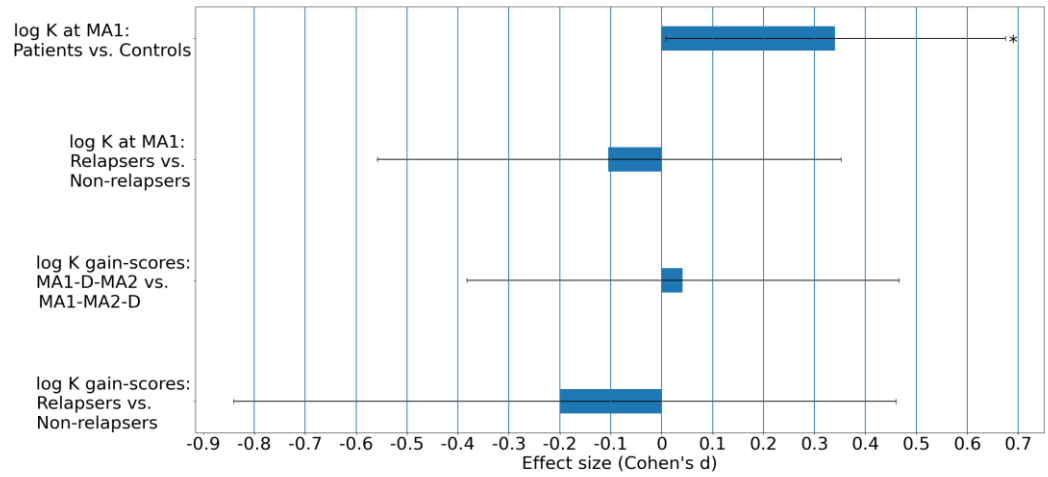

Figure 3 Effect sizes for group differences in *log K*. Cohen's d effect size, for various group comparisons. The top bar shows the comparison of log K at MA1 between controls and patients, where the effect size in this case indicates that the average of log K in the Patients group (at both sites) at MA1 is greater than the average of log K in the Controls group at MA1. The second bar from above shows the comparison of log K at MA1 between patients who subsequently relapsed and patients who did not, where the effect size in this case indicates that the average of log K in non-relapsers at MA1 is greater than the average of log K in relapsers at MA1. The third bar shows the comparison of the change in log K between the two timepoints (gain scores), between patients who discontinued their treatment at MA1 (MA1-D-MA2) and patients who continued their treatment until MA2 (MA1-MA2-D), where the effect size indicates that the average of gain scores in the MA1-D-MA2 group is greater than the average of gain scores in the MA1-MA2-D group . The bottom bar shows the comparison of the change in log K between the two timepoints (gain scores), between patients from the MA1-D-MA2 group who subsequently relapsed and patients from the MA1-D-MA2 group who did not, where the effect size indicates that the average of gain scores in the non-relapsers group was greater than the average of gain scores in the relapsers group. Error bars represent 95% confidence interval for Cohen's d effect size, estimated using MATLAB meanEffectSize function . Group difference p-value: * .01<p<.05.

As shown in Figure 4, depressive symptoms (measured by the HAM-D scale) were significantly correlated with baseline discount rate, $\log K_{MA1}$ (Spearman ϱ=0.24, p=0.003), an association which survived Bonferroni correction for multiple comparisons (p=0.022, corrected for 8 comparisons), and was also present when testing only on the patients' group (Spearman ϱ=0.23, p=0.025). Other questionnaire instruments did not exhibit significant correlations with $\log K_{MA1}$ (Figure 4). We note that baseline discount rate showed a

significant correlation with two *subscales* of the CTQ questionnaire, namely CTQ-physical abuse (Spearman ϱ =0.18, p=0.023) and CTQ-emotional neglect (Spearman ϱ =0.16, p=0.049). See Supplementary Figure S2 for the comparisons with other questionnaire subscales. When all questionnaire variables were entered into a linear regression model with *log* K_{MA1} as the dependent variable, only HAM-D emerged as a significant explanatory variable (coefficient estimate=0.19, $t(142)$=2.51, p=0.013). Coefficients and t-statistics for the remaining rating scales are provided in Supplementary Table 3.

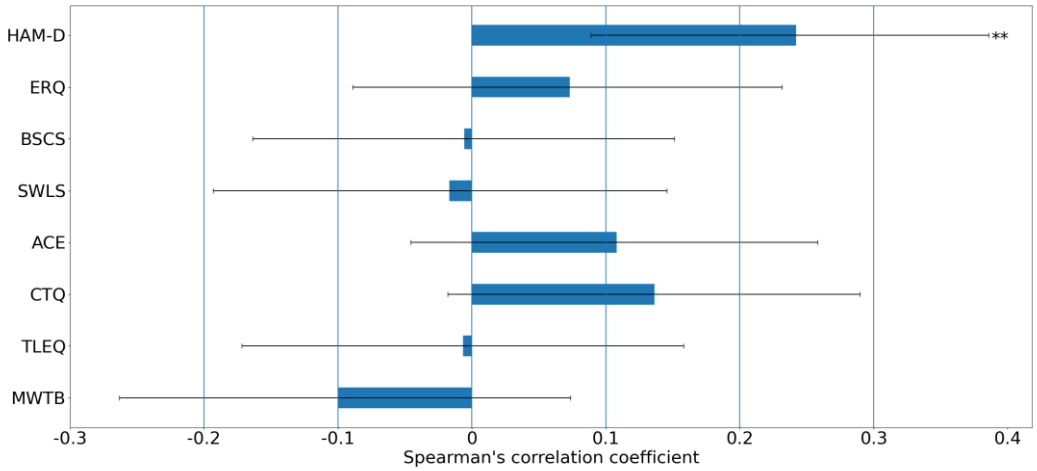

Figure 4 Correlations between *log K* at MA1 and rating scales. HAM-D=Hamilton Depression Scale, ERQ=Emotion Regulation Questionnaire (ERQ), BSCS=Brief Self-Control Scale, SWLS=Satisfaction with Life Scale, ACE=Adverse Childhood Experience, CTQ=Childhood Trauma Questionnaire, TLEQ=Traumatic Life Events Questionnaire, MWTB= Mehrfachwahl-Wortschatz-Intelligenztest. Error bars represent 95% confidence interval for Spearman's correlation coefficient estimated using 10,000 bootstrap iterations. Group difference p-value: * .01<p<.05, ** .001<p<.01.

We went on to test for an association between a change in depression across time, and baseline discounting (at MA1), in a mixed-effects linear regression with HAM-D scores as the dependent variable. We found a significant main effect of *log* K_{MA1} (coefficient estimate=0.56, $t(150)$=2.26, p=0.025). This result is consistent with the findings reported above of a correlation between *log* K_{MA1} and HAM-D at MA1. We found no significant main effect of timepoint (coefficient estimate=0.01, $t(150)$= 0.01, p=0.989); here, the positive coefficient indicates that the average participant showed a marginal, albeit non-significant, increase in HAM-D score across time. There was a significant [timepoint x *log K*] interaction (coefficient

estimate=-0.30, $t(150)$=-2.01, p=0.045). Here, contrary to our prediction, the negative coefficient indicates that participants who were more impulsive (higher *log K*) at baseline showed a greater reduction in depression score across time. We found no significant effect of discontinuation group(coefficient estimate=0.19, t(150)=0.22, p=0.820), nor a significant effect of the [discontinuation group x timepoint] interaction (coefficient estimate=-0.47, t(150)=-0.94, p=0.345).

Discussion

In this pre-registered analysis, we examined the potential of delay discounting as a behavioral marker of relapse after antidepressant discontinuation. There is *a priori* evidence to suggest that delay discounting might help predict illness trajectory following discontinuation of antidepressant medication (ADM). To the best of our knowledge, the present study is the first to prospectively examine i) whether discounting predicts future depressive relapse following ADM discontinuation, and ii) the effect of ADM discontinuation on delay discounting. Our results suggest that delay discounting is not altered by ADM discontinuation to a clinically meaningful extent. Furthermore, we found that neither baseline delay discounting, nor a change in discounting following ADM discontinuation were predictive of future depressive relapse. However, we did find significantly steeper delay discounting amongst patients with remitted depression, compared with controls (Cohen's d = 0.34), and a robust relationship between the discount rate and depressive symptoms (Spearman ϱ=0.24).

To our knowledge, the present study is the first to find significantly elevated delay discounting amongst medicated patients with remitted depression. This finding is consistent with previous studies that have observed a relationship between trait-level impulsivity (e.g., as assessed in self-report rating scales) and depression, which continues even in remission[59,60]. Furthermore, a previous study by Pulcu *et al.*[24], which compared delay discounting amongst people with remitted, unmedicated depression and healthy controls, found that averaged across reward sizes, patients with remitted depression showed marginally steeper discounting than controls (albeit this difference was not statistically significant). In both the study of Pulcu *et al.*, and the present study, depressive symptoms

were significantly correlated with discount rate across all participants. The elevated discounting seen in remitted depression might therefore reflect residual, sub-clinical depressive symptoms. Alternatively, although discounting is known to be elevated in acute depression, discounting might partly capture a trait-level vulnerability to depression, which persists despite symptom resolution.

In the current study, higher discounting at baseline was not predictive of future relapse following discontinuation; nor was baseline discounting associated with worsening depressive symptoms between the two timepoints of the study (up to six months apart). The relatively small sample size of this study may be underpowered to detect subtle relationships, particularly over the relatively short follow up period of the study. Nevertheless, our null finding suggests that, if discounting is indeed a trait-level vulnerability factor for depression, this effect is too small to be clinically meaningful over short-term follow up. Contrary to our prediction, higher impulsivity at baseline was associated with a marginally significant *decrease* in depressive score across time. We are uncertain as to the explanation for this effect. We speculate that higher impulsivity is linked to greater venturesomeness, which encourages exploration and thereby recovery from depression. However, since this finding is against our prior predictions, further replication is needed.

A secondary hypothesis was based on an idea that discounting would be a sensitive marker of psycho-physiological changes following ADM discontinuation. However, we did not observe an increase in impulsivity following ADM discontinuation. Specifically, we did not find a significant change in *log K* amongst remitted patients who discontinued their treatment (MA1-D-MA2 group), relative to remitted patients who continued their treatment (MA1-MA2-D group). This finding is also consistent with an AIDA study of effort-reward tradeoffs[40], where the authors found no effect of ADM discontinuation on choices of high-effort high-reward options. Although our finding may be the result of limited statistical power, the relatively small effect sizes obtained from the corresponding group comparisons (Cohen's d<0.1), as well as the significant group differences obtained in other comparisons, suggest otherwise.

We had hypothesized that discounting might be sensitive to decreases in serotonergic neuromodulation following antidepressant discontinuation. However, although discounting has been shown to be sensitive to serotonergic manipulations, it is unclear whether the elevated discounting observed in depression is linked to changes in serotonin. Furthermore, the directionality and temporality of the adaptive changes in the 5-HT system following antidepressant discontinuation are uncertain. Some evidence points to a reduction in the extracellular 5-HT levels following discontinuation[62,63], while other studies indicate a rebound above pre-treatment levels (see e.g.[63–66] and the references therein). Taking these considerations together, a lack of association between discounting and ADM discontinuation is not out of keeping with the state of existing knowledge concerning causal relationships between serotonergic function, depression and ADM.

Conclusion. Delay discounting is not strongly affected by ADM discontinuation and therefore appears to be of limited use as a biomarker for decisions related to anti-depressant discontinuation.

Data availability. The datasets generated and analysed during the current study are available from the corresponding author on reasonable request and in line with the ethical rules.

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