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

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29   **Abstract**

30   Approximately one third of people with Major Depressive Disorder (MDD) experience a

31   relapse within six months of discontinuing antidepressant medication (ADM), however,

32   reliable predictors of relapse following ADM discontinuation are currently lacking. A

33   putative behavioural predictor is delay discounting, which measures a person's impatience

34   to receive reward. Previous studies have linked delay discounting to both MDD and

35   reduced serotonergic function, rendering it a plausible candidate predictor. In this multi-site

36   study we measured delay discounting in participants with remitted MDD (N=97), before

37   and within six months after discontinuation of ADM, and in matched controls without a

38   lifetime history of MDD (N=54). Using predictive models, we tested whether either baseline

39   discounting, or an early change in discounting following ADM discontinuation, predicted

40   depressive relapse over a six month follow up period. We also tested differences between

41   remitted MDD and control groups in delay discounting at baseline, and associations

42   between discounting and depressive symptoms. We found that the remitted MDD group,

43   compared to the control group, showed significantly higher ($p<0.05$; Cohen's d=0.34)

44   discounting at baseline. In addition, baseline discounting was positively correlated with

45   depression rating scores (Spearman ϱ= 0.24). However, delay discounting did not increase

46   following ADM discontinuation. Neither baseline discounting, nor a change in discounting

47   following ADM discontinuation, predicted subsequent depressive relapse. We conclude

48   that delay discounting is elevated in remitted MDD treated with antidepressant medication.

49   However, delay discounting neither increases following ADM discontinuation, nor does it

50   prospectively predict depressive relapse. These results suggest that delay discounting in

51   Major Depressive Disorder has little relationship with illness trajectory following ADM

52   discontinuation.

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Introduction

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

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

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

88   In this study we evaluate delay discounting, which is thought to quantify a person's

89   impatience to receive reward, as a candidate behavioural predictor of depressive relapse

90   following antidepressant discontinuation[1]. Delay discounting can be quickly assessed, by

91   offering participants a series of choices between immediate and delayed rewards of varying

92   magnitude. Conventionally, such choices are used to estimate a parameter termed the

93   'discount rate', which captures how steeply the subjective value of reward decreases as it is

94   delayed. Higher discount rates imply a steeper decrease in reward value with delay, and

95   thereby greater impatience. The behavioral and neural correlates of delay discounting have

96   been extensively studied (see e.g. [20–23]).

97   Existing evidence suggests that delay discounting is a plausible candidate marker of

98   depressive relapse following antidepressant discontinuation. Firstly, studies have reported

99   higher delay discount rates amongst people with Major Depressive Disorder (MDD) when

100   compared to healthy controls[24-27]. Notably differences in discounting between depressed

101   participants and non-depressed controls are not found reliably across all studies and

102   comparisons. Some studies find no significant difference[28-29], while others find differences

103   from healthy controls only amongst sub-groups of depressed participants[24,27], or only for

104   larger rewards[26]. Nevertheless, a meta-analysis of seven case-control studies supports a

105   conclusion of elevated discounting in MDD, with a small effect size (Hedges g=0.38)[30]. The

106   greater impatience observed in MDD has been interpreted as resulting from the pessimistic

107   future outlook which is a feature of depression[4,31-26] and as reflecting the loss of evaluative

108   differentiation concerning future outcomes[37].

109   Secondly, most antidepressant medications are believed to increase serotonin levels,

110   which is thought to be crucial for their therapeutic effect[38,39], while discounting is also found

111   to be sensitive to serotonergic manipulations. Tryptophan depletion, which lowers brain

112   serotonin levels, induces acute symptomatic relapse in patients with remitted depression[40,41],

113   and has been found to increase discount rates in healthy participants[42-43] (though Tanaka *et*

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[1] The term 'relapse' is conventionally reserved for episodes within the first six months, after which the term 'recurrence' is usually employed. In this study, since the time from first episode varied amongst our patient group, we do not distinguish between relapse and recurrence, and adopt the term 'relapse' throughout.

114   *al.* did not replicate this effect)[44]. Furthermore, a small study found that discount rates were

115   reduced by acute administration of a selective serotonin reuptake inhibitor amongst

116   participants with Attention Deficit Hyperactivity Disorder[45]. More definitively, rodent

117   studies have demonstrated that stimulating serotonergic neurons in the dorsal raphe, or

118   their projections to medial prefrontal cortex, augments an animal's willingness to wait for

119   reward[46,47], while lesioning or blocking serotonergic neurotransmission increases

120   impatience[48-50].

121   In summary, evidence indicates that discounting is increased in MDD, increases

122   following serotonin depletion and decreases following enhancement of serotonin release.

123   Thus, delay discounting is a candidate marker of both serotonergic function and depressive

124   cognition. Based on these findings, our primary hypothesis was that patients with remitted

125   MDD who show higher delay discounting are at increased risk of relapse following

126   antidepressant discontinuation. A secondary hypothesis was that antidepressant

127   discontinuation results in an increase in delay discounting, and that the magnitude of this

128   early increase in discounting predicts subsequent depressive relapse. We tested these

129   hypotheses within the AIDA (Antidepressiva Absetzstudie) study – a two-center,

130   longitudinal, observational study of antidepressant discontinuation[51-53]. We also tested how

131   delay discounting is related to depression symptom scores and other psychometric data

132   amongst this sample of patients with remitted depression.

133

Methods and Materials

Participants and study design

136   Data from the AIDA study has been analysed previously[51-53]. However, the delay

137   discounting data reported here have not previously been examined. The dataset consists of:

138   i) participants treated with antidepressant medication (ADM), who decided to discontinue

139   their antidepressant medication independently from study participation, after being

140   diagnosed with Major Depressive Disorder, and ii) healthy control (HC) participants

141   matched for age, sex and education to the ADM group. Healthy controls were excluded if

142   there was a lifetime history of DSM IV Axis I or Axis II disorders, with the sole exception of

143   nicotine dependence. Recruitment criteria for the ADM group included: (a) at least one

144   severe[54] or multiple depressive episodes, (b) initiation of antidepressant treatment during

145   the last depressive episode, and (c) achieving stable remission, assessed by a score of less

146   than 7 on the Hamilton Depression Rating Scale 17[55] for 30 days. See[51-53] for detailed

147   inclusion and exclusion criteria.

148   All participants gave informed written consent and received monetary compensation

149   for their time. Ethical approval for the study was obtained from the cantonal ethics

150   commission Zurich (BASEC: PB_2016-0.01032; KEK-ZH: 2014-0355) and the ethics

151   commission at the Campus Charité-Mitte (EA 1/142/14), and procedures were carried out in

152   accordance with the Declaration of Helsinki.

153   As shown in Figure 1, participants were assessed and compared at Main Assessment

154   1 (MA1) to identify features characterising the remitted, medicated state. Next, patients were

155   randomised to either discontinue their medication at MA1 (MA1-D-MA2) or enter a waiting

156   period approximately matched to the length of discontinuation time (group MA1-MA2-D).

157   Patients in the waiting group discontinued their ADM after Main Assessment 2 (MA2).

158   Details of the randomisation procedure are provided in the Supporting Material. After

159   discontinuation, all patients entered a six month follow-up (FU) period, wherein some

160   patients experienced a relapse.

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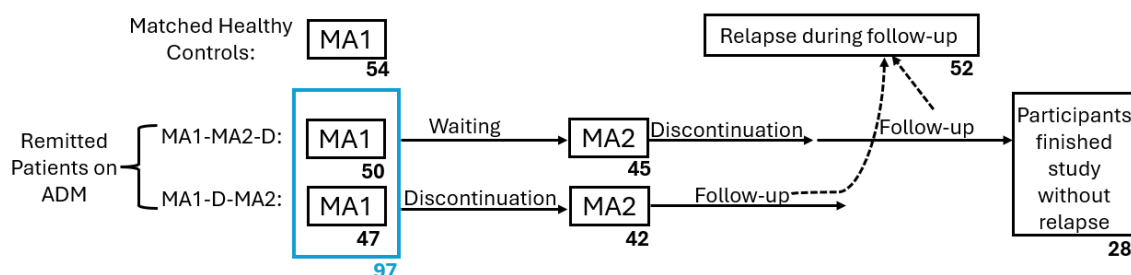
Figure 1: We recruited remitted patients treated with antidepressant medication (ADM) and
healthy controls matched for age, sex and education to the patients group. Patients were
assessed at Main Assessment 1 (MA1) to identify features characterizing the remitted,
medicated state. Next, patients were randomized 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").

169 Discounting was assessed at MA1 and MA2, to investigate the effects of discontinuation.
170 Patients in the MA1-MA2-D discontinued their ADM after MA2. After discontinuation, all
171 patients entered the follow-up (FU) period of 6 months, during which some patients
172 relapsed. Numbers below each box indicate the number of subjects in that group. The
173 numbers below each box indicate the number of subjects in the corresponding group.

174

175   The data analysis plan for the current study was preregistered[56], and is provided in

176 Supplementary Table 1. All participants answered rating questionnaires, among which, the

177 measures of prior interest for the present study were Hamilton Depression Scale (HAM-D),

178 Emotion Regulation Questionnaire (ERQ), Brief Self-Control Scale (BSCS), Daily Hassles,

179 Satisfaction with Life Scale (SWLS), Adverse Childhood Experience (ACE), Childhood

180 Trauma Questionnaire (CTQ), Traumatic Life Events Questionnaire (TLEQ), and the

181 Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B).

182   We also conducted a power analysis for group differences prior to the study

183 commencement. The description of which is provided in the Supporting Material.

Delay discounting tasks

185   Delay-discounting procedures estimate the indifference point at which a smaller but

186 immediately available reward, r, and a larger but delayed reward, R, have approximately

187 the same subjective value to the participant. Here, participants completed two delay

188 discounting tasks to estimate indifference points for rewards across a range of delays. The

189 first task was Kirby's monetary choice questionnaire (MCQ)[57], which consists of 27 items

190 each asking participants to choose between an immediate and a delayed reward. In the

191 second task, participants answered an adaptive version of the questionnaire[58], wherein a

192 discount rate is estimated after each choice the subject makes, and the next immediate and

193 delayed rewards offered are provided from the currently estimated indifference point. At

194 each step, this procedure elicits the most informative choice, based on a participant's

195 estimated discount rate. The procedure continues until a stable estimation of the indifference

196 point is reached[58]. Including two tasks, rather than one, was intended to bolster reliability.

197   In this study, rewards were hypothetical. Although one previous study found a

198 small reduction in discount rates for real as opposed to hypothetical rewards[59], a number of

199   other studies report no systematic differences in discounting for real and hypothetical

200   rewards[60-62], suggesting that assessing discounting for hypothetical rewards is a valid

201   procedure.

202   **Delay discounting model and model fitting procedure**

203   We modeled the participants' choices using a standard hyperbolic model[63]:

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

205   This equation describes the subjective value, V, of a reward, R, available after a delay

206   d. K is a discount rate, estimated from participants' indifference points. Higher values of K

207   reflect greater impatience and reduced tolerance for delay[52]. The hyperbolic model of delay

208   discounting is illustrated in Figure 2. A generalization of this hyperbolic model includes an

209   exponent on the delay term, which adjusts the curvature of the discount curve[64]. Here, since

210   we are interested in individual differences, we omit this exponent in favour of the standard

211   hyperbola, which captures variability in discounting with a single parameter, K.

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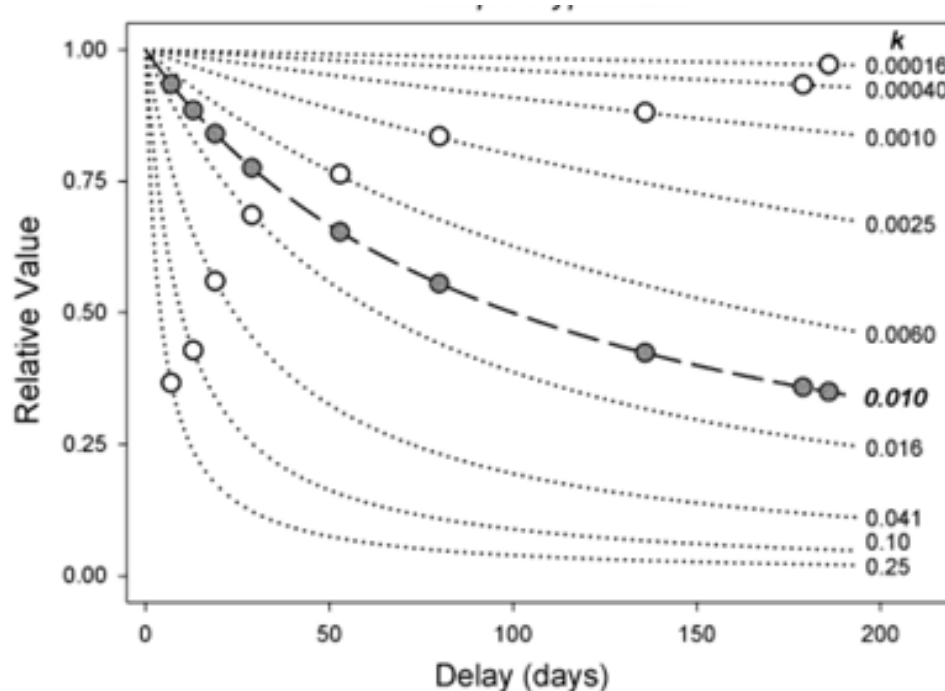
Figure 2: Illustration of the hyperbolic model of delay discounting for a subset of nine
questions from Kirby's monetary choice questionnaire (MCQ) consisting of small amount of
delayed reward (25-35). Each open white circle represents one of the nine questions: its X-
coordinate indicates how long one 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

218   delayed reward (relative value, V/R). Each dotted curve represents the hyperbolic delay

219   discount rate, K, at which a participant would be indifferent between immediate and

220   delayed rewards for each specific choice. The dashed curve corresponds to a discount

221   function with $K = 0.01$. A person with this fitted value of the discount rate would choose the

222   immediate rewards in the questions with K values larger than 0.01 (bottom four hyperbolic

223   curves), and would choose the delayed reward on the questions with K values smaller than

224   0.01 (top five hyperbolic curves). Open grey circles represent the subjective values, V(R, d),

225   predicted by the dashed curve for each value of delay (d) of the nine questions. Adapted

226   from [49,59,71].

227

228   We fitted the delay discounting model using a Bayesian hierarchical (mixed-effects)

229   logistic regression[66]. This general procedure is widely used to fit parameters in decision

230   making tasks, see e.g.[66-69]. In brief, estimated discount rate yields a difference in subjective

231   value between immediate and delayed rewards for each choice. A logistic sigmoid (softmax)

232   function, $\sigma(x) = \frac{1}{1+\exp(-x)}$, transforms this subjective value difference into a probability of

233   choosing the immediate reward on each choice. We used an optimization procedure to find

234   parameters that maximize the joint probability of each participant's observed choices,

235   assuming an empirical prior distribution over discount rates. This prior distribution, which

236   is estimated using Expectation-Maximization (EM), served to regularise the inference and

237   prevent parameters that are not well-constrained from taking on extreme values[66]. The

238   reader is referred to[66] for the full technical details of the routine.

239   To maximize reliability, we fitted the model to the concatenated answers of both the

240   classic and the adaptive versions of the questionnaires. We estimated the goodness-of-fit of

241   the resulting model using McFadden's pseudo-R^2, averaged across all subjects[70].

242   Furthermore, after fitting the model, we excluded subjects whose model accuracy is not

243   significantly better than chance, estimated by a corresponding binomial test with a

244   significance threshold of 0.05. Specifically, subjects for which $p = \sum_{i=k}^{n} \binom{n}{i} 0.5^i 0.5^{n-i} > 0.05$

245   were excluded, where p denotes the p-value of the binomial test, n is the number of

246   questions in the questionnaire and k is the number of correctly classified answers.

247   **Data analysis**

248   Analyses were performed in Matlab (R2023a) according to the pre-registered analysis

249   plan provided in Supplementary Table 1 and also in [56]. In each analysis step reported below,

250   we refer the reader to the corresponding analysis step from Supplementary Table 1, or

251   indicate the step was not part of the original analysis plan. In this study we report analyses

252   of discounting choice data. For the sake of clarity, we divide the analyses into three

253   categories: i) prediction of relapse, ii) effect of discontinuation, and iii) discounting *in*

254   *remitted MDD*.

255   Since previous studies show that discount rates, K, are log-normally distributed[71-72]

256   we test for differences in *log K* rather than K. Unless otherwise stated, paired and

257   independent-samples t-tests were used to compare group means. Given that each group

258   comprised at least 30 participants, the Central Limit Theorem supports the assumption that

259   the sampling distribution of the mean was approximately normal. Indeed, for each

260   comparison, normality and equal variance were tested using Kolmogorov-Smirnov

261   (MATLAB *kstest* function) and Bartlett tests (MATLAB *vartestn* test), respectively. For the

262   few comparisons where either test rejected the null hypothesis of normality or equal

263   variance, a non-parametric test was used: Wilcoxon Signed Rank for paired samples or Rank

264   Sum for independent samples. We report means and standard deviations (or, where

265   relevant, medians and interquartile ranges) for all comparisons in Supplementary Table 5.

266

267   *i)   Prediction of Relapse*

268   We started by testing for association between discount rate and relapse by using a

269   one-tailed two-sample t-test to test if *log K* at MA1 was greater in patients who relapsed than

270   in patients who did not relapse during follow-up. This test explores the potential of baseline

271   *log K* as a predictor of future relapse. We also used a one-tailed two-sample t-test to test if

272   the *change* in *log K* between MA1 and MA2 (gain scores) differed between subjects from the

273   MA1-D-MA2 group who relapsed during follow-up and subjects from the MA1-D-MA2

274   group who did not relapse during follow-up. This test examines whether a change in *log K*

275   following discontinuation is associated with subsequent relapse. The tests detailed in this

276   paragraph were not part of the pre-registered analysis plan.

277   In addition, to test for an association between time to relapse and discount rate, we

278   used MATLAB *coxphfit* function to fit a Cox proportional hazards model with days to

279   relapse as the dependent variable. We fitted two such models, with independent variables as

280   i) *log K* at MA1 (Step (4) in the analysis plan), or ii) *log K* at both MA1 and MA2 (Step (5) in

281   the analysis plan).

282   To examine whether discount rates can predict subsequent relapse, we fitted a

283   logistic regression model with an L1 regularization (known as "Lasso" [73]), as implemented by

284   the *lassoglm* function in Matlab, with relapse as the dependent variable and either *log K* at

285   MA1 (Step (4) in the analysis plan), or both *log K* at MA1 and *log K* at MA2 as independent

286   variables (Step (5) in the analysis plan). Consistent with the analysis plan, the model was

287   trained on subjects from the Zurich sample, with a view to testing on the Berlin sample. We

288   applied tenfold cross validation with stratification to optimize the value of the L1-

289   regularization parameter.

290   *ii)   Effect of discontinuation*

291   We also hypothesized that discontinuation at MA1 would be associated with an

292   increase in *log K* (between MA1 and MA2), assessed relative to the group who discontinued

293   at MA2. To test for this, we fitted a linear mixed effects model using MATLAB *fitlme*

294   function, with *log K* at both timepoints as the dependent variable, and group (i.e., MA1-D-

295   MA2 or MA1-MA2-D), timepoint (i.e., MA1 or MA2) and [group x timepoint], as

296   independent (fixed effect) variables (Step (2) in the analysis plan). We included a random

297   slope term for each participant.

298   *iii)   Discounting in remitted MDD*

299   We used a one-tailed two-sample t-test to test the hypothesis that *log K* at MA1 was

300   greater in patients than in controls (Step (1) in the analysis plan). We also tested for

301   associations between *log K* at MA1 and scores on the various rating scales, using simple

302   linear regression, with *log K* as the dependent variable. Additionally, we expressed pairwise

303   associations between *log K* at MA1 and each rating scale as a Spearman correlation

304   coefficient (Step (3) in the analysis plan).

305   Finally, we tested whether $\log K$ at MA1 was associated with a change in depression

306   (HAM-D) scores over time, independent of discontinuation (Step (6) in the analysis plan). To

307   do so, we fitted a linear mixed effect model, wherein the dependent variable is HAM-D

308   score (at MA1 or MA2), the independent variables (with fixed effects) are $\log K$ at MA1,

309   timepoint (MA1 or MA2), a [$\log K_{MA1}$ x timepoint] interaction, discontinuation group (MA1-

310   D-MA2 vs. MA1-MA2-D) and [discontinuation group x timepoint] interaction. We included

311   a random slope for each participant. Here, the [$\log K_{MA1}$ x timepoint] interaction term

312   expresses the extent to which a change in depression score across time depends on $\log K$ at

313   baseline, whereas the [discontinuation group x timepoint] interaction term controls for

314   possible confounding that results from testing on two discontinuation groups that differ in

315   the time of withdrawal. Here we hypothesized that participants with higher baseline

316   discounting would show less improvement in depressive symptoms across time.

317   Complementary analysis methods and results that appear in the *a priori* analysis plan

318   are provided in the Supplementary Material. As set out in the analysis plan, all comparisons

319   were performed first on the Zurich sample, with a view to testing on the Berlin sample as an

320   out-of-sample validation of predictive accuracy. However, where no significant associations

321   between $\log K$ and the variables of interest were found in either sample, we pooled both

322   samples to maximize power. We report these pooled analyses here.

323

324   **Results**

325   **Sample description**

326   Out of 104 patients with remitted MDD and 57 controls who were initially recruited,

327   97 patients (71 from Zurich and 26 from Berlin; 77% female, average age 34.78) and 54

328   controls (32 from Zurich and 22 from Berlin; 70% female, average age 33.52) answered the

329   discounting questionnaire at MA1. 47 and 50 patients were randomized at MA1 to the

330   discontinuation (MA1-D-MA2) and continuation group (MA1-MA2-D), respectively. 10

331   patients dropped out before MA2 and 7 more patients dropped during the follow-up period.

332   The 17 dropouts were excluded from the prediction of relapse analysis. Among the included

333   patients, 52 remained well (65%) and 28 (35%) relapsed during the follow-up period. The

334   numbers of participants in each group are also indicated in Figure 1. At baseline, HAM-D

335   scores in the remitted patient group, although below the clinical threshold for MDD, were

336   significantly higher than those in the control group (HAM-D controls mean = 0.38,

337   median=0, HAM-D patients mean = 1.81, median=1; two-sample, two-tailed t-test

338    $t(147)=5.15$, $p<0.001$; Wilcoxon rank sum test $p<0.001$).

Model fitting

340   Model accuracy met the (binomial test) accuracy criterion described above for all

341   participants, and therefore no participants were excluded. The average model accuracy was

342   85%; mean McFadden's pseudo-R^2 across subjects was 0.59, indicating a good fit to the data.

343   Discount rates obtained from the adaptive discounting questionnaire and the Kirby MCQ

344   were only moderately correlated (Spearman $\varrho=0.32$, $p < 0.001$).

345   In addition, no significant associations were found between log K at baseline and any

346   possible confounding factors tested. The details and results are provided in Supplementary

347   Table 2.

348   **(i)   Prediction of relapse**

349   We found no significant difference in $log K$ at MA1 between subjects treated with

350   ADM who relapsed during follow-up and subjects treated with ADM who did not relapse

351   ($t(78)=0.44$, $p >0.25$,two-tailed two-sample; Cohen's $d = 0.10$). Furthermore, a change in $log K$

352   following discontinuation (i.e., between MA1 and MA2 amongst the MA1-D-MA2 group),

353   did not differ significantly between participants who subsequently relapsed and those who

354   did not relapse ($t(37)=0.58$, $p>0.25$, one-tailed; Cohen's $d=0.20$). In a Cox proportional hazards

355   regression model, including $log K$ at both timepoints, neither $log K_{MA1}$ nor $log K_{MA2}$ were

356   significantly associated with days-to-relapse (Coefficient $log K_{MA1}$ =-0.02, $p>0.25$; coefficient

357    $log K_{MA2}$ =-0.08, $p>0.25$), nor was $log K_{MA1}$ associated with relapse when entered into a

358   separate regression model (Coefficient =-0.08, $p>0.25$).

359   In the prediction of relapse, the regularized regression weights were found to be all

360   zero, resulting in a balanced accuracy of 0.5 and reflecting the balanced proportion of the

361   majority class. For the sake of completeness, the distribution of baseline $log K$ in the different

362   relapse groups is shown in Supplementary Figure S1.

363   (ii)   **Effect of discontinuation**

364   Contrary to our secondary hypothesis, antidepressant discontinuation was not

365   associated with a significant increase in impulsive choice, relative to continuing medication.

366   Specifically, in a linear mixed effects model with *log K* as the dependent variable, we found

367   no significant [timepoint x discontinuation group] interaction ($\beta_{timepoint\ x\ group}$ =0.04,

368    $t(180)=0.15$, $p>0.25$). In other words, discontinuation did not significantly alter a change in *log*

369   *K* across time. Main effects of timepoint and group were also small and non-significant

370   (β_{group} =-0.05, $t(180)=-0.10$, $p>0.25$; $\beta_{timepoint}=0.10$, $t(180)=0.56$, $p>0.25$).

371   We further explored this null finding in a *post hoc* analysis, by performing a one-

372   tailed two-sample *t*-test on *log* K gain scores to test whether *log K* increased more in patients

373   who discontinued at MA1 (MA1-D-MA2) than in patients who discontinued at MA2 (MA1-

374   MA2-D). To prevent error accumulation due to the additivity of noise, in model fitting, the

375   difference between *log K* at MA1 and *log K* at MA2 was estimated concurrently with *log K* at

376   MA1. Again, we found no significant difference in the change in *log K* between MA1 and

377   MA2, among the MA1-D-MA2 group compared with the MA1-MA2-D group ($t(82)=0.19$, *p*

378   >0.25; Cohen's *d* = 0.04).

379   A possible explanation for these null results would be that our delay discounting

380   measure was unreliable. If this were the case, we would expect no consistent relationship

381   between discounting at MA1 and MA2. Contrary to this idea however, across all patients we

382   found a moderate correlation between *log K* at the two timepoints ($r=0.72$, $p<0.001$). Similar

383   test-retest correlations were observed in both the MA1-D-MA2 ($r=0.80$, $p<0.001$) and MA1-

384   MA2-D groups ($r=0.65$, $p<0.001$). These results indicate that the rank order of discounting

385   across participants was moderately stable over time, supporting the reliability of our

386   discounting measure.

387   A further possible explanation for observing no effect of discontinuation on

388   impulsivity would be that discontinuation produced no significant withdrawal syndrome in

389   the study participants. Against this, the MA1-D-MA2 group exhibited a statistically

390   significant increase in depressive symptoms following discontinuation (MA1 HAM-D mean

391   = 1.65, median=1; MA2 HAM-D mean=3.16, median=3; $t(39)=4.39$, $p<0.001$, two-tailed;

392   Wilcoxon signed rank $p<0.001$). No such symptom change was observed in the MA1-MA2-D

393   group, who did not discontinue medication until after the second timepoint (MA1 HAM-D

394   mean = 1.98, median=2; MA2 HAM-D mean=2.18, median=2; $t(40)=0.34$, $p=0.733$, two-tailed;

395   Wilcoxon signed rank $p=0.610$). Furthermore, symptom change between the two timepoints

396   in the MA1-D-MA2 group was significantly greater than that in the MA1-MA2-D group

397   (two-sample t-test, $t(79)=2.77$, $p=0.007$, two-tailed; Wilcoxon rank sum $p=0.013$). These

398   findings indicate a detectable effect of discontinuation.

399   **(iii)**   **Discounting** *in remitted MDD*

400   Group comparison of *log K* between healthy controls and patients with remitted

401   MDD (treated with ADM) at MA1 revealed significantly higher discount rates in the patient

402   group ($t(149)=2.03$ and $p =0.022$, one-tailed; Cohen's $d = 0.34$). Notably both groups showed

403   low levels of impulsivity, and the absolute difference in K between the two groups was

404   small. Mean K in the remitted MDD group was 0.0065, corresponding to indifference

405   between a reward of 75 euros received in 20 days and an immediate reward of 66 euros.

406   Mean K in the control group was 0.0037, corresponding to indifference between a reward of

407   75 euros received in 20 days and an immediate reward of 70 euros.

408

409
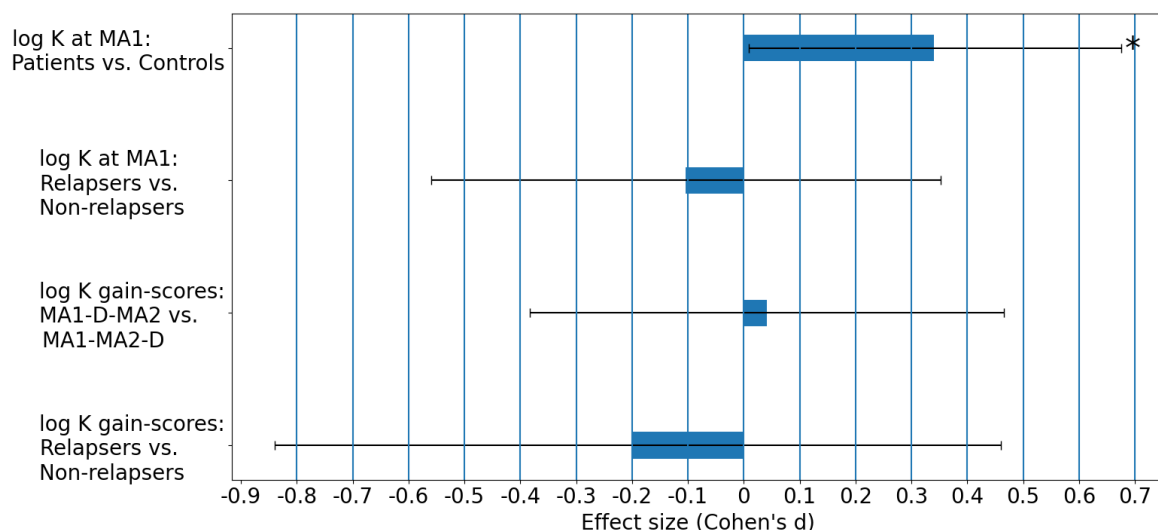
410   **Figure 3:** Cohen's d effect size, for various group comparisons. The top bar shows the

411   comparison of log K at MA1 between controls and patients, where the effect size in this case

412   indicates that the average of log K in the Patients group (at both sites) at MA1 is greater than

413   the average of log K in the Controls group at MA1. The second bar from above shows the

414   comparison of log K at MA1 between patients who subsequently relapsed and patients who

415   did not, where the effect size in this case indicates that the average of log K in non-relapsers

416   at MA1 is greater than the average of log K in relapsers at MA1. The third bar shows the

417   comparison of the change in log K between the two timepoints (gain scores), between

418   patients who discontinued their treatment at MA1 (MA1-D-MA2) and patients who

419   continued their treatment until MA2 (MA1-MA2-D), where the effect size indicates that the

420   average of gain scores in the MA1-D-MA2 group is greater than the average of gain scores in

421   the MA1-MA2-D group . The bottom bar shows the comparison of the change in log K

422   between the two timepoints (gain scores), between patients from the MA1-D-MA2 group

423   who subsequently relapsed and patients from the MA1-D-MA2 group who did not, where

424   the effect size indicates that the average of gain scores in the non-relapsers group was

425   greater than the average of gain scores in the relapsers group. Error bars represent 95%

426   confidence interval for Cohen's d effect size, estimated using MATLAB meanEffectSize

427   function . Group difference p-value: * .01<p<.05.

428

429   As shown in Figure 4, depressive symptoms (measured by the HAM-D scale) were

430   significantly correlated with baseline discount rate, $log\ K_{MA1}$ (Spearman ϱ=0.24, p=0.003), an

431   association which survived Bonferroni correction for multiple comparisons (p=0.022,

432   corrected for 8 comparisons), and was also present when testing only on the patients' group

433   (Spearman ϱ=0.23, p=0.025). Other questionnaire instruments did not exhibit significant

434   correlations with $log\ K_{MA1}$ (Figure 4). We note that baseline discount rate showed a

435   significant correlation with two *subscales* of the CTQ questionnaire, namely CTQ-physical

436   abuse (Spearman ϱ =0.18, p=0.023) and CTQ-emotional neglect (Spearman ϱ =0.16, p=0.049).

437   See Supplementary Figure S2 for the comparisons with other questionnaire subscales. When

438   all questionnaire variables were entered into a linear regression model with $log\ K_{MA1}$ as the

439   dependent variable, only HAM-D emerged as a significant explanatory variable (coefficient

440   estimate=0.19, $t(142)$=2.51, p=0.013). Coefficients and t-statistics for the remaining rating

441   scales are provided in Supplementary Table 3.

442
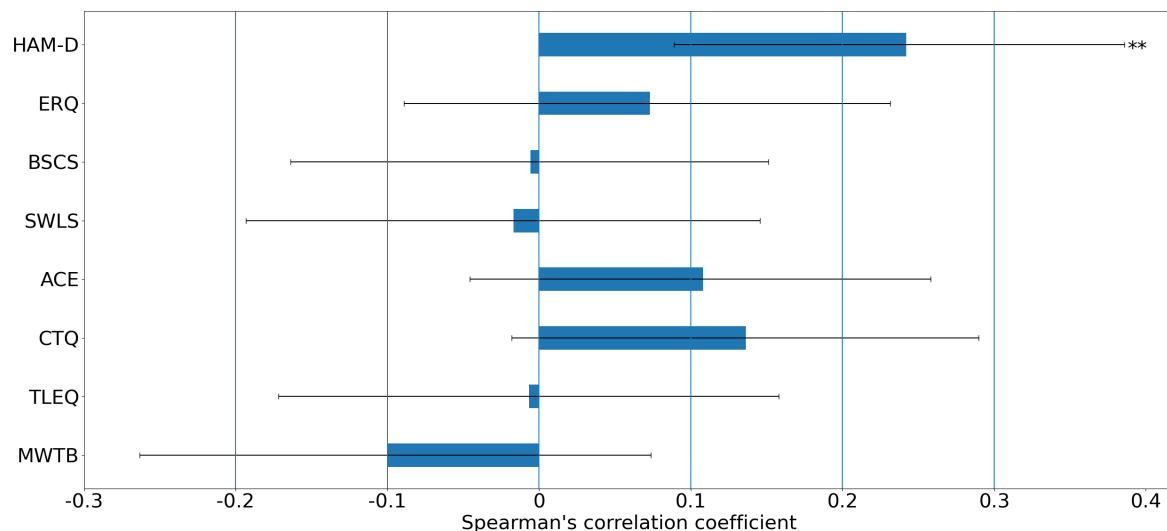
Figure 4: HAM-D=Hamilton Depression Scale, ERQ=Emotion Regulation Questionnaire (ERQ), BSCS=Brief Self-Control Scale, SWLS=Satisfaction with Life Scale, ACE=Adverse Childhood Experience, CTQ=Childhood Trauma Questionnaire, TLEQ=Traumatic Life Events Questionnaire, MWTB= Mehrfachwahl-Wortschatz-Intelligenztest. 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

463   of the [discontinuation group x timepoint] interaction (coefficient estimate=-0.47, t(150)=-

464   0.94, p=0.345).

465

466   **Discussion**

467   In this pre-registered analysis, we examined the potential of delay discounting as a

468   behavioral marker of relapse after antidepressant discontinuation. There is *a priori* evidence

469   to suggest that delay discounting might help predict illness trajectory following

470   discontinuation of antidepressant medication (ADM). To the best of our knowledge, the

471   present study is the first to prospectively examine i) whether discounting predicts future

472   depressive relapse following ADM discontinuation, and ii) the effect of ADM

473   discontinuation on delay discounting. Our results suggest that delay discounting is not

474   altered by ADM discontinuation to a clinically meaningful extent. Furthermore, we found

475   that neither baseline delay discounting, nor a change in discounting following ADM

476   discontinuation were predictive of future depressive relapse. However, we did find

477   significantly steeper delay discounting amongst patients with remitted MDD, compared

478   with controls (Cohen's *d* = 0.34), and a robust relationship between the discount rate and

479   depressive symptoms (Spearman ϱ=0.24).

480   We note that our observed correlation between delay discounting and depressive

481   symptoms may be attributable to subdomains of depressive symptoms. This possibility

482   accords with previous studies finding relationships between discounting and symptom

483   variables such as hopelessness, anhedonia[31] and suicidal ideation[24] or acts[35]. Owen et al.[37]

484   reported a loss of evaluative differentiation concerning future outcomes in patients with

485   MDD, which might serve as an explanation for our findings.

486   To our knowledge, the present study is the first to find significantly elevated delay

487   discounting amongst medicated patients with remitted MDD. This finding is consistent with

488   previous studies that have observed a relationship between trait-level impulsivity (e.g., as

489   assessed in self-report rating scales) and remitted depression[74,75]. A previous study by Pulcu

490   *et al.*[26], which compared delay discounting amongst people with remitted, medication-free

491   MDD and healthy controls, found that patients with remitted depression showed marginally

steeper discounting than controls, however this difference was statistically significant only for larger rewards. 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 here in remitted MDD might therefore reflect residual, sub-clinical depressive symptoms. In keeping with this hypothesis, the remitted patient group exhibited higher depressive symptom scores than the control group.

Alternatively, discounting might partly capture a trait-level vulnerability to depression, which persists despite symptom resolution. Previous studies find that delay discounting indeed has properties of a trait variable, being conserved across different types of reward[76], with moderate test-retest reliability[77]. Our combined delay-discounting score exhibited a similar degree of stability within-participants across the two time points of the study (r=0.72) to that recently reported in meta-analysis (r = .670, 95% CI [.618, .716])[77]. These findings suggest that delay discounting can be considered a trait variable. However, since our study did not measure discounting longitudinally in patients as they moved into remission, we have no direct evidence to support an hypothesis that steeper discounting is a vulnerability factor for MDD.

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. For example, a post-hoc power analysis for a two-tailed two-sample t-test with a type I error rate of $\alpha = 0.05$, comparing 28 relapsers and 52 non-relapsers, indicates a power of 0.8 to detect an effect size of $d = 0.66$ and a power of 0.95 to detect an effect size of $d = 0.85$. Furthermore, the power to detect a medium effect size of $d = 0.5$ is 0.55 (using G*-power 3.1[78]). While we do not provide evidence for the absence of effects, power considerations inform our interpretation and suggest that large effect sizes, greater than 0.5, are unlikely.

Another limitation that restricts our ability to accurately predict future risk of relapse is the limited six-month follow-up period, which may lead us to overlook patients who did not relapse during this time period but might have relapsed if observed for a longer

522   duration. Nevertheless, our null finding suggests that, if discounting is indeed a trait-level

523   vulnerability factor for MDD, this effect is too small to be clinically meaningful over short-

524   term follow up.

525   A potential limitation of our statistical analyses concerns how the hierarchical

526   Bayesian procedure used to estimate the discount rate was applied in the context of a

527   regularized regression analysis to predict relapse. Within the cross-validation framework

528   used to optimize the regularization parameter discount rate was not fitted separately for

529   training and validation sets of each fold, resulting in non-independent estimates between

530   these two sets, and potentially optimistic estimates of prediction accuracy. However, this

531   concern is mitigated in our specific case as the prediction results remain insignificant.

532   Furthermore, the issue does not affect the critical test of training the model on the Zurich

533   dataset and testing it on the Berlin dataset.

534   Contrary to our prediction, higher impulsivity at baseline was associated with a

535   marginally significant *decrease* in depressive score across time. We are uncertain as to the

536   explanation for this effect. We speculate that higher impulsivity is linked to greater

537   venturesomeness, which encourages exploration and thereby recovery from depression.

538   Alternatively, this unexpected finding might arise due to regression to the mean of

539   depressive symptoms across time. That is, since participants with higher baseline

540   impulsivity tended to show higher baseline depressive symptoms, if higher baseline

541   symptoms tended to regress to the mean over time, impulsivity also would appear to be

542   weakly associated with symptomatic improvement. However, since this finding is against

543   our prior predictions, further replication is needed.

544   A secondary hypothesis was based on an idea that discounting would be a sensitive

545   marker of psycho-physiological changes following ADM discontinuation. However, we did

546   not observe an increase in impulsivity following ADM discontinuation. Specifically, we did

547   not find a significant change in *log K* amongst remitted patients who discontinued their

548   treatment (MA1-D-MA2 group), relative to remitted patients who continued their treatment

549   (MA1-MA2-D group). This finding is also consistent with an AIDA study of effort-reward

550   tradeoffs[52], where the authors found no effect of ADM discontinuation on choices of high-

551   effort high-reward options. Although our finding may be the result of limited statistical

552 power, the relatively small effect sizes obtained from the corresponding group comparisons

553 (Cohen's $d<0.1$), as well as the significant group differences obtained in other comparisons,

554 suggest otherwise. Indeed, our finding of a small yet statistically significant increase in

555 depressive symptoms following ADM discontinuation, indicating that stopping medication

556 had a clinically detectable effect, further points to a dissociation between discounting and

557 discontinuation.

558 We had hypothesized that discounting might be sensitive to decreases in

559 serotonergic neuromodulation following antidepressant discontinuation. However,

560 although discounting has been shown to be sensitive to serotonergic manipulations, it is

561 unclear whether the elevated discounting observed in MDD is linked to changes in

562 serotonin. Furthermore, the directionality and temporality of the adaptive changes in the 5-

563 HT system following antidepressant discontinuation are uncertain. Some evidence points to

564 a reduction in the extracellular 5-HT levels following discontinuation[79,80], while other studies

565 indicate a rebound above pre-treatment levels (see e.g.[80-83]). Taking these considerations

566 together, a lack of association between discounting and ADM discontinuation is not out of

567 keeping with the state of existing knowledge concerning causal relationships between

568 serotonergic function, depressive disorders and ADM.

569 **Conclusion**. Delay discounting is not strongly affected by ADM discontinuation and

570 therefore appears to be of limited use as a biomarker for decisions related to anti-depressant

571 discontinuation.

572 **Data availability.** The datasets generated and analysed during the current study are

573 available from the corresponding author on reasonable request and in line with the ethical

574 rules.

575 **Code availability.** The MATLAB code used to analyse the data is available upon reasonable

576 request to the corresponding authors.

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Supporting Material Online

Randomisation Procedure

866   We assumed a priori that severity of a person's depressive illness might affect relapse

867 rates. This hypothesis was tested in a separate study[51]. Hence, to ensure that both groups

868 would contain a sample with equal distributions of severity, we stratified patients into a

869 severe and a non-severe group. If patients fulfilled either of the following criteria, they were

870 assigned to the severe group: 1) more than three prior episodes, 2) more than seven

871 depressive symptoms during the last episode, 3) severely impaired social functions, i.e.

872 strongly isolated, disabled or aggressive, 4) engagement in activities almost nonexistent, 5)

873   capacity to work almost nonexistent. We, additionally, stratified for site. Group membership

874   was allocated by a randomization algorithm. The first ten subjects at each site were not

875   randomized, but all assigned to the MA1-D-MA2 arm.

876   **Lasso regression modeling with *log K* at baseline as dependent variable and depression**
877   **rating questionnaire scores as independent variables**

878   To further examine whether depression rating questionnaires can predict discounting, we

879   used a regression model with both an L1 regularization, as implemented by the lassoglm

880   function in Matlab, with log K at baseline as the dependent variable and scores to depression

881   rating questionnaires as independent variables. We applied a tenfold cross validation to

882   optimize strength of the L1-regularisation parameter. This was repeated for 100 equally

883   spaced regularization parameter values ranging from 3.5×10^{-5} to 0.35, and the parameter

884   that resulted in the minimum cross-validated mean squared error was chosen.

885   The predictors having non-zero coefficients were HAM-D (coefficient estimate=0.126), CTQ

886   (coefficient estimate=0.002) and MWTB (-0.034), and the MSE was 2.6812. Predicted baseline

887   log K were found to be moderately correlated with true baseline log K (Spearman's ρ=0.303,

888   p<0.001).

889   Following the a priori analysis plan, we also carried out similar analysis in which the model

890   was trained on log K values of subjects from the Zurich sample, and then tested on log K

891   values estimated of subjects from the Berlin sample, serving as a hold out. The predictors

892   having non-zero coefficients were HAM-D (coefficient estimate=0.075) and MWTB (-0.041).

893   The MSE on the whole training (Zurich) sample was 2.718, and the MSE on the whole test

894   (Berlin) sample was 2.322. Predicted baseline values of log K in the test sample were

895   correlated with true baseline log K in the test sample, however this correlation did not reach

896   statistical significance (Spearman's ρ=0.219, p=0.1337).

897   *A priori* **power analysis**

898   The *a priori* power analysis reported here was conducted prior to the original AIDA study[2] to

899   estimate the required sample size for detecting a group difference (i.e. a t-test). We assumed

900   an effect size of $d = 1.2$ and an attrition rate of 20% over the six-month follow-up period.

901   Some patients may have re-entered therapy without meeting the criteria for a full relapse,

902   forming an intermediate group. We assumed that 30% of relapse patients would fall into this

903   category.

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904   Six months relapse rates on placebo ranges from 34-62%[3][4] and depend on length of the prior

905   treatment. Since we did not control the length of prior treatment, we assumed a relapse rate

906   of 40%. For a power of 0.95, and a two-sample two-tailed t-test, this yielded a N = 71 for the

907   patient group. To account for potential technical errors, we aimed to recruit at least N = 76

908   patients.

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922   **Supplementary Table 1 – a priori analysis plan**

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	Analysis	*Dependent Variable*	*Independent Variable(s)*	*Hypothesis*	*Statistical Method*	*Contrast of Interest*	*Intention-to-Treat*
(1)	*Impulsivity in depressed patients vs healthy controls*	Log K at MA1	Group: patient vs control	At MA1 *log K* is greater in patients than controls	Two sample *t*-test	Main effect of Group	No

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(2)	*Impulsivity as a function of antidepressant discontinuation*	Log K at MA1 and MA2	Group: early vs late discontinuation	Discontinuation is associated with an increase in *log K* between MA1 and MA2	Linear mixed effects regression modelling	Group x Time interaction	Yes
(3)	*Impulsivity as a function of questionnaire data*	Log K at MA1	HAM-D[1]	HAM-D scores are positively correlated with *log K*	Linear regression modelling, *t*-test on slope	Main effect of HAM-D	No
			SWLS[1]	SWLS scores are negatively correlated with *log K*	Linear regression modelling, *t*-test on slope	Main effect of SWLS	No
			ACE[1]	ACE scores are positively correlated with *log K*	Linear regression modelling, *t*-test on slope	Main effect of ACE	No
			HAM-D, ERQ, BSCS, SWLS, ACE, CTQ, TLEQ, MWT-B[1]	Exploratory analysis: a combination of questionnaire measures (and/or their latent factor structure) is associated with discounting	Linear regression modelling; sparse partial least squares regression, *t*-tests on slope	Main effects of questionnaire measures, or corresponding factors	No
			HAM-D, ERQ, BSCS, SWLS, ACE, CTQ, TLEQ, MWT-B[1]	Exploratory analysis: a combination of questionnaire measures (and/or their	Lasso regression modelling; leave one out cross validation within Zurich	Main effects of questionnaire data, or corresponding factors	No

				latent factor structure) *predicts* discounting	sample; test prediction on Berlin sample as a hold out		
(4)	*Relapse rate over time as a function of impulsivity*	Relapse in both patient groups	Log *K* at MA1	Higher *log K* at MA1 is associated with greater odds of relapse	Cox proportional hazard modelling	*K* x Hazard interaction	Yes
				Higher *log K* at MA1 *predicts* relapse	Lasso regression modelling; leave one out cross validation within Zurich sample; test prediction on Berlin sample as a hold out	Main effect of *K*	No
(5)	*Relapse over time in the patient group as a function of change in impulsivity following antidepressant discontinuation*	Relapse in early discontinuation patient group	Log *K* at MA1 and MA2	Increase in *log K* between MA1 and MA2 is associated with greater odds of subsequent relapse	Cox proportional hazard modelling	*K* x Time x Hazard interaction	Yes
				Increase in *log K* between MA1 and MA2 *predicts* subsequent relapse	Lasso regression modelling; leave one out cross validation within Zurich sample; test	*K* x Time interaction	No

				prediction on Berlin sample as a hold out			
(6)	*Depression score over time as a function of impulsivity*	Hamilton Depression Scale (HAM-D) scores	Log *K* at MA1	Higher *log K* at MA1 is associated with reduced recovery in HAM-D score over time	Linear mixed effects regression modelling	*K* x Time interaction	Yes

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925 1. Hamilton Depression Scale (HAM-D), Emotion Regulation Questionnaire (ERQ), Brief

926 Self-Control Scale (BSCS), Daily Hassles, Satisfaction with Life Scale (SWLS), Adverse

927 Childhood Experience (ACE), Childhood Trauma Questionnaire (CTQ), Traumatic Life

928 Events Questionnaire (TLEQ), Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B).

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938 **Supplementary Table 2 – *log K* differences with respect to potential confounders**

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Potential confounder	t statistic/Spearman ρ/F statistic	Degrees of freedom	P value	Cohen's d effect size
Gender (Male vs. Female)	t=0.24	149	0.806	0.04
Site (Zurich vs. Berlin)	t=1.72	149	0.086	0.30
Treated by general physician (GP) vs. not treated by GP	t=0.49	149	0.625	0.09

Treated by psychiatrist vs. not treated by psychiatrist	t=0.31	149	0.754	0.05
Treated by psychologist vs. not treated by psychologist	t=0.65	149	0.511	0.14
Medication classes (ANOVA)	F=0.84	2,94	0.431	-
Chronicity	Spearman's ρ =0.07	-	0.330	-

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941 *Note*. We tested for associations between *log K* at baseline (MA1) and different potential
942 confounding factors, namely: gender group, site (Zurich/Berlin), treatment group (treated by
943 general physician, psychiatrist, or psychologist), medication class and chronicity of
944 depression, where the latter is defined as the number of months sick within the last five
945 years Associations with dichotomous variables were tested using two-sample *t*-tests,
946 categorical variables by one-way ANOVA. We also tested a correlation between baseline *log*
947 *K* and chronicity of depression, a continuous variable. This step was not explicitly stated in
948 the original analysis plan.

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955 **Supplementary Table 3 – results of linear regression model having *log K* at baseline as**
956 **dependent variable and depression rating questionnaire scores as independent variables**

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Questionnaire	Coefficient estimate	95% confidence interval	t-statistic	Degrees of freedom	P value
ACE	-0.032	[-0.286,0.221]	-0.25	142	0.802
SWLS	0.001	[-0.061,0.064]	0.04	142	0.961
HAM-D	0.198	[0.042,0.354]	2.51	142	0.013
ERQ	0.067	[-0.107,0.241]	0.75	142	0.448
BSCS	0.016	[-0.023,0.055]	0.81	142	0.414
CTQ	0.019	[-0.018,0.057]	1.03	142	0.304
TLEQ	-0.011	[-0.061,0.037]	-0.47	142	0.637

MWT-B	-0.060	[-0.123,0.001]	-1.92	142	0.057

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Supplementary Table 4 – sparse partial least squares with *log K* at baseline as dependent variable and depression rating questionnaire scores as independent variables

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Questionnaire	Coefficient estimate	VIP score
ACE	-0.032	0.209
SWLS	0.016	0.375
HAM-D	0.198	1.683
ERQ	0.067	0.518
BSCS	0.016	0.591
CTQ	0.019	1.249
TLEQ	-0.011	0.677
MWT-B	-0.060	1.530

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Note. In line with our a priori analysis plan, we also fitted a partial least-squares model, using the MATLAB plsregress function. The latter approach finds linear combinations of the independent variables (depression questionnaires), that explain variance in the dependent variable (log K) and allows to further examine the importance of each explanatory predictor using the variable importance in projection (VIP) measure5.

Fitting a partial least squares regression to the data, where the logarithm of the discount rate is the dependent variable, and the scores to the depression rating questionnaire are the predictor variables explained 9.01% of the variance in the logarithm of discount rate. HAM-D, CTQ, and MWTB scores had the largest VIP scores among all 8 rating scales (VIP=1.683,1.249,1.530 respectively).

**Supplementary Table 5 – means and standard deviations of group comparisons**

Variable	Mean (Median)	Standard deviation (Interquartile range)
Log K Baseline Non-relapse	-5.167	1.522
Log K Baseline Relapse	-5.269	1.697
[Log K MA2-Log K MA1] Non-relapse	0.215	1.139
[Log K MA2-Log K MA1] Relapse	0.039	1.263
[Log K MA2-Log K MA1] MA1MA2D	0.157	1.036
[Log K MA2-Log K MA1] MA1DMA2	0.162	1.154
[HAM-D MA1] MA1MA2D	1.979 (2)	1.824 (1)
[HAM-D MA2] MA1MA2D	2.178 (2)	1.600 (2)
[HAM-D MA1] MA1DMA2	1.652 (1)	1.876 (3)
[HAM-D MA2] MA1DMA2	3.163 (3)	2.645 (4)

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5 S Wold, A Johansson, M Cochi (eds). *PLS-partial least squares projections to latent structures.* ESCOM Science Publishers: Leiden, 1993; 523–550.

|		
Log K Baseline Controls	-5.597	1.627
Log K Baseline Patients	-5.042	1.605
HAM-D MA1 Controls	0.377 (0)	0.814 (0.25)
HAM-D MA1 Patients	1.813 (1)	1.932 (3)

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975 *Note.* Medians and interquartile ranges are reported in brackets for groups where a Bartlett
976 test rejects the null hypothesis that both groups come from normal distributions with equal
977 variances.

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991 **Figure S1 Distribution of *log K* in relapsers and non-relapsers**

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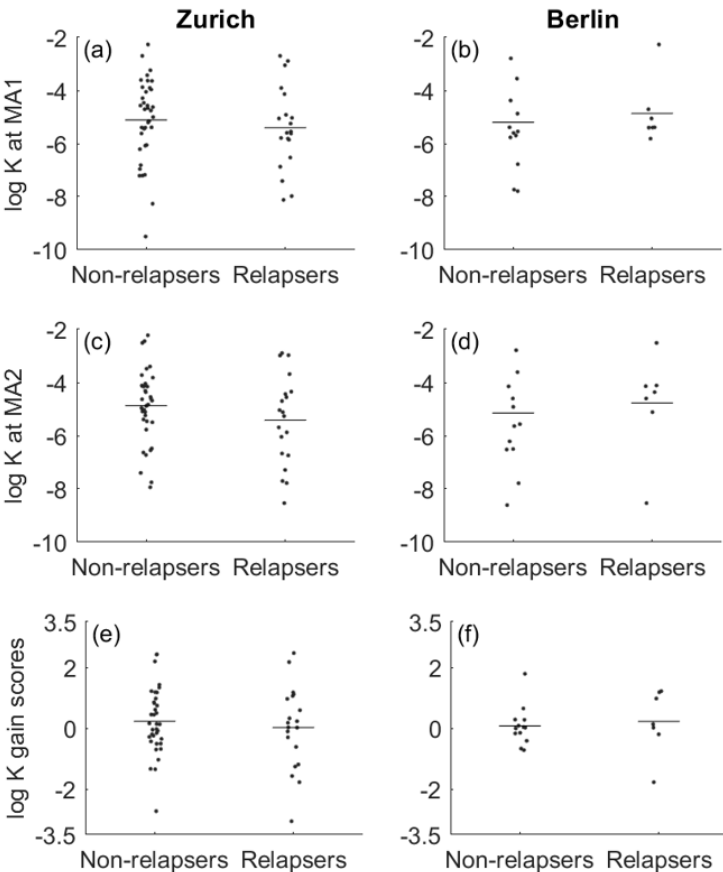
Note. Scatter plots of individual *log K* values in remitted patients who relapsed during follow up ("Relapsers") and patients who did not ("Non-relapsers"), in Zurich (a,c,e) and Berlin (b,d,f) sites, at either MA1 (a,b), MA2 (c,d) and gain scores (e,f). Horizontal lines mark the average *log K* value of the corresponding group.

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1007 **Figure S2 Correlations between *log K* at baseline and rating subscales**
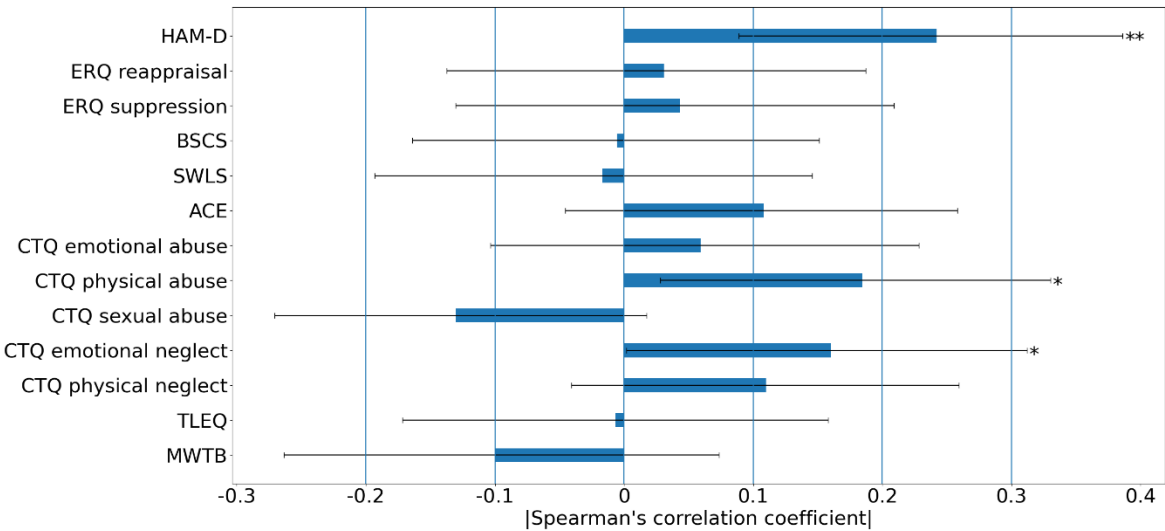
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1010 *Note.* HAM-D=Hamilton Depression Scale, ERQ=Emotion Regulation Questionnaire (ERQ),

1011 BSCS=Brief Self-Control Scale, SWLS=Satisfaction with Life Scale, ACE=Adverse Childhood

1012 Experience, CTQ=Childhood Trauma Questionnaire, TLEQ=Traumatic Life Events

1013 Questionnaire, MWTB=Mehrfachwahl-Wortschatz-Intelligenztest. Error bars represent 95%

1014 confidence interval for Spearman's correlation coefficient estimated using 10,000 bootstrap

1015 iterations. Group difference p-value: * .01<p<.05, ** .001<p<.01.

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