Delay discounting as a predictor of relapse following anti-depressant discontinuation

Analysis Plan

Giles Story, Isabel Berwian, Quentin Huys

Study Dataset

The existing study, described by Berwian et al. (2019a) is a two-centre, longitudinal, naturalistic observational study of antidepressant discontinuation. Berwian et al. recruited participants who decided to discontinue their medication independently from study participation after they had a) experienced one severe or multiple depressive episodes, b) initiated antidepressant treatment during the last depressive episode and c) now achieved stable remission. The final sample included 104 patients (age: 34.86 (11.1), 77% female) and 57 healthy controls (age: 34.12 (10.6), 70% female). The study aimed to examine predictors of relapse following antidepressant discontinuation.

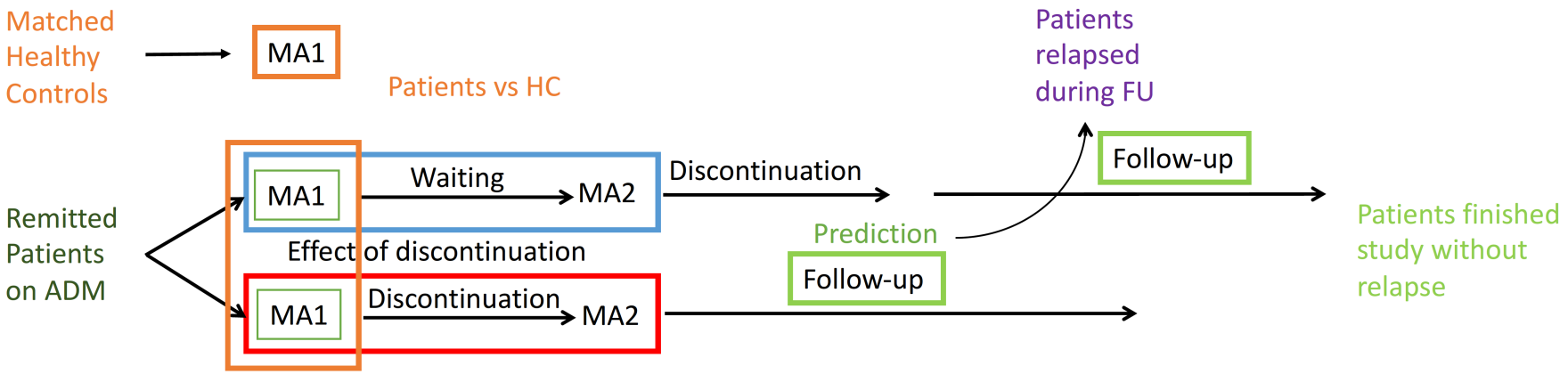

Figure 1. Study Protocol

As shown in Figure 1, participants were assessed and compared at main assessment 1 (MA1) to identify traits characterising the remitted, medicated state. Next, patients were randomised to either discontinue their medication until MA2 or enter a waiting period matched to the length of discontinuation time. Patients in the waiting group discontinued their ADM after MA2. After discontinuation, all patients entered the follow-up (FU) period of six months, whereas some patients had a relapse during this period and some patients finished this period without relapse.

Part 1: Delay Discounting

Delay discounting is a widely used measure of impulsivity, which elicits a person's willingness to wait to obtain delayed rewards, rather than accept smaller immediate rewards. Impulsivity on this measure is summarised as an individual's discount rate, encapsulating the extent to which the value of reward decreases with delay. Delay discounting can be assessed by offering participants a series of choices,

termed intertemporal choices, between immediate and delayed rewards of varying magnitude. The existing study collected intertemporal choice data at MA1 and MA2.

Aims of current study:

Previous studies have shown higher discount rates in people with depression compared with healthy controls. Previous work in humans has also revealed that discount rates increase following serotonin depletion, and are reduced by treatment with selective serotonin reuptake inhibitors. We therefore expect to observe increases in discounting following antidepressant discontinuation, offering a biomarker putatively predictive of subsequent relapse.

Analysis Plan:

All analyses described below, we will be first examined in the Zurich sample. The Berlin sample will serve as a replication sample. As the sample size in the Berlin sample is much smaller, we assume that we might not replicate the significance level achieved in the Zurich sample, but will aim at least at replicating the direction and size of the effect found in the Zurich sample.

We will first find the parameters of a generalized hyperbolic discount function which best explains the intertemporal choice data for each participant, at MA1 and MA2. We will also test if reduced models such as a simple hyperbolic model provide a more parsimonious fit to the data doing model comparison. Previous studies have shown that intertemporal preferences are well described by a generalised hyperbolic function, wherein a discount rate parameter, conventionally referred to as K, governs a decrease in reward value as it is delayed. We will fit such a function to participants' intertemporal choices using a hierarchical logistic regression to yield a discount rate, referred to as *K*, for each participant at each of the two time points. Higher *K* reflects greater impulsivity. The logarithm of *K* is approximately normally distributed in the population.

We will go on to examine relationships between *K* and other variables of interest. Our planned analyses are described in Table 1.

Table 1. Planned Analyses for impulsivity parameter

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
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 changes due to discontinuation and its impact on relapse	Log *K* at MA1 and MA2	Group: early vs late discontinuation	Discontinuation in patients who go on to relapse is associated with an increase in log *K* between MA1 and MA2	Linear mixed effects regression modelling	Group x Time x Relapse interaction	Yes
4) Impulsivity as a function of questionnaire data	Log *K* at MA1	IDS[1]	IDS scores are positively correlated with log *K*	Linear regression modelling, *t*-test on slope	Main effect of IDS	No
		SWLS[1]	SWLS scores are	Linear regression	Main effect of	No

			negatively correlated with log *K*	modelling, *t*-test on slope	SWLS	
		ACE[1]	ACE scores are positively correlated with log *K*	Linear regression modelling, *t*-test on slope	Main effect of ACE	No
		IDS, ERQ, BSCS, SWLS, ACE, CTQ, TLEQ, DS, 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
		IDS, ERQ, BSCS, SWLS, ACE, CTQ, TLEQ, DS, MWT-B[1]	Exploratory analysis: a combination of questionnaire measures (and/or their latent factor structure) *predicts* discounting	Lasso regression modelling; leave one out cross validation within Zurich sample; test prediction on Berlin sample as a hold out	Main effects of questionnaire data, or corresponding factors	No
5) Relapse rate over time as a function of impulsivity	Relapse in all patients	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	Lasso regression	Main effect of	No

			predicts relapse	modelling; leave one out cross validation within Zurich sample; test prediction on Berlin sample as a hold out	*K*	
6) 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 prediction on Berlin sample as	*K* x Time interaction	No

				a hold out		
7) 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

1. Inventory of Depressive Symptomatology (IDS), 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), Digit Span (DS), and the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B).

Part 2: Decision times

Background and aims of current study:

We previously showed that patients and in particular patients who go on to relapse after antidepressant discontinuation take longer to decide how much effort to invest for reward and that these decision times predict risk of relapse after discontinuation better than chance out-of-sample (Berwian et al., accepted). Modelling the behaviour of participants in this task with a drift-diffusion model, we found that the prolonged decision times are a result of increased boundaries. In line with these results, the core hypothesis of the present analysis states:

Hypothesis A:
Remitted patients on ADM and in particular those who go on to relapse have longer decision times.

These increased decision times could arise from

1) increased conflict in patients (they want the more immediate reward but also know that the later reward is rationally the better choice),
2) they have low self-confidence, feel insecure and need more persuasion before they can make a decision (might do more simulation and recall in line with a model-based approach)
3) ruminate more.

To our knowledge, no study examined decision times in a discount task in patients with depression and studies in other populations do not show conclusive evidence. According to theories of impulsivity, the alternative hypothesis might also be possible:

Hypothesis B:
Remitted patients on ADM and in particular those who go on to relapse have shorter decision times.

These shorter decision times could be due to
1) correlation of impulsivity as measured in temporal discounting with motor impulsivity
2) decreased deliberation e.g. due to cognitive impairments such as working memory deficits (i.e. decreased simulation and recall according to a model-based approach)
3) more impulsivity leading to steeper discounting, leading to more determined choice behaviour.

We will attempt to examine these options correlating decision times with according questionnaire data collected in the study (to the extent that we included according measures).

<u>Analysis plan:</u>

Raw behavioural data:

We will repeat the analyses outlined in the Table 1 above, but replace log K with decision times. In addition, we will replace the analysis number 4 in relation to the questionnaire data with the analysis outlined in Table 2.

Table 2. Planned Analyses for decision times and questionnaire data

Analysis	***Dependent Variable***	***Independent Variable(s)***	***Hypothesis***	***Statistical Method***	***Contrast of Interest***	***Intention-to-Treat***
Decision time as a function of questionnaire data	DT at MA1	Separately for the following measures:	Questionnaire scores are correlated with DT to examine the following hypotheses:	Linear regression modelling, *t*-test on slope	Main effect of Questionnaire measure	No
		MWTB;	B2			
		Digit span;	B2			
		TMT-A;	B2			
		TMT-B;	B2			
		Brooding subscale of RSQ;	A3			
		BSCS;	B3			
		Self-worth and decision difficulties item from IDS-CR	A2 A			

Decision times (DT), Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B), Trial-Making-Test A and B (TMT-A/B), Response Style Questionnaire (RSQ), Brief Self-Control Scale (BSCS), Inventory of Depressive Symptomatology-Clinician Rated (IDS-CR).

Analysis plan for discounting task - Version 2 – Date: 17.02.2020

Modelling:

In case the results indicate that decision times are associated with disease state or relapse, we will model the choice behavior and decision times jointly. To this end, we will use a drift-diffusion model in which the drift rate is determined by the difference of the value for the shorter and the latter option as determined by the model described in part 1 of this document. With regard to model formulation, model fitting, model and parameter recovery and model and parameter comparison, as well as prediction and replication, we will employ the methodological approach described in Berwian et al. (accepted).

Estimated parameters that relate to disease state or relapse will be subject to the analyses outlined in Table1 and 2 (replacing log K and decision times, respectively).

Exploratory analyses:

Based on the pattern of results in this study, we might include additional exploratory analyses and label them as such when reported.